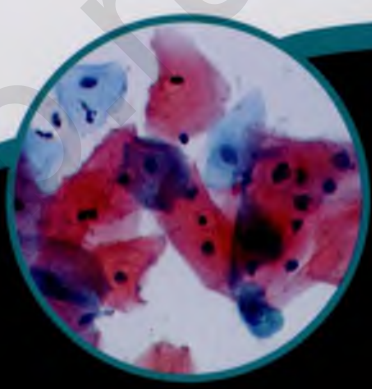
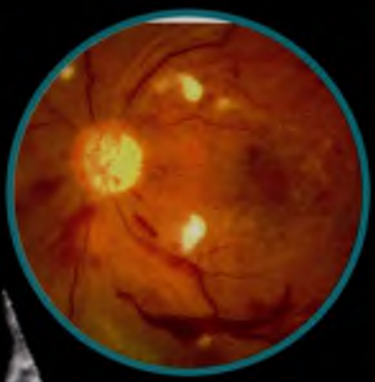
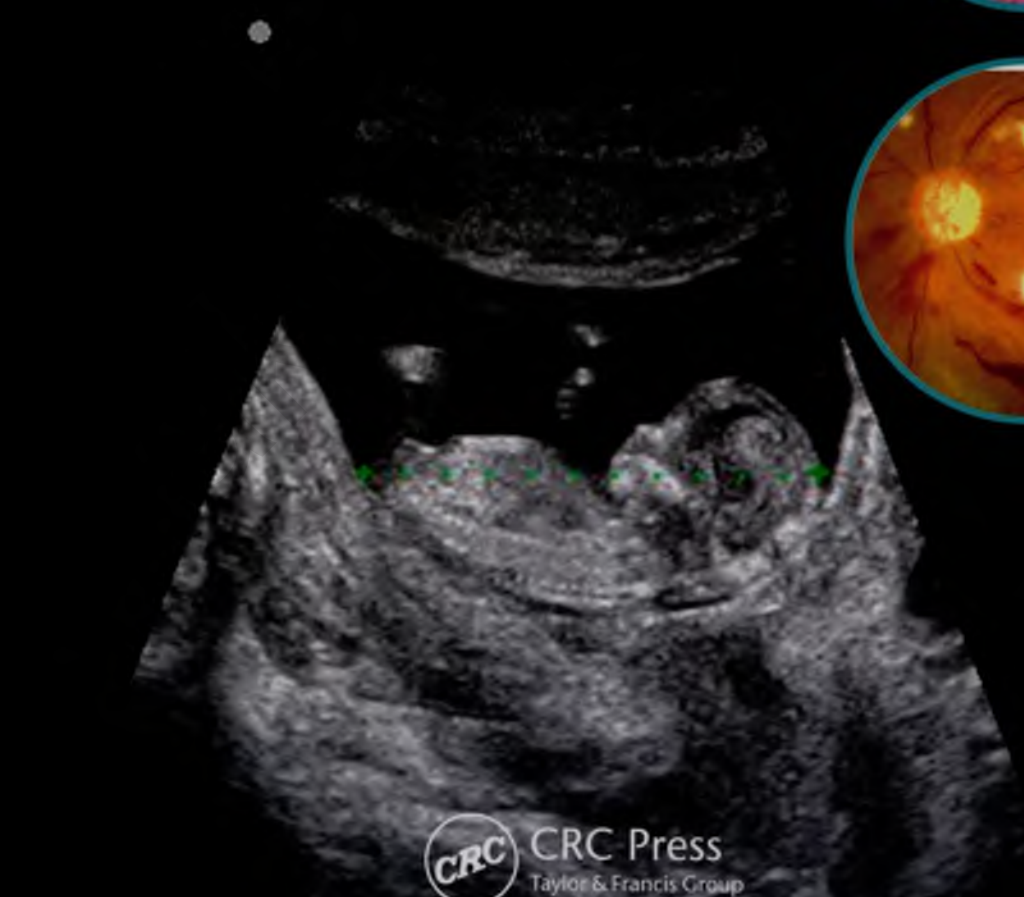
Second Edition

Differential Diagnosis in Obstetrics and Gynaecology: An A-Z

Tony Hollingworth







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Foreword to the First Edition

One of the major challenges in obstetrics and gynaecology is the need for a broad knowledge of medicine and surgery as well as the conditions specific to reproduction. The comprehensive nature of this book achieves this goal.

Differential Diagnosis in Obstetrics and Gynaecology covers everything you ever wanted to know about what can occur in pregnant and non-pregnant women. The editor has included experts in many specialties to contribute to this book which is particularly valuable as it takes the reader outside the realm of an obstetrician and gynaecologist. From minor symptoms to major symptoms the differential diagnoses are explored and offered in a way that is easy to read and leads the reader on to straightforward and practical management.

This book is suitable for all grades of healthcare professional, not only as a reference book but also for revising for any qualifying or licensing examination. Inevitably medical words are used but lay people would also find this book very useful.

The layout of the book is engaging as the text is interspersed with excellent illustrations and useful boxes highlighting important points. For the reader who would like to delve even further into each area there are up-to-date references.

Obstetrics and Gynaecology is a rewarding speciality but one that is forever confronting you with what you do not know. This book will undoubtedly help you to solve the problems and should be on the bookshelf of everyone who deals with women!

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Preface

This book is based on *French's Index of Differential Diagnosis*, which was first published in 1912. The aim of that book was 'to help in the differential diagnosis of any condition in medicine, surgery or any specialty that may be seen in general or hospital practice'. I was first asked to edit the gynaecological sections for the 2005 edition and the subsequent two editions. After the initial completion, I felt there was room for a similar type of book for obstetrics and gynaecology.

I enlisted the help of current and former colleagues as well as friends from around the world, to produce this book, which aims to cover many of the symptoms that may be commonly seen in a woman presenting to her gynaecologist or to her obstetrician during pregnancy. In some sections management of the symptoms has been addressed, but the main emphasis of this book is differential diagnosis. It was first published in 2008 and this is the second edition.

There has been a wider coverage of potential symptoms and I have tried to make the book as accessible as possible to all doctors regardless of specialty and grade, as well as midwives, nurses, medical students and patients alike. It includes algorithms, references and websites together with a glossary at the end of the book of common terms and terminology used in obstetrics and gynaecology.

I would like to acknowledge all the people who contributed as authors, providers of images or producers for both editions of the book. I would like to thank Paul Bennett who has been the production editor for this edition, Jeb Hogan who was the copyeditor, and Kate Nardoni and Cactus Design & Illustration for their beautiful diagrams. Finally, I would like to thank Robert Peden who has been both patient and persistent in seeing this edition onto the shelves, I am in his debt.

Tony Hollingworth
May 2015

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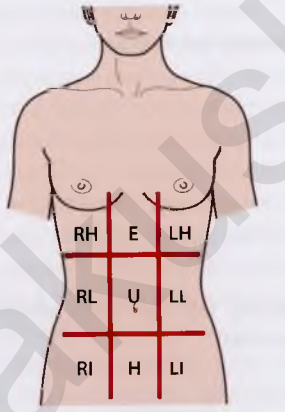
ABDOMINAL PAIN

Nigel Bickerton and Dilip Visvanathan

Each year in the UK, hundreds of thousands of patients are seen in accident and emergency departments across the country or are admitted on to a hospital ward following the sudden onset of abdominal pain (Fig. 1) as their main symptom. This group makes up 5–10 per cent of the total number of patients seen in UK hospitals. In the USA it has been estimated that this number is 5 million patients per year. Despite being seen by clinicians experienced in history-taking and clinical examination, and despite having undergone a series of clinical investigations, about 30 per cent of patients do not receive a specific diagnosis.

The term *acute abdomen* is used to describe the sudden onset of severe symptoms related to the abdomen and its contents. The symptoms may be due to pathological changes which require urgent surgical intervention. The pain may be somatic, visceral, or referred, all of which have different innervations. Somatic pain, transmitted through the somatic nerve fibres from the parietal peritoneum, may be caused by physical or chemical irritation of the peritoneum; the pain feels sharp, is very localised, and is constant until the cause of the pain is removed. Visceral pain is transmitted through the autonomic nerves. The quality of this pain is different from that of somatic pain, being dull, sometimes described as cramp-like. Women may describe the quality of visceral pain as 'like just before the start of a period'.



RH - Right hypochondrium
E - Epigastrium
LH - Left hypochondrium
RL - Right lumbar
U - Umbilical
LL - Left lumbar
RI - Right iliac fossa
H - Hypogastrium
LI - Left iliac fossa

Figure 1 Diagram of anatomical areas of the abdomen.

This section is meant to give only a broad overview of assessing abdominal pain in non-pregnant women, as many aspects of pain are discussed in other sections of the book.

A focused and precise history should usually point towards a diagnosis, which will usually be supported by the clinical examination even before undertaking further investigations.

The history should include the timing and nature of the onset of pain, together with its site (see Box 1) and radiating features plus any aggravating or alleviating factors. Though people often find the nature of the pain difficult to describe, precision in this area can be very valuable for making the correct diagnosis. The doctor needs to know whether the patient has constant, intermittent, or colicky pain. Colicky pain is the most difficult to describe, but a patient with this type of pain will often illustrate the pain with a hand or finger drawing a sine wave in the air, even to the crescendo–decrescendo representing pain intensity.

A full gynaecological history should be taken with specific reference to the possibility of pregnancy. Most units in the UK will do a urinary pregnancy test as a routine part of an emergency admission. All medicines prescribed or otherwise taken should be recorded, including recreational drug usage. Long-term prednisolone therapy should alert the clinician to the possibility of upper gastrointestinal perforation as a cause of acute pain. The history should include a review of all the systems with particular reference to the respiratory, cardiac, alimentary, and renal systems.

One significant risk in women with abdominal pain is that it will very often be attributed to a gynaecological cause. This can happen whatever route the woman takes into hospital. There are several ways that a doctor can improve the outcome of a woman's admission with abdominal pain. These start with remembering that it is best to think outside of our specialty for possible causes, while at the same time

Box 1 Causes of abdominal pain in relation to the site of symptoms

Epigastrium

- Stomach – dyspepsia, gastritis (alcohol, non-steroidal anti-inflammatory drugs), gastro-oesophageal reflux, gastric volvulus, ulcer, carcinoma
- Small bowel – duodenal ulcer
- Oesophagus – rupture (Boerhaave's syndrome), tear (Mallory–Weiss)
- Gallbladder – cholelithiasis, colic
- Pancreatitis – alcohol, gallbladder disease, bulimia
- Giardiasis – known in North America as beaver fever
- Vascular – visceral ischaemia, aortic aneurysm, splenic artery aneurysm
- Abdominal wall – epigastric hernia

Referred pain to the epigastrium includes:

- Myocardial ischaemia
- Inferior myocardial infarction
- Pericarditis
- Pneumonia – basal

Central/umbilical

- Bowel – irritable bowel syndrome (IBS), appendicitis, obstruction, Crohn's disease
- Pancreatitis
- Vascular – mesenteric artery thrombosis, aortic aneurysm
- Abdominal wall – umbilical hernia

Left upper quadrant/hypochondrium

- Stomach – gastritis, ulcer, carcinoma
- Pancreas – pancreatitis, carcinoma
- Large bowel – diverticulitis, perforation
- Spleen – leukaemia, lymphoma, infarct, rupture, malaria, infectious mononucleosis, kala-azar
- Kidney – pyelonephritis, hydronephrosis, calculi
- Viral – herpes zoster

Referred left upper quadrant includes:

- Lung – left lower lobe pneumonia, pulmonary embolus
- Cardiac – ischaemia or infarction

Right upper quadrant/hypochondrium

- Gallbladder – biliary colic, cholecystitis, carcinoma
- Liver – right heart failure, hepatic vein obstruction, malignancy, abscess, Fitz-Hugh–Curtis syndrome, HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome (in pregnancy)
- Small bowel – ulcer
- Large bowel – Crohn's disease, carcinoma
- Pancreas – pancreatitis, carcinoma
- Kidney – pyelonephritis, hydronephrosis, calculi
- Viral – herpes zoster

Referred right upper quadrant includes:

- Lung – right lower lobe pneumonia, pulmonary embolus
- Cardiac – ischaemia or infarction

Left lower quadrant/iliac fossa

- Bowel – constipation, gastroenteritis, colitis, diverticulitis, IBS, obstruction, carcinoma, carcinoma with perforation
- Reproductive – ectopic pregnancy, ovarian cyst accident, pelvic inflammatory disease (PID), mittelschmerz
- Abdominal wall – herniae: inguinal, femoral, umbilical, psoas abscess

- Urological – cystitis, ureteric colic
- Vascular – aneurysm
- Viral – herpes zoster

Right lower quadrant/iliac fossa

- Bowel – constipation, gastroenteritis, colitis, diverticulitis, IBS, appendicitis, obstruction, Crohn's, Meckel's diverticulum, carcinoma, carcinoma with perforation, caecal volvulus
- Reproductive – ectopic pregnancy, ovarian cyst accident, PID, mittelschmerz
- Abdominal wall – herniae: inguinal, femoral, umbilical, psoas abscess
- Urological – cystitis, ureteric colic
- Vascular – aneurysm
- Viral – herpes zoster

Medical causes of diffuse/generalised abdominal pain

- Pneumonia
- Diabetic ketoacidosis
- Henoch–Schönlein purpura
- Sickle cell crisis
- Acute intermittent porphyria
- Familial Mediterranean fever – paroxysmal peritonitis
- Lead poisoning
- Infections – malaria, typhoid fever, cholera, giardiasis
- Drugs – heroin withdrawal

recognising that common things happen commonly. It is also important to remember that certain conditions are more common at certain ages.

A woman with acute abdominal pain may need to be examined by several doctors over a short period of time, to ensure reach the correct diagnosis, but also because the patient's symptoms and signs may change as the condition that is causing the pain develops. This should be performed mindful that the examination itself can cause pain. Patients with severe pain will require analgesia, and nowadays there is no place for the view that analgesia masks clinical signs and should be withheld.

Physical examination should have commenced through observation during the history-taking, noting any dyspnoea during conversation, and seeing whether the patient stays still or is unable to get comfortable in any position. Blood pressure, pulse rhythm and rate, respiratory rate, and urinalysis should be recorded. A shocked patient will needs resuscitation while history-taking and examination are taking place.

Despite the complaint of abdominal pain, the examination should begin with the heart and lungs, to ensure that pneumonia, pleurisy, or atrial fibrillation leading to mesenteric artery thrombosis is not missed. The abdomen should be inspected in good light to avoid missing the erythematous streak of shingles before the characteristic vesicles develop. Absent abdominal wall excursion with breathing is suggestive of peritonitis.

Auscultation of the abdomen is often skimmed over by gynaecology trainees, yet can provide crucial information. Active bowel sounds of normal pitch (compare with your own) are often suggestive of non-surgical disease, e.g., self-limiting gastroenteritis. High-frequency bowel sounds in runs or clusters suggest bowel obstruction. The totally silent abdomen is the most worrying and requires the urgent attention of a general surgical colleague.

Abdominal palpation should always commence distant to the most painful area, eventually covering all quadrants. The clinical signs of guarding and rebound tenderness are then sought. Patients find a demonstration of rebound tenderness extremely uncomfortable, thus it should not be serially repeated 'just to make sure'. Recent studies have shown that severe abdominal pain induced by coughing has a comparable sensitivity and a higher specificity than a positive rebound tenderness test for the presence of peritonitis.

All patients should have the common sites for herniae examined. A bimanual examination of the pelvic organs should be followed by rectal examination to exclude blood or a local mass, if appropriate.

Investigations should be aimed at narrowing down the differential diagnosis rather than ordering a massive 'fishing' list of expensive and very often unnecessary tests. The majority of blood investigations are not specific to a diagnosis, and the results should be interpreted together with the clinical picture rather than separately.

Imaging for the acute abdomen may include an erect chest X-ray and supine abdominal X-rays looking for gas under the diaphragm or signs of bowel obstruction. In the USA, computerised tomography (CT) studies are more commonly used to assess possible cases of appendicitis; CT has a high sensitivity and specificity for this condition. CT is less reliable for pelvic organ diagnosis, and ultrasound scanning is still the modality of choice for assessing pain of possible gynaecological origin.

ABDOMINAL PAIN IN PREGNANCY

Ramesh Kuppusamy and Dilip Visvanathan

Abdominal pain in pregnancy is a very common symptom. In the majority of women the exact cause cannot be found, though it is thought to be physiological from musculoskeletal adaptations to an enlarging gravid uterus.[1] The causes of abdominal pain in pregnancy can be classified into physiological and pathological. The pathological causes can be sub-classified into pregnancy related, pregnancy exacerbated, and other concomitant pathology (Box 1).

Box 1 Causes of abdominal pain in pregnancy

Physiological causes
- Round ligament pain
- Braxton Hicks contractions

Pathological causes

Pregnancy related
- Threatened miscarriage or preterm labour
- Hyperemesis gravidarum with heartburn or intercostal muscle sprain
- Ovarian hyperstimulation syndrome
- Ectopic pregnancy
- Haemorrhage into an ovarian cyst, cyst rupture
- Placental abruption
- Acute liver swelling with severe pre-eclampsia
- Uterine rupture
- Acute polyhydramnios from twin–twin transfusion
- Chorioamnionitis with prelabour rupture of membranes

Conditions made worse with pregnancy
- UTI – cystitis and acute pyelonephritis
- Red degeneration of a uterine fibroid
- Torsion of a dermoid cyst or pedunculated fibroid
- Acute retention of urine in a retroverted gravid uterus

Other concomitant pathology
- Acute appendicitis
- Renal calculi
- Acute intestinal obstruction
- Cholelithiasis and acute cholecystitis
- Acute pancreatitis
- Peptic ulcers
- Trauma

Pregnancy-related causes of abdominal pain

The pregnancy-related causes of abdominal pain listed in Box 1 are described in detail in other sections of this book.

Pregnancy-exacerbated conditions that present with abdominal pain

Urinary tract infection (UTI)

UTI is more common during pregnancy owing to incomplete emptying of the bladder from head engagement, relaxation of the ureters from progesterone and back pressure on the pelvicalyceal system of the kidney from the enlarging uterus. UTIs complicate 1–3 per cent of all pregnancies. Universal screening for asymptomatic bacteriuria is done in all women at booking in the UK. Treatment of screen-positive women is thought to prevent 70 per cent of acute pyelonephritis. The difference in clinical presentation is that the classical symptoms of dysuria and frequency of micturition may not always be present. A dull aching loin pain with tenderness in the renal angle would suggest involvement of the kidney. A urine dipstick analysis would show nitrites and leucocytes. A midstream urine (MSU) specimen for microscopy culture and sensitivity will confirm the diagnosis with the growth of 105 colony-forming units/mL. Symptomatic women

should be treated empirically with antibiotics according to local protocols. A 7-day course is sufficient, and a test of cure with a repeat urine culture has been recommended.[1] Prompt recognition of pyelonephritis and early systemic empirical antibiotic therapy is essential to prevent severe sepsis and septic shock.

Torsion of an ovarian cyst or pedunculated subserous fibroid

Torsion of the vascular pedicle leads to acute severe ischaemia, and the patient will present with acute abdominal pain, nausea, and vomiting. Presentation is usually in the second trimester of pregnancy or in the puerperium, when there is space in the pelvis to undergo torsion. Clinical examination may reveal a patient who lies still in bed and may have tenderness in the lower abdomen. Signs of rebound tenderness, guarding, and rigidity are uncommon. Ultrasonography is important in making the diagnosis. The most consistent feature of a twisted ovary is an enlargement of the ovary to a mean diameter that is greater than 4 cm. The ovarian follicles usually are found in the periphery of the ovary; this is described as the 'string of pearls' sign. A coexistent mass (usually a dermoid cyst) may be found in the ovary. Free fluid in the pouch of Douglas is almost always present. More recently ultrasonologists have concentrated on studying the vascular pedicle itself. Grayscale ultrasound can demonstrate the twisted ovarian pedicle. Doppler studies show a target-like appearance that has been described as the 'whirlpool' sign. The presence of this sign indicates that the ovary is still viable. Absence of blood flow to the ovary would indicate that the ovary is not viable. These additional features help in pre-operative counselling – where every attempt should be made to conserve the ovary by untwisting it at surgery. Early diagnosis is therefore imperative if oophorectomy is to be avoided.

Torsion of a subserous fibroid will cause a similar picture – the presence of a fibroid is generally obvious from the booking scan. Ultrasound would show similar enlargement and free fluid in the pouch of Douglas and a twisted pedicle. Clamping the pedicle and removing the fibroid would be indicated, with the route of surgery depending on the stage of the pregnancy, size of the fibroid, comorbid factors, and the woman's wishes.

Red degeneration of a uterine fibroid

Uterine fibroids are regularly diagnosed at the first-trimester booking ultrasound scan. In most pregnancies the fibroids remain the same size. In a few women they may actually shrink in size, while some may enlarge in pregnancy. If the enlargement is rapid, the fibroid may outstrip its own blood supply, causing an acute ischaemic necrosis, referred to as red degeneration of a fibroid. The woman may present at any time in her pregnancy. The clinical presentation is usually of acute pain over the site of the fibroid. If the fibroid is in the anterior wall of the uterus it may be palpable and very tender. An ultrasound scan may show intramural fluid collection or cystic spaces within the substance of the fibroid. Pain scores can be very high, necessitating admission and the administration of narcotic analgesia.

Acute retention of urine

Acute retention of urine secondary to a gravid uterus usually presents in the first trimester of pregnancy with the retroversion of the uterus causing bladder outlet tract obstruction. Acute pelvic pain with a visible tense mass in the suprapubic region will point to the diagnosis. Conservative measures include bladder drainage and sometimes even a vaginal pessary to reposition the uterus. The condition usually resolves after 12 weeks' gestation when the uterus rises out of the pelvis.

Concomitant pathology in pregnancy causing abdominal pain

Acute appendicitis in pregnancy

The occurrence of acute appendicitis (Fig. 1) is approximately 1 in 5000 pregnancies. It can affect the reproductive outcome by an increase in pregnancy loss in early pregnancy or preterm labour in later pregnancy. The presenting symptoms may be non-specific, with nausea, vomiting, and anorexia. Occasionally a clue may be that the pain started around the umbilicus. Diagnosis can be difficult in the third trimester as the enlarging gravid uterus displaces the appendix upwards. The typical features of acute tenderness in the right iliac fossa, especially McBurney's point, may then be lost. Furthermore, up to 25 per cent of women are afebrile.[3] Perforation of the appendix is therefore more common in pregnancy, due to delays in diagnosis and, it is thought, to a displaced omentum that is unable to localise the infection. Leucocytosis occurs as a physiological change in pregnancy, and so it may not be able to be distinguished from the changes that occur in acute appendicitis. Diagnosis can be helped with

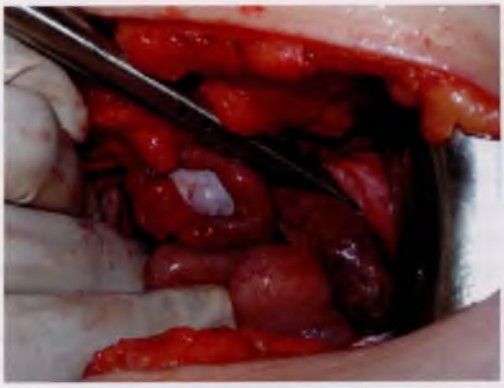


Figure 1 An acutely inflamed appendix before removal. The patient was 24 weeks pregnant. Note the position of the appendix and the relative size of the structure compared with the right uterine tube.

the performance of compression sonography which shows a dilated appendix (usual diameter is <6 mm), though the change in anatomy in advanced pregnancy may be difficult to interpret.

The commonest indication for laparotomy in pregnancy is acute appendicitis. Laparotomy (performed by a senior surgeon) must not be delayed, as it can otherwise be associated with significant maternal morbidity and sometimes mortality.

Renal calculi

Renal calculi occur in 1 in 1500 pregnancies. The incidence is the same as that in non-pregnant women. The clinical presentation is that of continuous acute loin to groin pain with acute exacerbations if a calculus moves. The patient is unable to lie still and is usually very restless with this pain, unlike in most of the other conditions described in this section. Urine analysis will usually show microscopic haematuria. The main investigation in pregnancy is renal ultrasonography. Intravenous urography and CT scan are limited in its uses owing to the pregnancy, and magnetic resonance imaging (MRI) is of limited value. Fortunately up to 80 per cent of calculi will be passed spontaneously, and supportive treatment with hydration, analgesics, and smooth muscle relaxants is all that is required. If a stone gets impacted and causes hydronephrosis, then interventions such as ureteroscopy and stone manipulation, stent placement, or a nephrostomy are required to prevent urosepsis.

Acute pancreatitis

Acute pancreatitis in pregnancy is fortunately rare, occurring every 4000–1100 pregnancies.[4] Most cases are secondary to biliary stones and present in the third trimester. Other causes are:

- cholelithiasis;
- hyperlipidaemia;
- hyperparathyroidism;
- alcohol;
- trauma.

Current obstetric practice has shown a trend towards an increasing body mass index (BMI) and a later age of pregnancy – both factors suggesting an increase in this incidence in the future. Acute pancreatitis may present with an acute onset of epigastric pain that radiates straight through to the back usually accompanied by nausea and vomiting. Because of involvement of the retroperitoneal space, the patient feels more comfortable leaning forwards. The reported presentations in pregnancy are variable, though fever is common with blood tests showing a fall in haematocrit and a polymorphonuclear leukocytosis. Increased levels of serum amylase (over 1000 U/L) and serum lipase over three times the normal are usually seen. While these levels help with diagnosis, they do not indicate the severity of the condition or progression when done serially. Elevated aspartate aminotransferase (AST), elevated lactate dehydrogenase levels, hyperglycaemia, and hypocalcaemia are indicative of severe disease. Complications include the formation of a pancreatic pseudocyst and abscess formation, sepsis, maternal metabolic acidosis, and even maternal death. Acute pancreatitis can cause preterm labour. Terminating the pregnancy is not a usually advocated. There is no specific treatment for acute pancreatitis – early diagnosis, early involvement of the multidisciplinary team, optimal supportive therapy, early recognition of severe and progressive disease, and intensive care is essential if maternal mortality is to be avoided. Surgical intervention may become necessary for the treatment of biliary calculi, which may include endoscopic retrograde cholangiopancreatography (ERCP) and even cholecystectomy. Radiology-guided treatments must be discussed with the woman and every attempt made to ensure that radiation exposure is minimised.

Acute cholecystitis

Cholecystitis presents in very much the same way as in a non-pregnant woman. The effects of physiological changes in pregnancy tend to cause biliary stasis, which predisposes to biliary sludge and calculi. Clinical presentation is with upper right quadrant

pain, nausea, vomiting, and chills. Examination will reveal acute tenderness in the right hypochondrium. Ultrasound diagnosis will show thickening of the gall bladder wall and fluid surrounding it. Surgical intervention by laparoscopy is possible in early pregnancy and is advocated to prevent acute pancreatitis.

Acute intestinal obstruction

The incidence of acute intestinal obstruction is 1 in 2500–3500 pregnancies and occurs in the second and third trimesters. The most frequent symptom is abdominal pain. Associated symptoms include vomiting. Constipation in pregnancy is relative uncommon (other than in the case of a sigmoid volvulus). Clinical examination may reveal tenderness, which can be generalised, and increased peristalsis, which may be audible even without auscultation of the abdomen. Abdominal distension may not be obvious, especially with upper small intestinal obstruction, and can also be masked by the gravid uterus. Small intestinal obstruction is far more common in pregnancy than obstruction of the large bowel. This is caused mainly by pre-existing adhesions (up to 70 per cent) followed by a volvulus. Clinical examination includes checking for previous scars in the abdomen and for intact hernial orifices, including in the femoral canal. Complications of unrelieved intestinal obstruction are ischaemia of the proximal segment, perforation of the bowel wall, peritonitis, sepsis, and even maternal death. Clinical features of complications include fever, tachycardia, and signs of peritonism on abdominal palpation. A single erect anteroposterior X-ray of the abdomen is helpful in making the diagnosis, with features of air-fluid levels in dilated small bowel loops seen in 82 per cent of cases. These loops of small bowel may be seen in the periphery of the film and are due to displacement of the bowel by the gravid uterus. There will be very small gas shadows in the collapsed distal large bowel. Free air under the diaphragm would indicate bowel perforation.

Sigmoid volvulus is the second most common cause of obstruction in pregnancy and occurs at a time when there is maximum space for rotation to occur – at the beginning of the second trimester and the puerperium. It also occurs at the time of head engagement and lightening of the pregnancy. There are many case reports of this condition – the first reported in 1946.[5] Absolute constipation is a presenting symptom in these women, while vomiting is not a prominent one. Clinically, there is usually gross abdominal distension, with the abdominal X-ray showing a grossly dilated sigmoid colon loop that covers the entire film. It has the appearance of coffee bean and is thus referred to as the 'coffee bean' sign. There is absence of gas in the distal rectum.

Treatment is usually by nasogastric decompression and fluid resuscitation. If there is no clinical improvement, early recourse to laparotomy is required to prevent perforation and gangrene of the bowel. A sigmoid volvulus may be decompressed with the passage of a rectal tube.

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ABDOMINAL SWELLINGS IN PREGNANCY

Ramesh Kuppusamy and Dilip Visvanathan

Abdominal swellings may present at any stage of pregnancy. In early pregnancy the diagnosis would be similar to that of a non-pregnant female. However, as pregnancy advances, any abdominal mass may be displaced upwards and laterally, a fact that must be borne in mind when making a diagnosis. Furthermore, signs of peritonitis in abdominal swellings of an inflammatory nature can be markedly altered, possibly resulting in misdiagnosis with potential serious consequences.

Abdominal swellings may be classified according to the anatomical layer of the abdomen, which comprises the:

- anterior abdominal wall;
- peritoneal cavity;
- retroperitoneal space.

Abdominal swellings arising from the anterior abdominal wall

The layers of the abdominal wall that may give rise to abdominal wall swellings is shown in Box 1.

Box 1 The layers of the abdominal wall that may give rise to abdominal wall swellings

- Skin and appendages
- Subcutaneous tissue
- Herniation of intra-abdominal contents through the wall

Lumps can arise from the skin and its appendages. Skin swellings are diagnosed by the fact that they do not move independently of the overlying skin. A punctum may be visible in sebaceous cysts, which may be tender and erythematous if they become infected. Other skin lesions that may have surface elevation are malignant melanomas. While these are relatively rare, they are important, as they cause the highest death rates of all skin cancers. Diagnostic confusion may occur as pigmented naevi may change during pregnancy owing to an increase in junctional activity with the changing hormonal levels. It is important to be aware of the ABCDE criteria (Table 1) for a changing mole, which may help in the early diagnosis of melanomas, particularly the superficial spreading type.[1,2] It is important to remember that with amelanotic melanomas this may not apply, but any change compared to other lesions or within the lesion should be promptly investigated.

The commonest subcutaneous swelling is a lipoma, which is usually a soft lobulated lump with a soft edge giving rise to the 'slipping' sign. The overlying skin can be made to move independently of a lipoma, and asking the woman to tense her abdominal muscles will make the lump more prominent.

Table 1 The ABCDE criteria for the early detection of melanomas

Asymmetry	Half the lesion does not match the other half
Border	The edges are ragged, notched, or blurred
Colour	Pigmentation is not uniform and may display shades of tan, brown, or black; white, reddish, or blue discoloration is of particular concern
Diameter	A diameter greater than 6 mm is characteristic, although some melanomas may have smaller diameters; any growth in a naevus warrants an evaluation
Evolving	Changes in the lesion over time are characteristic

Swellings can also be due to herniation of abdominal contents through areas of potential weakness of the abdominal wall, the commonest being the umbilicus. True umbilical hernias are rare in comparison to paraumbilical ones. Like all herniae, these masses have an expansile cough impulse and are usually reducible on lying supine. As the neck of these paraumbilical herniae is usually wide, complications of irreducibility and strangulation are relatively uncommon. Herniation can also occur through previous incisions, including those made for caesarean sections, and usually occur at the lateral edge of the Pfannensteil scar. A condition that occurs especially with repeated pregnancy is divarification of the recti. This is a defect of the median raphe and is palpable below the level of the umbilicus.

Abdominal swellings arising from the abdominal cavity

Generalised abdominal distension

Swellings arising from the peritoneal cavity may cause generalised or localised abdominal swelling. The 5 Fs – Fluid, Faeces, Fetus, Flatus, and Fat, as well as large fibroids and ovarian cysts – should be considered when there is generalised abdominal distension. In the later stages of pregnancy, these conditions may be suspected when the abdominal enlargement is greater than would be expected for the gestational age. A symphysiofundal height greater than that expected for the gestational age may be due to uterine fibroids that are making the uterus larger, excess amniotic fluid, a large baby, or the upward displacement of a gravid uterus by an ovarian cyst. An appropriate symphysiofundal height is found if the generalised abdominal distension is secondary to faeces or flatus, where a history of constipation plus or minus vomiting is elicited. Clinical examination may reveal visible peristalsis. In all these conditions the flanks are not distended. If the flanks are distended and there is shifting dullness on percussion when turning from the prone to the lateral position, then ascites should be considered.

The advances in ultrasound allow for accurate fibroid mapping in the gravid uterus. Cervical fibroids are particular important as they may affect the mode of delivery. Subserous pedunculated fibroids are prone

to torsion in the second trimester of pregnancy and during the puerperium. Most intramural fibroids do not change in size in pregnancy. Fibroids, however, are prone to undergo red degeneration (where the fibroid outgrows the blood supply and haemorrhagic necrosis occurs) at any time during the pregnancy and puerperium.

Ovarian cysts that cause generalised abdominal distension are usually mucinous cystadenomas. Ultrasound features include the presence of septae making the cyst multiloculated. There are now simple rules applied for ultrasound features to ascertain whether the cyst is benign (B) or malignant (M). It is rare for ovarian cysts in pregnancy to be malignant and have M features. If a benign cyst is diagnosed early in pregnancy, then ovarian cystectomy may be performed laparoscopically, ideally in the early second trimester.

Localised abdominal swellings

A localised abdominal swelling is best classified based on the location in which it would usually present (see Fig. 1 in Abdominal pain). Masses that arise from the pelvis have been considered in Pelvic swellings and will not be dealt with here.

Mass in the right hypochondrium

The possible causes of a mass in the right hypochondrium are shown in Box 2.

Box 2 The anatomical origins of masses in the right hypochondrium

- Normal variant – Riedel's lobe
- Enlargement of the liver
- Enlargement of the gallbladder

Riedel's lobe is a normal variant, an extension of the right lobe of the liver towards the anterior axillary line. Liver masses descend during inspiration, do not have a palpable upper limit, and are dull to percussion up to the 8th rib in the anterior axillary line. Enlargement of the liver may be generalised or localised. Generalised enlargement may be due to infections, cirrhosis, chronic active hepatitis, cirrhosis, or myeloproliferative disorders. If the surface of the liver is irregular, polycystic disease and carcinoma must be excluded. Liver enlargement may be accompanied by jaundice in infective hepatitis, biliary tract obstruction secondary to carcinoma or gallstones, primary or secondary malignancy of the liver, and cirrhosis. (See Jaundice and liver disease in pregnancy.)

Gallbladder enlargements present as globular swellings below the tip of the 9th rib. The upper border cannot be felt, and the mass is mobile and moves downwards with inspiration. The gall bladder may be enlarged with the accumulation of bile, mucus, or pus. This can occur through an obstruction of the cystic duct or of the common bile duct. The commonest cause is calculi, though it can be due to carcinoma of the head of the pancreas, which is extremely uncommon in pregnancy. Courvoisier's law state that if the gallbladder is palpable in a patient who is jaundiced the cause of the obstruction is unlikely to be a calculus. This is based on the assumption that chronic inflammation secondary to calculi causes fibrosis of the gallbladder, thereby making it difficult to distend and present as an abdominal swelling. In acute cholecystitis, pressure at the tip of the 9th rib causes the patient to catch her breath at the end of inspiration due to the inflamed gallbladder impinging on it (Murphy's sign).

Mass in the epigastrium

The possible causes of a mass in the epigastrium are given in Box 3.

Box 3 The anatomical origins of masses in the epigastrium

- Enlargement of the left lobe of the liver
- Enlargement of the stomach
- Enlargement of the pancreas

Localised enlargements of the left lobe of the liver can present with a mass in the epigastrium. Epigastric pain in the presentation in a woman with severe pre-eclampsia would be due to tension on the liver capsule, which can very rarely rupture with fatal consequences. Carcinoma of the stomach rarely presents in pregnancy, and it is highly unlikely that a mass can be felt. This mass is usually hard and irregular, and is pre-dated by symptoms of anorexia and weight loss. Diagnosis is made usually before a mass is palpable.

A pancreatic pseudocyst can be palpated as a mass in the epigastrium. It may occur as a consequence of acute pancreatitis. Acute pancreatitis

occurs in 1 in 3333 pregnancies and is most commonly secondary to gallstone disease and hypertriglyceridaemia, which is made worse by pregnancy. There is a collection of fluid around the pancreas or in the lesser sac. Pancreatic pseudocysts are usually very difficult to feel, as the stomach is anterior to it, thereby making it difficult to delineate and resonant to percussion. However, there is slight movement of the mass with respiration.

Masses in the left hypochondrium

The structures that can enlarge to give rise to a mass in the left hypochondrium are shown in Box 4.

Box 4 The anatomical origins of masses in the left hypochondrium

- Enlargement of the spleen
- Extension of masses from the epigastrium (stomach and pancreas)

The spleen has to enlarge considerably to become palpable below the left costal margin. Once is enlarges it grows toward the umbilicus. Small enlargements may be felt by tilting the patient towards the examiner, lifting the lower ribs forwards and asking the patient to breathe deeply. The edge of the spleen may then be palpated at the end of inspiration. Depending on the cause of splenic enlargement the edge may be soft or firm and a splenic notch may be palpable.

Splenomegaly occurs in the following situations:

- *Infection*: splenomegaly in pregnant women is common in areas endemic for malaria. There is an increase in size in the first trimester owing to an increase in parasitaemia. The splenomegaly can be massive in chronic malaria and therefore prone to rupture by blunt trauma to the upper abdomen or lower chest. Other infective causes include Epstein–Barr virus infection, leptospirosis, and typhoid fever.
- *Congestion*: usually secondary to portal vein hypertension and splenic vein thrombosis.
- *Haemolysis*: seen in hereditary spherocytosis.
- *Myeloproliferation*: can be present in both myeloid and lymphatic leukaemia, polycythaemia rubra vera, and myelosclerosis.
- *Infiltration*: sarcoidosis and other neoplasms.

Patients with splenomegaly may also have coexisting hepatomegaly. Hepatosplenomegaly may be due to primary liver disease or haematological disease. Ascites, jaundice, caput medusae, and bilirubin in the urine are suggestive of primary liver disease, while generalised lymphadenopathy and a splenic rub are suggestive of haematological problems. Investigations that can help with the differential diagnosis include a full blood count, a blood picture, thick and thin blood film for malarial parasites, and tissue biopsy of lymph nodes or the liver.

Masses in the right and left lumbar regions

The anatomical origins of masses in the loin are shown in Box 5.

Box 5 The anatomical origins of masses in the loin

- Enlargement of the kidney
- Extension of masses from the right hypochondrium

The characteristics of an enlarged kidney are that it is present in the loin, may be palpated bimanually, moves with respiration, and is ballotable. It is not dull to percussion because of the overlying bowel.

In normal pregnancy there is dilatation of the renal pelvis and the ureter. Hydronephrosis is thought to be due to the endocrinological changes of pregnancy and secondarily due to pressure effects of pregnancy. Owing to the dextrorotation of the uterus in pregnancy it is more common for hydronephrosis to occur in the right kidney. Women usually present with pain in the loin. In the majority of cases, however, the kidneys are not palpable, the hydronephrosis being diagnosed by ultrasonography.

Palpable kidneys in pregnancy are rare and may be due to gross hydronephrosis, large renal cysts, or malignancy (hypernephroma).

Masses in the umbilical region

The anatomical origins of masses in the umbilical region are shown in Box 6.

Box 6 The anatomical origins of masses in the umbilical region

- Aortic enlargement
- Mesenteric cyst
- Moderate splenomegaly

Abdominal aortic aneurysms are typically located in the umbilical region. They have expansile pulsations and if large may be visible on inspection, especially in the thin patient. The upper limit of most abdominal aortic aneurysms is felt as they commonly arise below the level of the renal arteries.

Abdominal aortic aneurysms are more common in males and over the age of 60. They are therefore extremely rare in pregnant women. The more common aneurysms that have been reported during pregnancy are thoracic in women with Marfan's syndrome.

Mesenteric cysts are usually located in the centre of the abdomen. They are tensely cystic, may be fluctuant, and have a fluid thrill. They are dull to percussion and although freely mobile at right angles to the root of the mesentery cannot move along the line of the mesentery. Mesenteric cysts may occur in pregnancy and are usually an incidental finding in early pregnancy. They are best dealt with by the general surgeons.

Mass in the right iliac fossa

The anatomical origins of masses in the right iliac fossa are shown in Box 7.

Box 7 The anatomical origins of masses in the right iliac fossa

- Distension of the caecum
- Distension and enlargement of the terminal ileum
- Distension of the appendix
- Enlargement of ileo caecal lymph nodes
- Enlargement of the iliac lymph nodes
- Collection of fluid under the psoas fascia
- Focal enlargement of the iliac bones

Appendicular mass

Acute appendicitis usually presents with central abdominal pain which later localises to the right iliac fossa. Nausea and vomiting are usually common. Tenderness may be elicited in the right iliac fossa, typically being maximal at McBurney's point (Fig. 1 in Abdominal pain), with signs of peritonism (guarding and rebound – see Abdominal pain). In advancing pregnancy, due to upward displacement of the appendix, the localising symptoms and signs are easily missed and the signs of peritoneal irritation are often masked. An appendicular mass may therefore form and be found in the right lumbar region or may even extend to the right hypochondrium. Such a mass is usually difficult to delineate, tender, dull to percussion, and may be fixed in its posterior limit. If there is no resolution, an appendicular abscess may result in association with systemic features of pain, swinging fever, and tachycardia.

The appendicular abscess has the same characteristics of the appendicular mass but is extremely tender, though the signs of peritonism may not be marked. The white cell counts, though elevated, may be in the normal range for pregnancy. It is therefore important to bear this diagnosis in mind as the fetal loss increases from less than 2 per cent if the appendix is unruptured to almost 30 per cent if it ruptures.[3] Ultrasonography is utilised to measure the width of the appendix (usually less than 3 mm). The probe is placed over the appendix and the pressure is gradually increased to displace overlying bowel gas. A dilated appendix (>6 mm) which does not get compressed and is without any peristalsis is supportive of a diagnosis of appendicitis. The diagnostic dilemma is ensuring that it is the appendix that is getting measured on ultrasound.

Inflammatory bowel disease (IBD)

IBD may present as a mass in the right iliac fossa or as gross abdominal distension. The terminal ileum swells and can be palpated as a sausage-shaped mass in the right iliac fossa. It often lies in a transverse position. Symptoms include fever, vomiting, abdominal pain, diarrhoea, rectal bleeding, and mucous discharge and tenesmus. Complications such as abscess, toxic megacolon, and bowel obstruction can be missed because of the altered signs in pregnancy and also if the patient is receiving steroid therapy. Perforation of the bowel leads to a high fetal and maternal mortality rate if not diagnosed and treated early. Box 8 gives the criteria for diagnosis by Jalan et al.[4] for the diagnosis of toxic dilatation of the colon from a study of 55 cases. Usually, IBD tends to improve during pregnancy.

Enlarged ileocaecal lymph nodes

Enlarged ileocaecal lymph nodes may present as a mass in the right iliac fossa. Typically they are firm and immobile, and the margins are difficult to delineate. Palpation of other lymph nodes is important, as it may be part of a generalised lympadenopathy. Tuberculosis may present in this way and is becoming more common in pregnancy.[5]

Box 8 The criteria for the diagnosis of toxic megacolon

- One of the following:
  - Dehydration
  - Electrolyte imbalance
  - Altered mental state
  - Hypotension
- Three of the following:
  - Fever
  - Tachycardia (greater than 120 bpm)
  - Increased white cell count
  - Anaemia
- X-ray findings of transverse colon diameter greater than 6 cm.

Psoas abscess

A psoas abscess may be felt as a soft, compressible mass in the right iliac fossa. This is due to the tracking down of fluid below the psoas sheath. The lower limit of the mass would therefore be below the level of the inguinal ligament. Tuberculosis of the dorsal spine is one of the main causes of a psoas abscess. Constitutional features such as loss of appetite, loss of weight, night sweats and backache are usually present. It may also lead to restriction of hip movements.

Mass in the suprapubic region

Masses in the suprapubic region usually arise from the pelvis. This is discussed in Pelvic swellings.

Mass in the left iliac fossa

The commonest mass that presents in the left iliac fossa is the inflammatory mass of diverticulitis though this is uncommon in pregnancy. A long-standing history of altered bowel habit (mainly constipation) is usually present. Pain with nausea and vomiting is a presenting feature. Clinical examination reveals a mass which is very tender, with indistinct margins and localised peritonitis. The mass may be palpable on bimanual examination of the pelvis in the early stages of pregnancy.

Abdominal swellings arising from the retroperitoneal space

Retroperitoneal tumours are ones in which there is no definite organ of origin. Even though the pancreas, kidneys, and adrenal glands are anatomically retroperitoneal, they are not considered here.

Retroperitoneal tumours in pregnancy are rare and restricted to case reports in the literature. Malignant tumours are more common than benign ones. The commonest malignant tumour is a liposarcoma, with a lymphangioma being the commonest benign tumour. They rarely present in pregnancy as an abdominal mass and are usually discovered at caesarean. They can obstruct labour. They are soft to firm in consistency, immobile, and may have transmitted pulsations. Diagnosis is confirmed by biopsy.

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AMNIOTIC FLUID ABNORMALITIES

Dhivya Chandrasekar and Peter Muller

Amniotic fluid volume (AFV) should be assessed at every antenatal ultrasound examination. AFV can be readily assessed via ultrasound. The reason for this recommendation is that abnormalities in amniotic fluid volumes may act as clues to various fetal abnormalities and adverse perinatal outcomes.[1,2] Amniotic fluid volumes are characterised as the following:

- normal;
- oligohydramnios (diminished amniotic fluid);
- polyhydramnios or 'hydramnios' (excessive amniotic fluid).

Measurement of amniotic fluid volume

Measurement of amniotic fluid via ultrasound may be by both subjective and objective means. Subjective assessment of AFV refers to visual interpretation without sonographic measurements. The ultrasonographer scans the uterine contents and subsequently reports the AFV as oligohydramnios, normal, or polyhydramnios. The subjective assessment of AFV by an experienced examiner had a similar sensitivity to the other techniques for identifying AFVs. The subjective technique and the quantitative ultrasound methods all identified normal volumes well, but determined low and high volumes poorly.[3]

The most common objective approaches are by measuring AFV via the amniotic fluid index (AFI) and the single deepest pocket (SDP).

The SDP measurement refers to the vertical dimension of the largest pocket of amniotic fluid not containing umbilical cord or fetal extremities and measured at a right angle to the uterine contour. The horizontal component of this vertical dimension must be at least 1 cm. The SDP measurement has been interpreted as follows:

- oligohydramnios – depth of 0–2 cm;
- normal – depth of 2.1–8 cm;
- polyhydramnios – depth greater than 8 cm.

AFI measurement is calculated by first dividing the uterus into four quadrants using the linea nigra for the right and left divisions and the umbilicus for the upper and lower quadrants. The maximum vertical amniotic fluid pocket diameter in each quadrant not containing cord or fetal extremities is measured in centimetres; the sum of these measurements is the AFI (Figure 1a and 1b). The AFI can be interpreted according to the following thresholds[4]:

- oligohydramnios – 0 to greater than 5 cm;
- normal – 5–25 cm;
- polyhydramnios – greater than 25 cm.

Currently, there is insufficient evidence to recommend any additional antenatal assessments when there is borderline AFI (5.1–8 cm).[5]

A normogram based on gestational age has also been introduced.

The AFI, secondary to the small gravid uterus, may have limited use in measuring AFV in pregnancies prior to 24 weeks' gestation. Normal sonographic reference intervals for a single deepest pocket have been developed for gestational ages 11–24 weeks.[6]

A systematic review of well-designed randomised trials compared the AFI to the SDP for predicting adverse antepartum, intrapartum, and perinatal outcome and found the AFI was no better than the SDP for predicting an adverse outcome.[7] The AFI diagnosed significantly more cases of oligohydramnios (RR 2.3), which led to significantly more intervention (induction of labour increased two-fold and caesarean delivery increased 1.5-fold) without improving perinatal outcome.

It appears that operator experience has little effect on the accuracy of ultrasound estimates of AFV. It is important to realise, however, that these measurements seem to be no more accurate in diagnosing abnormal AFV than subjective assessments by experienced sonographers.[8]

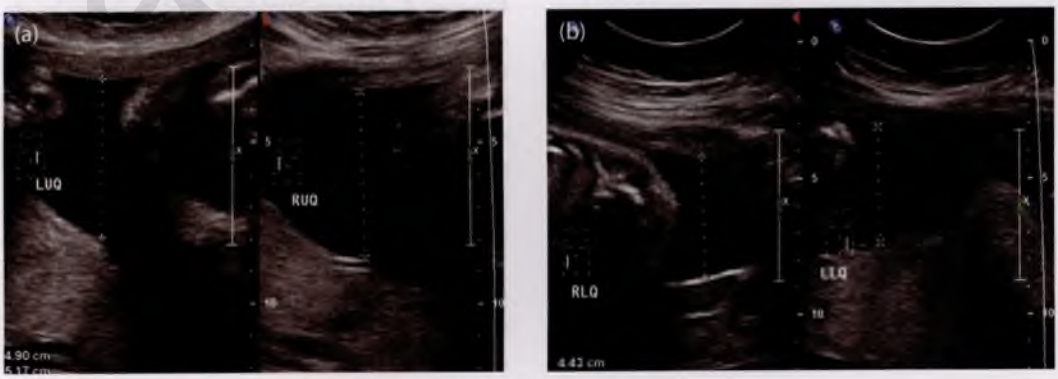

Figure 1 Amniotic fluid index performed by measuring the sum of the maximum vertical amniotic pocket in each quadrant of the abdomen: (a) upper two quadrants; (b) lower two quadrants.

Normal amniotic fluid volume

There is a characteristic pattern of AFV change. AFV increases early in pregnancy, peaks at 28–32 weeks, and starts to diminish from 33 weeks onwards.[9]

Despite individual variation ranging from 0.5 to 2 L, there appears to be steady regulation of this peak volume. It is fair to say that this regulation occurs with an adjustment of fetal production and removal of amniotic fluid during the pregnancy. Amniotic fluid transport to and from the amniotic cavity is controlled mainly by fetal renal excretion (production) and fetal swallowing (removal). The fetal respiratory tract, fetal membranes, and placenta play a small part in the transport of amniotic fluid. Fetal urine production appears to begin at approximately 9 weeks' gestation, but it is not the primary source of amniotic fluid until between 14 and 18 weeks' gestation. The latter finding is important in understanding abnormalities of AFV in the early and mid second trimester. Amniotic fluid fulfils many roles in the development of the fetus, including protection from trauma, cord compression, and infection (bacteriostatic properties), as well as facilitating fetal lung, musculoskeletal, and gastrointestinal development.

Oligohydramnios

Oligohydramnios, diminished amniotic fluid, found on ultrasound, is relatively common. The diagnosis of oligohydramnios via ultrasound (Fig. 2) can be made subjectively by the inability to locate obvious pools of amniotic fluid surrounding the fetus or objectively by either the AFI (<5 cm) or SDP (<2 cm).

Adverse pregnancy outcome is associated with the diagnosis of oligohydramnios,[10] but the fetal/neonatal prognosis depends on the cause, severity, gestational age at onset, and duration of oligohydramnios. On the other hand, oligohydramnios as an isolated finding in the third trimester is commonly associated with a good outcome.[11] Since accurate ultrasound evaluation of AFV has its limitations, one must be careful not to misuse the diagnosis of reduced amniotic fluid to pursue invasive pregnancy interventions such as induction of labour. Despite this controversy, it is reasonable to evaluate ultrasound evidence of reduced amniotic fluid to ascertain whether it is truly an isolated finding.

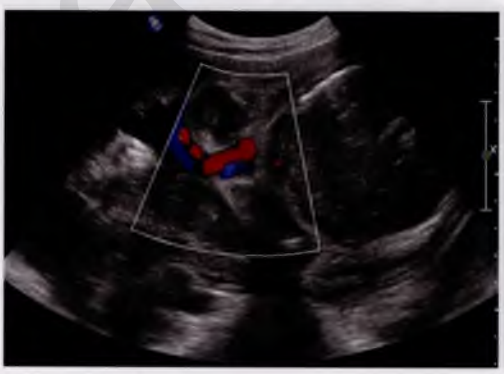

Figure 2 Severe oligohydramnios in a growth-restricted fetus. Notice that the umbilical cord fills the remaining amniotic fluid space.

Conditions commonly associated with oligohydramnios are listed in Box 1.

Box 1 Causes of oligohydramnios

- Maternal
  - hypertension, pre-eclampsia, and diabetes
- Fetal
  - rupture of membranes, postdates, chromosomal abnormalities, congenital abnormalities such as renal agenesis, bladder outlet obstruction, multicystic dysplastic kidneys, and infantile polycystic kidneys
- Placental
  - twin-to twin-transfusion syndrome, placental insufficiency
- Drug induced
  - ACE inhibitors, PG synthetase inhibitors
- Idiopathic

ACE, angiotensin converting enzyme; PG, prostaglandin.

The most likely etiologies of oligohydramnios vary according to severity and the trimester in which they are diagnosed.

Fetal anomalies/aneuploidy

Congenital abnormalities and fetal aneuploidy are commonly associated with oligohydramnios seen in the second trimester. The majority of fetal anomalies involve the genitourinary system, but skeletal, central nervous system and cardiovascular defects are also seen in association with oligohydramnios. It is important to remember that oligohydramnios secondary to renal anomalies may not be evident until 18 weeks' gestation, as the maternal contribution of amniotic fluid remains high until 14–18 weeks. Comprehensive fetal morphology ultrasound assessment is required particularly of the fetal kidneys and bladder. Renal agenesis, bladder outlet obstruction, multicystic dysplastic kidneys, and infantile

polycystic kidneys can usually be accurately diagnosed by transabdominal ultrasound. Renal agenesis can be confirmed by the inability to locate kidneys bilaterally and the absence of fluid in the fetal bladder. Further evaluation for renal agenesis includes the use of colour Doppler to locate the bilateral renal arteries and the appearance of 'lying down' adrenal glands. Multicystic dysplastic kidneys and infantile polycystic kidneys will demonstrate bilaterally enlarged hyperechoic or cystic kidneys. Bladder outlet obstruction associated with posterior urethral valve syndrome will demonstrate an enlarged bladder with a 'keyhole' appearance and significant renal pelvic dilatation. Secondary to the severe oligohydramnios, definitive antenatal diagnosis of these fetal conditions via transabdominal ultrasound may at times be difficult.

Transvaginal ultrasound in the early second trimester may be helpful in delineating hard-to-visualise fetal anatomy. Amnioinfusion has been advocated as a way to improve the ultrasound resolution, but the advent of fetal magnetic resonance imaging (MRI) for the most part has offered a non-invasive modality to confirm the earlier ultrasound findings. Secondary to the severe oligohydramnios, fetal karyotype evaluation via amniocentesis can be difficult. However, placental biopsy is an option in these instances. Other than posterior urethral valve syndrome, where fetal interventions in selected cases may improve outcome, these conditions are considered lethal secondary to the pulmonary hypoplasia that develops in these fetuses.

Rupture of membranes

The diagnosis of ruptured membranes can readily be made based on clinical history and examination. Presence of pool of fluid in the vagina at sterile speculum examination is highly suggestive of ruptured membranes. Several tests have been used to confirm rupture of membrane; the most widely used tests are the nitrazine test,[12] which detects pH change, and the ferning test, with a sensitivity of 90 per cent. False positive rate was 17 per cent for nitrazine test and 6 per cent for the ferning test.

Ultrasound examination demonstrating oligohydramnios can also be used to confirm the diagnosis. AmniSure® (AmniSure International LLC, Boston, MA, USA), a rapid immunoassay, has been shown to be accurate in the diagnosis of ruptured membranes, with a sensitivity and specificity of 98.9 per cent and 100 per cent, respectively.[13]

The earlier the preterm premature rupture of membranes (PPROM), the more guarded the prognosis. PPROM with resultant severe oligohydramnios prior to 24 weeks' gestation runs the added risk of pulmonary hypoplasia, although not generally to the extent seen in bilateral fetal renal abnormalities. There is insufficient evidence to recommend amnioinfusion in very preterm PPROM as a method to prevent pulmonary hypoplasia.[14] Amniotic leakage after amniocentesis in the second trimester, where resealing of the amnion leakage is common, has a reasonably good prognosis with over a 90 per cent survival.[15] There is insufficient evidence to recommend fibrin sealants as routine treatment for second-trimester oligohydramnios caused by PPROM.[14]

Fetal growth restriction (FGR)

Small for gestational age (SGA) is defined as an estimated fetal weight (EFW) or abdominal circumference (AC) less than the 10th centile.[16] FGR is not synonymous with SGA, as 50–70 per cent of SGA fetuses are constitutionally small. Growth restriction implies a pathological restriction of the genetic growth potential. Uteroplacental insufficiency results in fetal redistribution of blood flow to vital organs such as the brain, heart and adrenal glands, and away from the kidneys, resulting in oligohydramnios. Interpretation of amniotic fluid volume should be based on single deepest vertical pocket.[16] The patient's clinical history and examination may give clues to risk factors for fetal growth restriction (FGR) such as substance abuse, chronic hypertension, previous obstetric history and birth weights, and developing pre-eclampsia. Asymmetric fetal biometric parameters (head circumference-abdominal circumference discordance) are commonly seen when FGR is seen in the late second and third trimester, while severe FGR in the second trimester may exhibit symmetric growth restriction.

Other findings on ultrasound may include early maturation of the placenta (i.e. early placental calcification). Maternal and fetal Doppler velocimetry may offer further clues. In a high-risk population, abnormal uterine artery Doppler at 20–24 weeks has a moderate predictive value for a severely SGA neonate.[17] Umbilical artery Doppler will commonly demonstrate increased placental resistance seen in uteroplacental insufficiency. Early in the development of FGR, fetal middle cerebral artery (MCA) Doppler will show 'brain sparing' consistent with fetal blood flow redistribution. MCA Doppler may be a more useful test

in SGA fetuses detected after 32 weeks of gestation where umbilical artery Doppler is typically normal.[18] In the term SGA fetus with normal umbilical artery Doppler, an abnormal middle cerebral artery Doppler (PI <5th centile) has moderate predictive value for acidosis at birth and should be used to time delivery. This is exhibited by increased diastolic flow velocity and a decreased pulsatility index. Although no single antenatal study can confirm FGR, a series of abnormal ultrasound evaluations in conjunction with clinical history allow one to make a calculated diagnosis and provide a reasonable management plan.

Perinatal morbidity and mortality are inversely proportional to the gestational age of diagnosis. In early-onset severe FGR, referral to a fetal medicine specialist for fetal surveillance should be considered.

Iatrogenic

Oligohydramnios can be secondary to numerous iatrogenic causes. These may include fetal procedures, such as chorionic villus sampling or amniocentesis, and various medications. A good clinical history will help to exclude these causes. Both non-steroidal anti-inflammatory drugs and angiotensin-converting enzyme inhibitors decrease renal perfusion and can result in oligohydramnios. Fortunately, in a majority of cases discontinuing these medications results in a reversible form of oligohydramnios.

Postdates

The fall of amniotic fluid volume in the postdate pregnancy is a reflection of the uteroplacental insufficiency that generally occurs at these later gestations. Although monitoring amniotic fluid volume and induction of labour with evidence of oligohydramnios is commonly advocated, there is controversy concerning whether perinatal outcome is improved by such manoeuvres.

Polyhydramnios

Polyhydramnios, or 'hydramnios', is defined as an excessive amount of amniotic fluid. Polyhydramnios can be determined subjectively in the third trimester by the presence of obvious pockets of amniotic fluid surrounding all sides of the fetal abdomen (Fig. 3). Polyhydramnios can be objectively determined by either the AFI (greater than 24 cm) or deepest vertical pocket (greater than 8 cm). Since the incidence of fetal abnormalities correlates with the severity of polyhydramnios, a deepest vertical pocket of 12 cm and 16 cm has been used to define moderate and severe polyhydramnios, respectively. In general, these semi-quantitative measurements tend to underestimate the actual AFV.

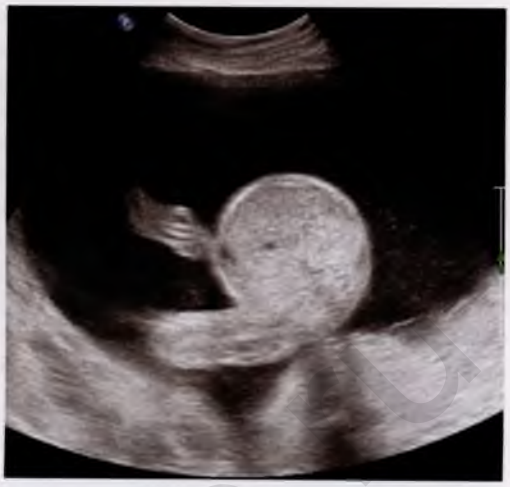

Figure 3 Polyhydramnios in a fetus with a large unilateral pleural effusion. The subsequent chest deviation inhibits normal swallowing, which produces the polyhydramnios.

Congenital abnormalities

Polyhydramnios with fetal anomalies is most likely related to an interruption of normal fetal swallowing. In general, polyhydramnios secondary to fetal anomalies does not occur prior to 25 weeks' gestation. Since a multitude of congenital abnormalities can be associated with excessive amniotic fluid, comprehensive morphology ultrasound assessment is the first line of evaluation for this condition.

Sites of fetal abnormalities associated with polyhydramnios include:

- gastrointestinal tract;
- central nervous system;
- respiratory and thoracic;
- skeletal dysplasias;
- myotonic dystrophy;
- cardiovascular;
- fetal and placental tumours.

Specific ultrasound findings that have been associated with polyhydramnios include:

- stomach not seen;
- dilated bowel loops;
- neck, chest or abdominal masses;
- diaphragmatic hernia;
- intracranial malformations;
- facial clefts;
- significantly shortened long bones with a small chest circumference;

- severe limb contractures or arthrogryposis;
- congenital heart disease;
- placental masses.

Offering karyotype evaluation with ultrasound-detected fetal anomalies or FGR is recommended, but aneuploidy is rare in isolated polyhydramnios.

Maternal diabetes

There is a clear association of polyhydramnios with macrosomia. Although maternal diabetes is not always the precipitating factor, testing for maternal diabetes and obtaining fetal biometry for evidence of the accelerated abdominal circumference and fetal weight often seen with poorly controlled diabetes are suggested.

Hydrops

Hydrops is defined as fluid present in two body cavities (pleural effusion, pericardial effusion, ascites, or skin oedema) and is readily visible on ultrasound. Polyhydramnios presents in 40 to 75 per cent of pregnancies complicated by non-immune-related hydrops fetalis (NIHF) and is often the initial indication for the sonographic evaluation of the pregnancy. Unfortunately, the aetiology of non-immune hydrops can be elusive in 20 to 40 per cent of cases.[19]

Twin–twin transfusion syndrome

Approximately 15 per cent of monochorionic/diamniotic twin pregnancies will develop twin–twin transfusion syndrome, thus underscoring the importance of early ascertainment of chorionicity of all multiple pregnancies. Twin–twin transfusion syndrome is demonstrated by amniotic fluid discordance between the recipient (deepest vertical pocket of >8 cm) and donor (deepest vertical pocket of <2 cm). Referral to a specialist experienced in the management of this condition is recommended.

Idiopathic

The amniotic fluid volume peaks in the early third trimester, and this normal variant must not be confused with pathologic polyhydramnios. Commonly the AFV will be in the mild or borderline level, but will return to normal as the pregnancy progresses. However, moderate or severe polyhydramnios is rarely idiopathic, and thorough evaluation is warranted.

Prognosis and management

The prognosis depends solely on the aetiology for the polyhydramnios. Preterm labour, preterm premature ruptures of the membranes and placental abruption have all been associated with moderate to severe polyhydramnios. Amnioreduction can be used to treat symptomatic polyhydramnios with an overall low risk of complications.[20] Oral indomethacin has been used to reduce fetal urine production and enhance uptake in the lungs. Although maternal side effects are small, common risks to the fetus include early constriction of the ductus arteriosus and even oligohydramnios. Because these complications are generally reversible and the risk of ductal constriction increases with gestational age, close fetal monitoring is mandatory and indomethacin is not recommended after 32 weeks' gestation. There is currently controversy in the literature on whether the antenatal use of indomethacin increases the neonatal risk of necrotising enterocolitis and intraventricular haemorrhage.

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ANAEMIA IN PREGNANCY

Jai B Sharma

Anaemia is the commonest medical disorder during pregnancy. The World Health Organization (WHO) definition for diagnosis of anaemia in pregnancy is a haemoglobin (Hb) concentration of <11 g/dL (7.45 mmol/L) and a haematocrit of <0.33. The overall prevalence of anaemia varies in different countries, affecting approximately 18 per cent of pregnant women in industrialised countries but about 56 per cent (35–75 per cent) of pregnant women in developing countries. It is responsible for significant maternal and perinatal mortality and morbidity throughout the world, but more so in developing nations.

The classification of anaemia is given in Box 1. Hereditary anaemias are less common and are seen more often in particular geographical areas. Thus thalassaemias are seen more frequently in Asia, while sickle cell haemoglobinopathies are common in Africa in areas where *falciparum* malaria is prevalent.

Haemoglobinopathies

Structure of normal haemoglobin

Normal Hb is composed of four subunits, with a single haem group (which binds to and later releases oxygen) and four species-specific globin chains. The haem group is an iron molecule with four pyrrole rings attached to it. Two pairs of globin chains (two alpha and two beta) are attached to the pyrrole rings to make up normal Hb. The integrity of the haem

Box 1 Types of anaemia during pregnancy

Hereditary causes

- Thalassaemias
- Sickle cell haemoglobinopathies
- Other haemoglobinopathies
- Hereditary haemolytic anaemias

Acquired causes

- Nutritional
  - iron-deficiency anaemia (microcytic hypochromic anaemia)
  - folate-deficiency anaemia (megaloblastic anaemia)
  - cyanocobalamin-deficiency anaemia (megaloblastic anaemia)
- Anaemia due to marrow failure (aplastic or hypoplastic anaemia)
- Anaemia due to inflammation, chronic disease, or malignancy
- Anaemia due to acute blood loss
- Acquired haemolytic anaemias

moiety and the amino-acid sequence of the globin chains determine the structure of the globin chains and the interaction between the four subunits of the Hb.

Thalassaemias

Thalassaemias are characterised by impaired production of one or more of the globin chains. They are *alpha thalassaemia* (if both alpha chains are impaired), *alpha thalassaemia trait* (if one chain is defective), *beta thalassaemia* (if both beta chains are impaired) and *beta thalassaemia trait* (if one beta chain is impaired).

People with beta thalassaemia usually die before reaching reproductive age; however, with repeated blood transfusions and chelation therapy, pregnancies have been reported. More important and common, however, is thalassaemia minor (trait), which is an important differential diagnosis of iron-deficiency anaemia; it can be identified through blood indices and HbF and HbA_2 levels (Table 1). If the mother has the thalassaemia trait, the father should be tested for the trait. If both are positive for the trait, then prenatal diagnosis of the fetus is indicated, as there is a 1:4 chance of the fetus having thalassaemia major. Termination of the pregnancy may be offered in this situation.

Table 1 Differential diagnosis of iron-deficiency anaemia (IDA) and thalassaemia

Characteristics	Normal	IDA	Thalassaemia range
Mean corpuscular volume (MCV, fL)	75–96	Reduced	Very reduced
Mean corpuscular Hb (MCH, pg)	27–33	Reduced	Very reduced
Mean corpuscular Hb concentration (MCHC, g/dL)	32–35	Reduced	Normal
Fetal Hb (HbF)	<2%	Normal	Raised
HbA_2	2–3%	Normal	Raised
Red cell width		High	Normal

Sickle cell haemoglobinopathies

Sickle Hb results from a single beta-chain substitution of glutamic acid by valine at codon 6 of the beta globin chain. It may have serious implications in pregnancy and women may manifest with sickle cell crises, an acute emergency with infarction in various organs due to intense sequestration of sickled erythrocytes, causing severe pains, especially in the bones. It can happen in pregnancy, during labour, or during puerperium, especially in oxygen-deficient conditions, e.g. general anaesthesia. Treatment is intravenous hydration, oxygen administration, and red-cell transfusions. Prenatal diagnosis is indicated in sickle-cell trait women with sickle-cell trait husbands, with advice of termination of an affected pregnancy.

Nutritional anaemias

The sources of various nutrients required for erythropoiesis are given in Table 2.

Table 2 Sources of various nutrients required for erythropoiesis

Nutrients	Sources
Iron	Haem iron: animal blood, flesh, viscera (liver, kidney), red meat, poultry, and fish (including mussels) Non-haem iron: green leafy vegetables, cereals, seeds, vegetables (peas, baked beans), eggs, roots, and tubers
Folic acid	Green vegetables (spinach and broccoli), fruits, liver, kidney
Cyanocobalamin	Meat, fish, eggs, milk
Ascorbic acid	Citrus fruits like orange, lemon, amla (Indian gooseberry)
Other B vitamins	Green leafy vegetables and fruits

Iron-deficiency anaemia (IDA)

This is the commonest type of anaemia and is classically described as a microcytic hypochromic anaemia. It is much more common in developing countries owing to poor dietary habits (intake of low-bioavailability diet poor in iron and proteins, and with an excess of inhibitors of iron absorption such as phytates), defective iron absorption caused by intestinal infestations of hookworm and other worms. Schistosomiasis, chronic malaria, frequent pregnancies at short intervals, menorrhagia, and blood loss from haemorrhoids are other causes of IDA. Multiple pregnancy is also an important cause of anaemia, resulting from increased iron and folic acid requirements.

Clinical features of IDA in pregnancy

The various symptoms and signs that can occur in anaemia during pregnancy are shown in Box 2. However, it must be noted that these symptoms or signs may be absent, especially in mild to moderate anaemia.

Box 2 Clinical features of anaemia during pregnancy

Symptoms

- Weakness
- Lassitude/tiredness/exhaustion
- Indigestion
- Loss of appetite
- Palpitations
- Dyspnoea (breathlessness)
- Giddiness/dizziness
- Swelling (peripheral)
- Generalised anasarca (generalised fluid collection in peritoneal and thoracic cavity)
- Congestive cardiac failure (in severe cases)

Signs

- Pallor
- Glossitis
- Stomatitis
- Oedema
- Hypoproteinemia
- Soft systolic murmur in mitral area owing to hyperdynamic circulation
- Fine crepitations at bases of lungs owing to congestion (severe cases)

Effects of anaemia on pregnancy

These are shown in Box 3. There may be no maternal or fetal effects, especially in mild or moderate anaemia.

Box 3 Effects of anaemia on pregnancy

Maternal effects

- Weakness
- Lack of energy
- Fatigue
- Poor work performance
- Palpitations
- Tachycardia
- Breathlessness
- Increased cardiac output
- Cardiac decompensation
- Cardiac failure
- Increased incidence of preterm labour
- Pre-eclampsia
- Sepsis

Fetal effects

- Preterm babies
- Small for gestation babies
- Increased perinatal mortality
- Low iron stores in newborns
- Iron-deficiency anaemia
- Cognitive and affective dysfunction in the infant
- Increased incidence of diabetes and cardiac disease in later life

Diagnosis of IDA in pregnancy

Although Hb estimation is the most practical method of diagnosis, being cost effective and easy to perform, blood indices and other diagnostic modalities are required for diagnosis, as shown in Table 3. Not all investigations are required for all cases. Hb, blood indices, and peripheral blood film may be adequate in the majority of cases of IDA. In developing countries, stool examination for ova and cysts should be undertaken consecutively for 3 days in all cases as well as peripheral blood film for malaria parasite in endemic areas. Other specific tests may be performed in the presence of other clinical signs. Bone marrow examination is not usually required except in cases of kala-azar or suspected aplastic anaemia.

Table 3 Diagnosis of iron-deficiency anaemia (IDA) in pregnancy

Characteristic	Calculation	Normal range	IDA
Haemoglobin (Hb, g/dL)	Sahli's method	11–15	<11
Mean corpuscular volume (fL)	PCV/RBC	75–96	<75
Mean corpuscular Hb (pg)	Hb/RBC	27–33	<27
Mean corpuscular Hb concentration (g/dL)	Hb/PCV	32–35	<32
Peripheral blood film		Normocytic normochromic picture	Microcytic hypochromic picture
Serum iron (μg/dL)		60–120	<60
Total iron binding capacity (TIBC, μg/dL)		300–400	>350
Transferrin saturation			<15%
Serum ferritin (μg/dL)		13–27	<12
Free erythrocyte protoporphyrin (FEP, μg/dL)		<35	>50
Serum transferrin receptor			Increased

PCV, packed cell volume; RBC, red blood cells.

Treatment of IDA in pregnancy

In an average pregnancy, the requirements are:

- basal iron, 280 mg;
- expansion of red cell mass, 570 mg;
- fetal transfer, 200–350 mg;
- placental, 50–150 mg;
- blood loss at delivery, 100–250 mg.

After deducting iron conserved by amenorrhoea (240–480 mg), an additional 500–600 mg of iron is required in pregnancy. It can be fulfilled by 4–6 mg/d of absorbed iron. The requirements are 4 mg/d (2.5 mg/d in early pregnancy, 5.5 mg/d for weeks 20–32, and 6–8 mg/d from week 32 onwards).

Prophylaxis

Prevention of iron deficiency is usually possible with a good balanced diet in the absence of ongoing blood loss. Health education by the midwife or obstetrician regarding diet is important. Pregnant women should be encouraged to eat iron-rich foods like green and leafy vegetables, spinach, mustard, turnip greens, cereals, and sprouted pulses. They should avoid tea and coffee, which contain tannins – known inhibitors of iron absorption.

Considerable research has been published on the role of routine iron supplementation in pregnancy, including a Cochrane review. The meta-analysis of trials has concluded that there is clear evidence of improvement in haematological indices in women receiving iron supplements during pregnancy, but no conclusions could be drawn regarding either harmful or beneficial effects for the mother or the baby. The reviewers felt that there was no evidence to advise against a policy of routine iron supplementation in pregnancy and that such a policy should be implemented in high-prevalence areas. However, there is no doubt that routine iron supplementation should be given to all pregnant women in non-industrialised countries. WHO has recommended universal oral iron supplementation for pregnant women (60 mg elemental iron and 25 μg folic acid once or twice daily) through the primary health care system for 6 months in pregnancy in countries with a prevalence of <40 per cent and for an additional 3 months postpartum in countries where the prevalence is >40 per cent. In India, the government has recommended a daily intake of 100 mg elemental iron with 500 μg of folic acid in the second half of pregnancy for a period of at least 100 days. Twice weekly or weekly iron supplements have also given equally good results in some studies, but it is still not universally accepted. In addition, treatment for hookworm with 400 mg single-dose albendazole or 100 mg twice daily for 3 days of mebendazole is recommended in the second half of pregnancy.

The treatment for IDA is oral iron therapy in therapeutic dosage (200 mg elemental iron with 5 mg folic acid per day). On average, there is an increase in Hb of 0.8 g/dL per week. Reticulocyte count starts to increase within 5–10 days of oral therapy. Side effects are common (10–40 per cent), are mainly gastrointestinal, such as nausea, vomiting, constipation, abdominal cramps, and diarrhoea, and are dose related. There is no scientific evidence that any particular brand is superior to any others. Slow-release preparations are often associated with a decrease in side effects, but this is mainly due to decreased absorption of iron. It can be taken with ascorbic

acid (orange juice). Patients who do not tolerate standard iron preparations may be given carbonyl iron. Indications of response to therapy are feeling of well-being, improved appearance, better appetite, and haematological response.

There is no advantage in using parenteral iron over oral iron if the latter is well tolerated, but it can be used for patients who cannot tolerate oral iron. The iron requirement is calculated as follows:

$$\text{Elemental iron (mg)} = [\text{Normal Hb} - \text{patient's Hb (g/dL)}] \times \text{weight (kg)} \times 2.21 + 1000$$

Iron sorbitol injection, which allows rapid absorption owing to its low molecular weight, can be given by deep intramuscular injection after sensitivity testing, but is associated with pain and staining at the injection site. It is administered by repeat injections over a 2-week period.

Iron dextran can be given by the intramuscular or intravenous route. Highly fractionated low-molecular-weight iron dextran can be used with minimum side effects. Newer preparations of iron sucrose can be given as single infusion or repeat intravenous injections. These should be given between 30 and 34 weeks' gestation as they will take 6–8 weeks to achieve their optimal effect. Recombinant erythropoietin can be used with parenteral iron for renal disease patients during pregnancy, but can also be used as a blood substitute in Jehovah's Witness patients and for iron-deficiency anaemia that is unresponsive to oral or parenteral iron.

Blood transfusion is required for obstetric haemorrhage or for severe anaemia in later pregnancy.

Folate-deficiency anaemia

Folate (folic acid) is needed in higher dosage during pregnancy because of the increased cell replication that is taking place in the fetus, uterus, and bone marrow. The recommended daily intake is 800 µg. Its deficiency is common during pregnancy, especially in developing nations, and is mainly due to inadequate dietary intake but can be due to malabsorption syndrome and gastrointestinal diseases. It is more common in women with multiple pregnancy, hookworm infestations, bleeding haemorrhoids, haemolytic conditions (chronic malaria), and other infections. Antifolate medications, such as antiepileptic drugs (phenytoin, primidone), pyrimethamine, and trimethoprim can cause its deficiency. In developing countries, deficiency of both iron and folic acid are common.

The patient may be asymptomatic or may be unwell with loss of appetite, vomiting, diarrhoea, or unexplained fever. There may be pallor, bleeding spots in the skin, enlarged spleen and liver, and neuropathy.

Folate deficiency may cause neural tube defects, abortions, growth retardation, abruptio placentae, and pre-eclampsia. There is some evidence that the incidence of abortion, premature babies, small-for-date babies, and poor folate levels in neonates are higher in babies born to mothers with folate deficiency.

Diagnosis

This is determined by the haemoglobin concentration and blood tests shown in Table 4.

Treatment

The WHO recommends a daily folate consumption of 800 µg in the antenatal period and 600 µg during

Table 4 Diagnosis of folate-deficiency anaemia

Characteristic	Normal range	Folate deficiency
Haemoglobin (Hb, g/dL)	11–15	<11
Mean corpuscular volume (fL)	75–96	>96
Mean corpuscular Hb (pg)	27–33	>33
Mean corpuscular Hb concentration (g/dL)	32–35	Normal
Peripheral blood film	Normocytic normochromic picture	Megaloblastic picture with hypersegmentation of neutrophils, neutropenia, and thrombocytopenia
Serum folate (ng/mL)	>3	<3
Red cell folate (ng/mL)	>150	<150
Serum iron (µg/dL)	60–120	Normal
Serum lactate dehydrogenase		Increased
Homocysteine		Increased

the lactation period. To meet this requirement, pregnant women should be encouraged to eat more green vegetables (spinach and broccoli) and offal (liver and kidneys).

Treatment of established folic acid deficiency is 5 mg oral folic acid per day, which should be continued for at least 4 weeks following delivery. A response can be gauged by a fall in the serum lactate dehydrogenase levels within 3–4 days and an increase in reticulocyte count in 5–8 days.

Cyanocobalamin (vitamin B12)-deficiency anaemia

This is a rare cause of megaloblastic anaemia in pregnancy, as the daily requirement of 3 μg/d is easily met with a normal diet. Pernicious anaemia caused by lack of intrinsic factor resulting in lack of absorption of vitamin B12 is rare during pregnancy, as it usually causes infertility. Findings are the same as in folate deficiency. Vitamin B12 levels are lower in the blood (<90 μg/L). The deoxyuridine suppression test can distinguish between B12 and folate deficiency. Treatment is with parenteral cyanocobalamin (250 μg) every month.

Key points

1. Anaemias, especially nutritional ones, are very common during pregnancy and are a major health problem. They are more common in non-industrialised nations, and are a significant cause of maternal and perinatal mortality and morbidity.
2. Iron-deficiency anaemia continues to be the commonest anaemia during pregnancy owing to dietary habits, and can be easily treated by oral or parenteral iron therapy.
3. Folate-deficiency anaemia is also common but can be easily treated by oral folate supplementation.
4. Thalassaemias and sickle cell haemoglobinopathies are seen in certain geographic areas, and are associated with significant morbidity.

BACK PAIN IN PREGNANCY

Nigel Bickerton, revised by Natassia Rodrigo and Sharmista Williams

Outside of pregnancy, the lifetime incidence of low back pain ranges from 50 to 70 per cent. Sciatica is less common fortunately, with a lifetime incidence of 10–40 per cent. All structures of the lower spine and pelvis – the muscles, ligaments, joints, intervertebral discs, and nerve roots – can cause back pain.

Back pain is the commonest musculoskeletal symptom in pregnancy, with one third of women reporting it to their carers. However, the discomfort and disability owing to backache often worsen as the pregnancy progresses, which results in a high proportion of women eventually reporting symptoms. Between 50 and 80 per cent of women admit to some degree of back pain during pregnancy. The pain may be associated with certain activities only, or it may be so severe that the woman has such limited mobility as to be at risk of venous thrombosis.

Back pain most frequently presents between the fifth and seventh months (20–28 weeks) of pregnancy. It may present earlier, especially in women with pre-pregnancy pain. The two commonest types of back pain are lumbar and sacral/pelvic.

Predictors for back pain in pregnancy include:

- age – younger women are more likely;
- history of lower back pain during menstruation;
- history of lower back pain outside pregnancy;
- history of lower back pain in a previous pregnancy.

Lumbar pain tends to be central over the lower lumbar vertebrae but may be associated with radiation of pain into the legs. The symptoms are similar to those experienced by the non-pregnant back-pain sufferer. It is usually aggravated by prolonged maintenance of the same position, be it sitting at a desk or standing up. Sacral/pelvic pain in pregnancy is approximately four times commoner than lumbar pain. Women describe pain over the sacrum that may be symmetrical or unilateral. It may radiate into the pubis and down the buttocks into the back of the thighs. Rolling over in bed, rising from a seat, and climbing stairs tend to make the pain worse.

The majority of pregnancy-related back pain is caused by a combination of the hormonal effects on joint laxity, postural changes, and a change in the centre of gravity. Imaging has shown that the lordosis

of the lumbar vertebrae in reality decreases during the latter half of pregnancy.

There is evidence to suggest that women who are overweight or who smoke cigarettes have a higher chance of developing back pain in pregnancy. Undertaking physical activity and maintaining fitness before pregnancy reduces the risk of back pain during pregnancy. Most pregnancy-related back pain tends to resolve quickly in the postpartum period. One third of sufferers will continue to have back pain for 4 weeks after delivery, and one sixth for 9 weeks postpartum.

In the majority of cases of back pain in pregnancy, the origin is mechanical. However, on closer questioning, pre-pregnancy symptoms may be elicited. Most mechanical back pain is of sudden onset after lifting or straining. In contrast, pregnancy-related back pain tends to be of a more gradual onset. The woman should be asked about any previous physical injury. In areas of the world affected by civil conflict, it is often women and children who suffer injuries that will cause them problems in later life.

The other causes of back pain are myriad and fortunately they are rare in pregnancy; in fact, many of these causes are likely to affect fertility and result in difficulties in becoming pregnant. However, a list of causes is included for completeness (Box 1). Most cases of back pain are benign, as in non-pregnant women. The clinician, however, must be aware of specific symptoms requiring the exclusion of serious causes, which include:

- persistent and progressive pain;
- presence of neurological symptoms;
- weight loss;
- recent significant changes in symptoms.

The management of mechanical back pain in the absence of any evidence of prolapsed inter-vertebral disc consists of exercise which has been shown to reduce lumbosacral pain but which has to be tailored to the stage of pregnancy. Acupuncture has also been shown to be beneficial. Rigid belts may be of some help, but there is no conclusive evidence of their value.

In an increasing litigious world, the subject of back pain has become linked with litigation related to misdiagnosis and failure of diagnosis of more serious problems. The two diagnoses that should not be missed are:

- acute lumbar disc herniation;
- cauda equina syndrome.

The intervertebral discs are made up of a fibrous outer part that in health surrounds a central area of gel. In disc prolapse, the gel extrudes through a weakness in the fibrous wall of the disc. The weakest part of the disc is posterolateral (Fig. 1) and, when gel extrudes at this point, it may press on spinal nerve

Box 1 Causes of back pain

Mechanical
- Muscle pain
- Prolapse of intervertebral disc
- Spondylolisthesis
- Lumbar spondylosis
- Fibromyalgia
- Osteoarthritis
- Spinal stenosis

Traumatic
- Fracture of vertebra
- Soft tissue injury
- Foreign body migration, including shot pellets and shrapnel

Inflammatory
- Rheumatoid arthritis
- Ankylosing spondylitis
- Reiter's syndrome
- Psoriatic arthritis

Infective
- Osteomyelitis
- Tuberculosis

Metabolic
- Osteomalacia
- Paget's disease of bone
- Osteoporosis and vertebral collapse

Tumours
- Primary of bone – benign or malignant
- Secondary of bone
- Multiple myeloma

Haematological
- Sickle cell disease

Referred from other organs
- Gastric ulcer
- Duodenal ulcer
- Gallbladder disease
- Pancreatitis
- Renal – infection, stones or tumour

Vascular
- Aneurysm

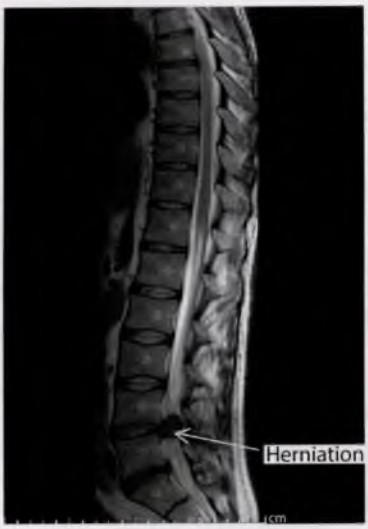

Figure 1 Magnetic resonance scan showing a posterolateral intervertebral disc prolapse at the L4/5 level. This was associated with neurological symptoms. Image courtesy of Dr Carl Wright, FRCR, Ysbyty Glan Clwyd, Bodelwyddan.

roots emerging from the spinal canal. The onset of pain is usually both sudden and severe, with nerve root pain that follows the dermatome involved, usually extending below the knee. In addition, there may be radiation of pain to the sacroiliac region and to the buttocks. In general, though not always, the pain is worse in the leg than in the back. The majority of disc herniations are unilateral.

The nerve root affected will determine the site of the pain. For example, unilateral disc herniation at the L4–5 level will compress the L5 nerve root, giving pain in that dermatome; L5–S1 herniation will affect the S1 nerve root.

Midline rather than posterolateral disc herniation causes the cauda equina syndrome. The pressure effect is on several roots of the cauda equina. The disc lesion causing this is usually at the L4–5 level. In addition to back and buttock pain, the patient may note perianal pain (S2–4 dermatomes). The patient may develop urinary symptoms, including difficulty in voiding urine, increased frequency, or even overflow incontinence. In addition, foot numbness and difficulty in walking may develop either slowly or rapidly. Patients with suspected disc prolapse should be assessed and managed as a matter of urgency by an orthopaedic surgeon or neurosurgeon, according to local practice. Patients with bladder symptoms or anal sphincter tone deficit become a neurosurgical emergency, as delay in decompression may lead to permanent disability.

Examination of these patients may reveal a limited straight leg raise plus loss of power and sensation in the lower limb corresponding to the nerve root affected. If imaging is needed, then MRI can be safely undertaken in pregnancy.

BELL'S PALSY IN PREGNANCY

Bhavini Patel and Anish Bahra

Introduction

Bell's palsy is a lower motor neuron weakness of the facial (7th cranial) nerve the aetiology of which is unknown. A viral cause is currently favoured based upon the isolation of herpes simplex virus-1 genome from the facial nerve endoneurial fluid of sufferers.[1] A recent study revealed the incidence of Bell's palsy to be 37.5/100,000 person-years.[2]

The facial (7th) nerve and its connections

Anatomy

The schematic anatomy of the facial nerve is shown in Figure 1. The facial nerve innervates the muscles of facial expression and the stapedius muscle, which dampens sound waves in the inner ear. The nervus intermedius is the branch of the facial nerve containing sensory and parasympathetic fibres. The nervus intermedius carries sensory perception from the external auditory meatus, nasopharynx, and nose, and (via the chorda tympani) taste from the anterior two-thirds of the tongue. Parasympathetic fibres innervate the lacrimal, submandibular, and sublingual glands.

There are a number of important landmarks of the facial nerve:

- The facial nerve originates at the level of the pons (brain stem); here the nerve curls around the abducens nucleus, which co-ordinates movement of the eyes.
- The facial nerve then enters the internal auditory meatus with the nervus intermedius and the vestibulocochlear (8th) nerve. The facial nerve courses the facial canal in the petrous temporal bone, ultimately synapsing in the geniculate ganglion.
- Distal to the ganglion the nerve gives off a motor branch to the stapedius and the chorda tympani. The chorda tympani joins the mandibular branch of the trigeminal (5th) nerve to convey taste and sensation, respectively, from the anterior two-thirds of the tongue.
- The nerve exits the skull through the stylomastoid foramen and runs through the parotid gland, where it branches to supply the muscles of facial expression.

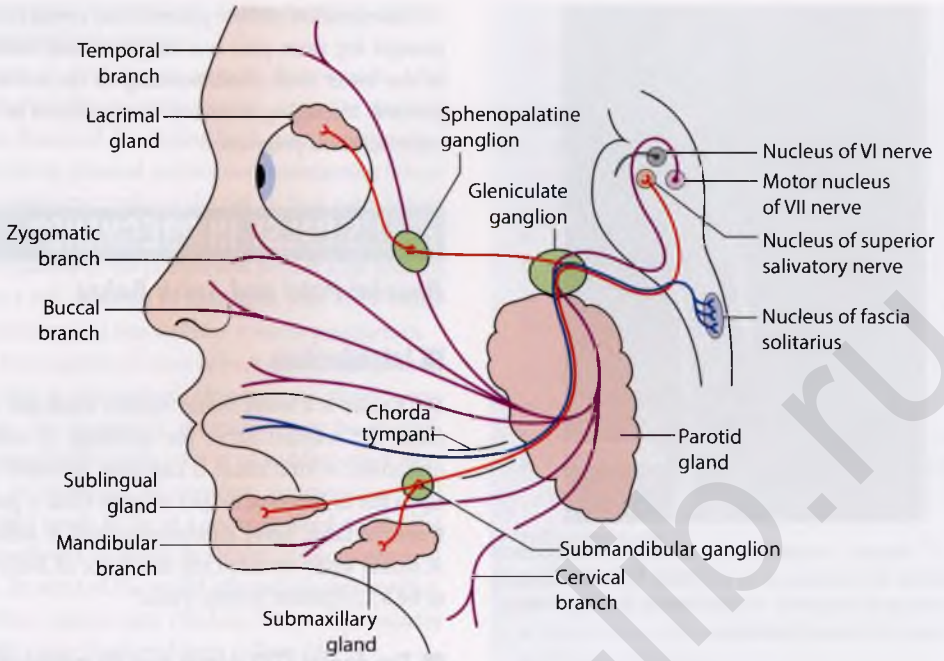

Figure 1 Anatomy of facial nerve.

- The central connections of the facial nerve ascend by way of the facial nerve nucleus from a) the lower part of the face to the ipsilateral (same side) motor cortex, and from b) the upper part of the face bilaterally to the motor cortex on each side.

Lower motor neurone lesions

Figure 2 shows the difference between an upper motor neurone and lower motor neurone lesion of the facial nerve. A lower motor neurone lesion will cause weakness affecting the whole side of the face, thus the upper and lower face. If the patient is unable to close the eyes symmetrically and there is asymmetry of the lines in the forehead, the patient is likely to have a lower motor neuron facial nerve palsy.

A lower motor neurone facial palsy can occur with any lesions affecting the facial nerve nucleus, the facial nerve as it curls around the sixth cranial nerve nucleus (the abducens), the geniculate ganglion, along the course of the facial nerve through the facial canal, and the terminal branches which supply the muscles of the face and parotid gland.

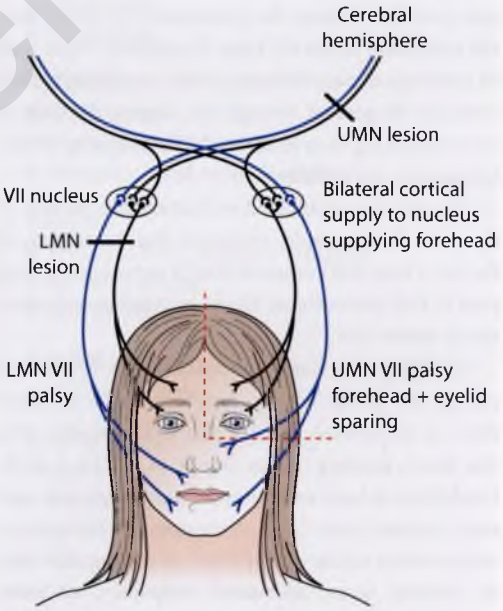

Figure 2 Upper motor neuron (UMN) versus lower motor neuron (LMN) facial nerve lesion: left, a typical Bell's palsy with the whole of the ipsilateral side involved; right, a typical UMN lesion with sparing of the forehead.

Upper motor neurone lesions

A patient who has weakness affecting the lower face on one side, but sparing the upper face, will have an upper motor neurone lesion affecting the supranuclear connections of the facial nerve and nucleus.

Clinical assessment of facial weakness

When a patient presents with weakness of the face, the first step is to ascertain whether the weakness affects both the upper and lower face or the lower face only – i.e., whether this is a lower or upper motor neurone weakness. Once established, the history and additional symptoms and signs should guide the clinician regarding the site of the lesions and hence potential aetiology (see Table 1):

1. Ask the patient to look straight ahead. Check for asymmetry of facial lines.
2. Ask the patient to smile, blow her cheeks out and raise her eyebrows. Then test for power.
3. Ask the patient to press her lips together. Try to overcome this on each side of the mouth.
4. Ask the patient to close her eyes tightly. Try to open the eye on each side. To know whether the patient is making adequate effort at eye closure, look for Bell's phenomenon. If the patient has full range of eye movements normally, when asked to squeeze her eyes tightly the globe will automatically roll upwards and outwards; this is the normal palpebral-oculogyric reflex. This phenomenon can be seen if you are able to prise the eyes open; this is easier when there is weakness of the orbicularis oculi, which affects eye closure. If the patient's attempt at eye closure can be easily overcome but without there being deviation of the eyeballs up and out, it is likely that the patient is not putting full effort into eye closure rather than there being a manifestation of weakness of the orbicularis oculi muscles.

The problem in the diagnosis can occur because one expects the entire one side of the face to be equally weak. It is more common to see a patient have a mouth droop and unequal forehead lines. Just as a patient can have a mildly weak limb, she can have a mildly weak face. Careful observation of the face will make the diagnosis easier.

Bell's palsy

Clinical presentation

Bell's palsy is an isolated lower motor neurone weakness of the facial nerve, acute at onset and unilateral.

Table 1 Lesions of the facial nerve and its connections

Anatomical site	Type of facial weakness	Other features	Causes
Supranuclear connections	Upper motor neurone	Contralateral upper motor neurone hemiparesis	Infarct Tumour deposit Inflammatory lesion
Pons	Lower motor neurone	Abducens (6th) nerve palsy causing failure of abduction of the ipsilateral eye Contralateral upper motor neurone hemiparesis	Infarct Tumour deposit Inflammatory lesion, e.g. demyelination
Cerebellopontine angle	Lower motor neurone	Deafness Vestibular features Ipsilateral cerebellar signs Contralateral upper motor neurone hemiparesis Late involvement of the abducens (6th), glossopharyngeal (9th), and vagal (10th) nerves	Acoustic neuroma Meningioma Tuberculosis Sarcoidosis
The facial canal in the petrous temporal bone	Lower motor neurone	Hyperacusis (nerve to stapedius) Loss of taste in anterior two-thirds of the tongue (chorda tympani)	Middle ear infection Cholesteatoma Fracture skull base
Geniculate ganglion	Lower motor neurone	Pain and vesicles in the auditory canal An acute weakness of the face is more likely to be Bell's palsy, while a slowly occurring weakness would suggest a structural or infiltrative lesion	Infection and reactivation of herpes zoster Idiopathic (Bell's palsy) Compression by meningioma, cholesteatoma, schwannoma, arteriovenous malformation
Peripheral branches of the facial nerve	Weakness affecting the muscles innervated by the branches affected (lower motor neurone)	Additional local and systemic features	Local lesions of the parotid gland – tumour, infection, sarcoidosis

Typically individuals experience pain around or behind the ear followed by evolution of unilateral upper and lower facial muscle weakness for a few hours up to a couple of days. Patients may complain of dribbling of saliva from the affected side, or facial asymmetry may have been noticed. Involvement of the branches of the facial nerve result in additional symptoms such as impaired tolerance to ordinary levels of noise (hyperacusis) and disturbed sense of taste on the same side. The prognosis is good. In a large series of untreated individuals with Bell's palsy, 85 per cent began to recover within 3 weeks after onset. Of the remaining individuals, partial recovery occurred within 3–6 months. Only 16 per cent of all sufferers had a permanent motor or autonomic disability. About 10 per cent of patients may have recurrence of the problem in the future.[3,4]

Late complications of Bell's palsy occur 3–4 months after onset of the paralysis. A patient may develop ipsilateral involuntary narrowing of the palpebral aperture when other facial muscles are voluntarily moved (synkinesis). Aberrant reinnervation of secretory fibres to the lacrimal glands can result in gustatory (crocodile) tearing, causing lacrimation during eating.

Bell's palsy in pregnancy

There is conflicting data on the incidence of Bell's palsy in pregnancy. One study looking at patients with Bell's palsy found that 46 of the 1701 affected women were pregnant when diagnosed, giving a 2.7 per cent incidence. This is higher than 0.2 per cent reported in the general population.[3] In another study of 242,216 pregnancies, only 42 women had Bell's palsy, giving an incidence of 0.017 per cent.[5]

There are a few studies suggesting a link between hypertensive disorders in pregnancy and Bell's palsy.[5–7] In one study, there was a five-fold increase in hypertensive disorders in women with Bell's palsy in pregnancy or puerperium; the data suggested that a pregnant woman presenting with Bell's palsy should be further assessed for pre-eclampsia.[6]

The risks of having Bell's palsy in pregnancy

There is limited evidence as to how to counsel patients with Bell's palsy in pregnancy. Overall, there is no congenital risk of Bell's palsy for the fetus. The only study reviewing this data was a retrospective study of women presenting with Bell's palsy in pregnancy. It suggested an increased risk of preterm deliveries, caesarean sections, and low infant birth weight.[7] Of the 41 patients, 3 had twin births (7 per cent). Discounting these cases, the incidence of preterm delivery (a mean gestational age of presentation was 35.4 weeks) and low birth weight was still twice that of unaffected pregnancies. Studies have shown that mean gestational age and birth weight are likely to be lower in women with pre-eclampsia, with a higher rate of caesarean sections.[8] The complications in women presenting with Bell's palsy in pregnancy thus may be related to underlying hypertensive disorders or pre-eclampsia rather than the Bell's palsy itself.

Investigations

There is no routine indication for an MRI brain scan in individuals with a typical presentation of Bell's palsy. Imaging is indicated only if there are additional neurological signs suggesting an alternative pathology (Table 1). If imaging (MRI) is done in Bell's palsy, the most common abnormality is contrast enhancement of the distal intracanalicular and labyrinthine parts of the facial nerve and the geniculate ganglion; tympanic and mastoid aspects of the facial nerve can also be involved.

The majority of individuals with Bell's palsy will have a complete recovery. Electrodiagnostic tests add little value to management especially in individuals with incomplete weakness. In those individuals with complete paralysis the risk of incomplete recovery is higher. Electrodiagnostic testing may help to identify those with a poorer prognosis who may be candidates for reconstructive surgery. Testing is most informative when done between 7 and 14 days after symptom onset. Electroneuronography records the amplitude of responses over selected facial muscles following electrical stimulation of the main trunk of the facial nerve, compared with the unaffected side. If the amplitude is less than 10 per cent of the normal side, some individuals may still recover full function, but most do not. Electromyography may provide further information in this group of individuals. In electromyography a needle is inserted into the facial muscles and depolarisations are recorded at rest and following voluntary attempts to contract the muscles.[9]

Management of Bell's palsy

Early intervention

General management

The most important aspect of management is eye care during the recovery period. Weakness of eye closure

results in corneal drying and epithelial ulceration. There is a risk of blindness from infective keratitis and corneal revascularisation. The risk is increased owing to the additional lack of tearing.[10]

- Lubricating eye drops should be used during the day.
- An eye patch which does not abrade the cornea can be used to protect the exposed cornea.
- The eye should be taped closed when sleeping.
- Uncommonly, to protect the eye (globe), a temporary tarsorrhaphy may be used, or a temporary ptosis can be induced by botulinum toxin to the levator muscle of the eyelid.

Specific management

There are no guidelines specifically for treatment of Bell's palsy in pregnancy. The American Academy of Neurology guidelines, which include the data from the Cochrane Database Systematic Reviews, recommend that all patients with new onset of Bell's palsy should be offered steroids to increase their chances of functional recovery.[11,12] The benefit of additional antiviral medication is very modest (<7 per cent). The most commonly used antiviral, acyclovir, is safe in pregnancy. If a patient is offered antivirals, she should be informed that the treatment will not add much value to steroids alone.[13]

Trials to date have used varying regimens of steroid use. There are only two Class I studies which randomised patients to steroids and placebo. Both studies enrolled patients within 3 days of the onset of facial weakness. Both studies used prednisolone. One study used prednisolone 60 mg once daily for 5 days followed by a 5-day taper.[14] The second study used prednisolone 25 mg twice daily for 10 days.[15]

There is currently no supportive evidence for decompressive surgery in the management of Bell's palsy.

Late intervention

Late sequelae of Bell's palsy include residual paresis, associated movements caused by aberrant reinnervation of regenerating nerve fibres (*synkinesis*), and contracture. Less commonly, individuals can develop dry eye and 'crocodile tears'; aberrant reinnervation results in salivary secretory fibres destined for the salivary glands via the facial nerve being redirected to the lacrimal gland. This results in tearing during salivation.[3]

Aberrant reinnervation in synkinesis or crocodile tears can be managed with botulinum toxin therapy.[16] Reconstructive surgery may be required for residual weakness to ensure protection of the globe and for cosmetic purposes.

Summary

An obstetrician is likely to see a few cases of Bell's palsy (Fig. 3) in his or her career. It is important to recognise the disorder as an isolated idiopathic and largely benign facial nerve palsy with good prognosis. The diagnosis is clinical, and further investigation is required only in atypical cases, particularly where there is additional focal neurology. Functional outcome can be improved with treatment with corticosteroids if started within 72 hours of symptoms onset. General eye-care during the recovery period remains imperative.

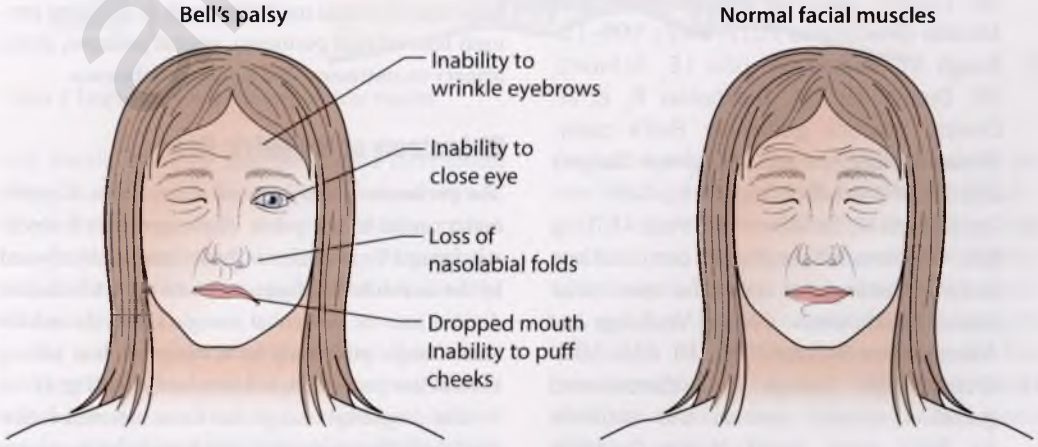

Figure 3 Bell's palsy.

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BIRTH INJURIES, MATERNAL

Jai B Sharma

Perineal trauma is common, especially after the birth of a first child, and is responsible for considerable long-term maternal morbidity, such as complete perineal tear, relaxed perineum, genital prolapse, stress urinary incontinence and faecal incontinence.

Anatomy of the pelvic floor

The perineum is the diamond-shaped area of pelvic outlet caudal to the pelvic diaphragm with boundaries formed by the inferior pubic rami anteriorly and by the sacrotuberous ligament posteriorly. It is further divided into the urogenital triangle anteriorly and the anal triangle posteriorly by a transverse line joining the anterior parts of the ischial tuberosities (Fig. 1).

The urogenital triangle has three superficial muscles: the bulbospongiosus, which encircles the vagina

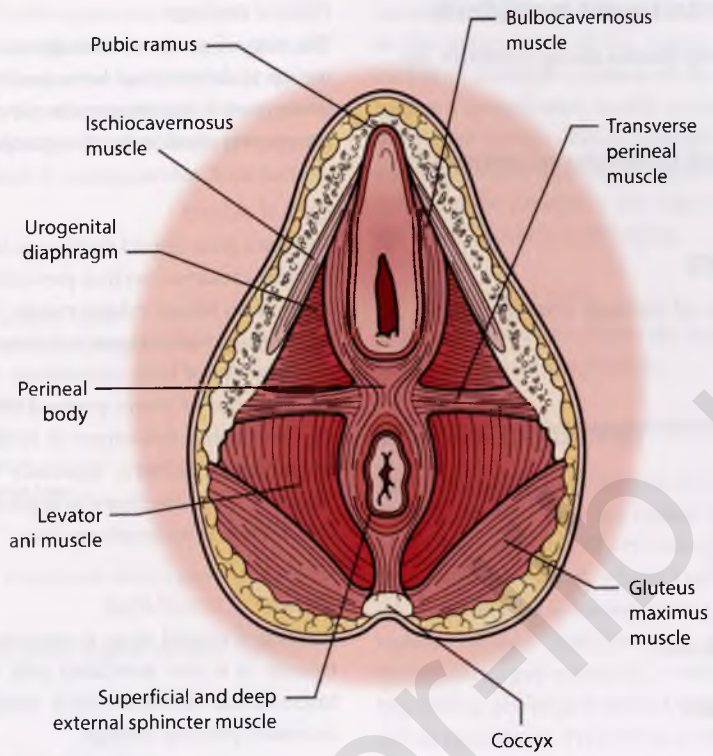

Figure 1 Transverse view of the perineal muscles.

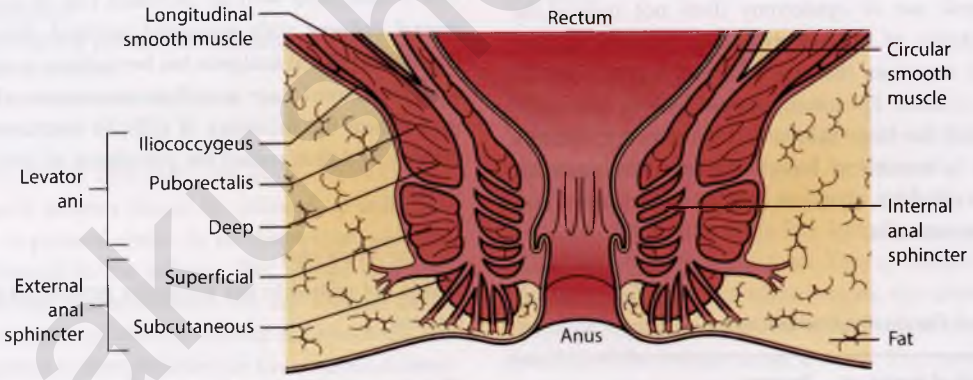

Figure 2 Longitudinal view of the anal sphincter muscles.

and inserts anteriorly into the corpus cavernosum clitoridis; the superficial transverse perineal muscle, which lies transversely; and the ischiocavernosus muscle, which lies laterally in the labia. Deep muscles include the deep transverse perineal muscles and the levator ani (Fig. 1).

The anal triangle is posterior, and includes the anal sphincter and ischiorectal fossae. The perineal body is a fibromuscular area between the vagina and the anal canal in which there is interlacing of muscle fibres from the bulbospongiosus, the superficial transverse perineal muscle, and the external anal sphincter muscle.

The anorectum consists of the lower 3.5 cm of the anal canal and the rectum. The external anal sphincter is composed of three parts: subcutaneous, superficial, and deep. The internal anal sphincter comprises the circular muscles of the rectum separated from the external anal sphincter by longitudinal muscles, which are a continuation of the longitudinal muscle of the rectum (Fig. 2).

Types of genital trauma in childbirth

The classes of genital trauma during childbirth are:

- perineal tears;
- cervical tears;
- genital haematomas (in the vagina and perineum);
- uterine rupture.

Perineal tears

The various types of perineal tears are shown in Table 1.

Risk factors

The various risk factors for perineal floor trauma are as follows:

- big baby;
- prolonged labour;
- precipitate labour;
- difficult labour;
- shoulder dystocia;
- occipitoposterior delivery;
- breech delivery;
- instrumental delivery.

Prevention of perineal tear

Role of episiotomy

Liberal use of episiotomy does not reduce the incidence of third-degree tears. Midline episiotomy increases the risk of third-degree tears by 4.5–6 times. Episiotomy should only be used judiciously for large babies, forceps delivery, where a tear is imminent, breech delivery manipulations for shoulder dystocia, and other intrauterine manipulations.

Table 1 Classification of perineal tears

Grade of tear (class)	Features
First degree	Laceration (tear) involving the vaginal epithelium or perineal skin only
Second degree	Involvement (tear) of the perineal muscles but not the anal sphincter
Third degree	Involvement of anal sphincter
Grade 3a	Tear of <50% thickness of the external sphincter
Grade 3b	Tear of >50% thickness of the external sphincter
Grade 3c	Tear of the internal sphincter
Fourth degree	Third-degree tear with involvement of anal epithelium

Perineal massage

The use of perineal massage in the weeks leading up to delivery has been associated with slightly lower rates of episiotomy; the prevalence of perineal trauma was equal in the two groups studied.

Mode of delivery

This has a great impact on the rate of perineal trauma. Elective caesarean section prevents damage to perineum from labour-related events. Ventouse delivery is associated with less perineal trauma than is forceps delivery. Use of both instruments is associated with a higher rate of severe perineal damage than a single instrument. Episiotomy is recommended before instrumental delivery, especially forceps delivery. Ventouse may sometimes be applied without episiotomy if there is no imminent tear.

Duration of second stage

Prolonged second stage is associated with perineal trauma. It is also associated with increased risk of instrumental delivery, which itself is a factor for increased perineal damage.

Epidural analgesia

This is associated with an increased risk of instrumental delivery with associated perineal damage. However, epidural analgesia has been shown to allow a passive second stage in nulliparous women, which may reduce the incidence of difficult instrumental delivery and thus reduce the prevalence of perineal trauma.

Position for delivery

This is not related to any particular type of perineal trauma.

Management of first- and second-degree perineal tears

Minor first-degree lacerations may not need suturing provided they are not bleeding. However, all first and second-degree tears should be meticulously sutured for optimum outcome.

Prerequisites for suturing of perineal tears are:

- proper lighting;
- adequate analgesia, preferably epidural analgesia;
- capable assistance;
- good exposure and proper examination to avoid missing the apex or other lacerations, especially of the anal sphincter, are important for proper suturing.

Third-degree and fourth-degree perineal tears

Any damage to internal or external anal sphincter causes faecal incontinence or faecal urgency, and is a serious condition if not repaired well at the time of delivery. The prevalence is 2.8 per cent in primigravidae and 0.4 per cent in multigravidae. Risk factors are as follows:

- nulliparity;
- big baby;
- prolonged second stage of labour;
- persistent occipitoposterior position and face to pubes delivery;
- instrumental delivery;
- midline episiotomy;
- epidural analgesia;
- previous third-degree tear;
- shoulder dystocia.

A classification of perineal tears is given in Table 1.

Repair of third- and fourth-degree perineal tears

Prerequisites are:

- written consent;
- spinal or effective epidural analgesia;
- repair performed in an operating theatre;
- repair performed by a trained obstetrician (at least a registrar);
- good lighting and adequate exposure;
- good assistance;
- proper instruments and sutures.

Future delivery after third- and fourth-degree tears

All such patients should be followed up and managed in perineal clinics by an obstetrician with special interest in the subject. They should have anal ultrasound and manometry for any residual deficit in the sphincter. Women without any symptoms and any deficit in the sphincter can have vaginal delivery under the observation of an obstetrician or a senior midwife. However, women with anal incontinence or residual sphincter damage should be counselled to have an elective caesarean section in their next delivery. There is no evidence that prophylactic episiotomy prevents sphincter damage in future deliveries, hence episiotomy should be used only if indicated for obstetric reasons.

Injuries to the cervix

Small (<0.5 cm) cervical tears are common in obstetric practice; however, deep cervical tears are less common but are more dangerous. They may extend to the upper third of the vagina, and may cause partial or complete avulsion of the cervix from the vagina. Cervical tears usually occur in difficult and obstructed labour, delivery through an incompletely dilated cervix, or as a part of extensive genital injuries involving the perineum, the vagina, and sometimes the lower segment of the uterus.

Repair of cervical tears

The prerequisites for repair are similar to those for third- and fourth-degree tears.

Genital haematomas

Acute puerperal haematomas are seen 1 in 1000 to 4000 deliveries. They are caused by complications of episiotomy in 85–90 per cent of cases, especially in difficult deliveries where complete haemostasis could not be achieved during suturing. Other causes include instrumental, vaginal delivery, primiparity, pre-eclampsia, multiple pregnancy, big babies, prolonged second stage of labour, and vulval varicosities. Prevention is by adequate suturing of perineal and vaginal tears and episiotomy, and by achieving complete haemostasis at the time of repair.

Types of genital haematomas

Infralevator haematomas

Infralevator haematomas are usually associated with vaginal delivery and are limited by the levator ani muscles superiorly, the perineal body medially, and the Colles fascia and fascia lata laterally, and may extend into the ischiorectal fossa. They are caused by injury to small labial or vulvar vessels, the inferior vesical or vaginal branch of the uterine arteries, or branches of the inferior rectal arteries. They usually present as vulval or perineal pain out of proportion to the episiotomy, and as local swelling in the perineum, vulva, or vagina, with ischiorectal mass with discoloration. There may be associated continuous vaginal bleeding or urinary retention. Small non-expanding haematomas of less than 3 cm can be managed expectantly.

Expanding or large haematomas require surgical management to prevent pressure necrosis, septicaemia, bleeding, and even death. Thorough rehydration and resuscitation are mandatory before their evacuation under sufficient analgesia, good assistance, and proper lighting for adequate exposure. All blood clots

must be evacuated after opening the haematoma. All bleeding vessels must be secured tightly with 1-0 vicryl sutures, complete haemostasis must be achieved, and the dead space should be obliterated using vicryl sutures.

All patients should be given antibiotics and analgesics in the postoperative period. Foley's catheter should be used for 24 hours. The patient should be followed up for any recurrence of the haematoma.

Supralevator haematomas

Supralevator haematomas are serious haematomas that have no fibrous boundaries and arise from branches of the uterine artery, the pudendal artery, or the inferior vesical artery. Bleeding can extend into the broad ligament, the presacral space, and the retroperitoneal space. They may present as rectal pain and pressure. They can also manifest as enlarging vaginal or rectal masses with signs and symptoms of shock. There may be continued vaginal bleeding or even cardiovascular collapse. Broad ligament haematomas may cause upward and lateral displacement of the uterus, which feels well retracted. The revealed vaginal bleeding may not be significant. They may occur as an extension of a cervical tear into the fornices or into the uterus, or may appear in the presence of uterine rupture.

The management of supralevator haematomas requires laparotomy after resuscitating the patient. This will require a general anaesthetic as opposed to a regional block. Blood will need to be available, and the patient will require antibiotic cover. In the case of broad ligament haematoma, care must be exercised to avoid injury to the ureters. Complete haemostasis must be achieved by securing all bleeding vessels. In the case of rupture of the uterus, hysterectomy may be required. Sometimes angiographic embolisation of the vessels may be required. Postoperatively, all patients must be monitored carefully for vital signs and any recurrence of haematomas, and adequate blood, antibiotics, and analgesics should be administered.

Uterine injuries

A uterine injury can be part of another genital injury that extends into the uterus, such as cervical lacerations extending into the lower uterine segment, injury to the uterine vessels, the rupture of a previous scar, or the rupture of an unscarred uterus in cases of obstructed labour. Rupture of the uterus is a serious condition with high maternal and perinatal mortality and morbidity. The patient presents with features of obstructed labour followed by features of shock, vaginal bleeding, abdominal distension and tenderness. There may be haematuria. Fetal heartbeat is usually absent.

Management includes immediate resuscitation with adequate hydration, blood transfusion, intravenous antibiotics, and urgent laparotomy under general anaesthesia. The uterus can be salvaged if there is a clean cut, such as in a scar rupture; however, in most occurrences of uterine rupture in obstructed labour, the margins are ragged. Caesarean hysterectomy is usually required in such cases. Complete haemostasis must be achieved, which may require the ligation of anterior division of the internal iliac artery. One has to be careful to avoid injury to the bladder and ureters in such cases. Postoperatively, patients need careful monitoring, bladder drainage by Foley's catheter, intravenous antibiotics, analgesics, and adequate blood and hydration.

Further reading

RCOG Greentop Guideline. 29: Management of third and fourth degree perineal tears. 2007.

BIRTH INJURIES, NEONATAL

John Ho

Birth injury is defined as an impairment of the newborn body function or structure due to an adverse event that occurred at birth. The injury could be caused by trauma during the birth process or by perinatal conditions that lead to fetal hypoxia, or both. Birth injuries may be avoidable by obstetric intervention, or may be completely unavoidable.

Negligence claims involving obstetrics represent the highest value claimed against the NHS. From 2000 to 2010, the NHS paid out £3.1 billion in compensation. Two categories, namely cerebral palsy and management of labour along with cardiotocography (CTG) interpretation, account for 70 per cent of the total value of all maternity claims.[1] Brain damage at birth and cerebral palsy claims can result in extensive damages awards, as babies affected by

birth asphyxia will often need lifelong care. Sadly, the number of birth injury claims is climbing faster than the rate of births in the UK.

Incidence and risk factors

Figures for major birth trauma in the UK are not routinely collected. In a Canadian study, the overall risk of fetal trauma in term (>37 weeks) singleton fetuses was estimated at 2.0 per cent.[2] The overall risk in caesarean sections is lower, at 1.1 per cent.[3] Mortality due to birth trauma is uncommon, accounting for less than 2 per cent of neonatal deaths. Certain conditions are associated with an increased risk of birth injury (see Box 1).

Box 1 Conditions with increased risk of birth injury

- Macrosomia (birth weight over 4000 g)
- Prolonged labour
- Cephalopelvic disproportion
- Maternal obesity
- Abnormal fetal position (particularly breech presentation)
- Instrumental deliveries (forceps or a vacuum device)
- Prematurity

Birth injuries can be caused by the direct pressure effect on the baby or hypoxic injury to the brain. Occasionally birth injury can be caused by the resuscitation of the baby. Various types of injuries are listed in Box 2.

Box 2 Types of birth injuries

- Cranial injuries
- Intracranial haemorrhage
- Peripheral nerve injuries
- Spinal cord injuries
- Abdominal bleeding
- Fractures
- Hypoxic injury

Cranial injuries

Caput succedaneum is a diffuse subcutaneous, extraperiosteal fluid collection with poorly defined margins. Unlike a cephalohaematoma, it can extend across the suture lines and the midline (Fig. 1). It can be caused by the pressure of the presenting part against the birth canal or by vacuum extraction. Caput succedaneum is occasionally haemorrhagic. The majority of cases do not cause any complications and will resolve within a few days after birth.

Subgaleal (subaponeurotic) haemorrhage is a collection of blood between the periosteum and the aponeurosis (Fig. 2). About 77 per cent of cases follow an instrumental delivery. This condition is highly associated with vacuum-assisted delivery, with an incidence of 4.6 per 1000 vacuum-assisted deliveries.[4] It appears as a boggy swelling usually

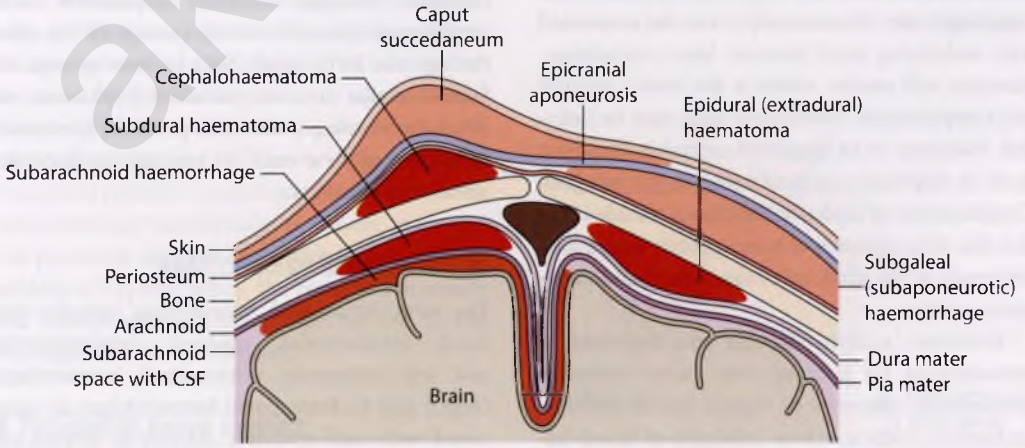

Figure 1 Types of cranial haemorrhage. CSF, cerebrospinal fluid.

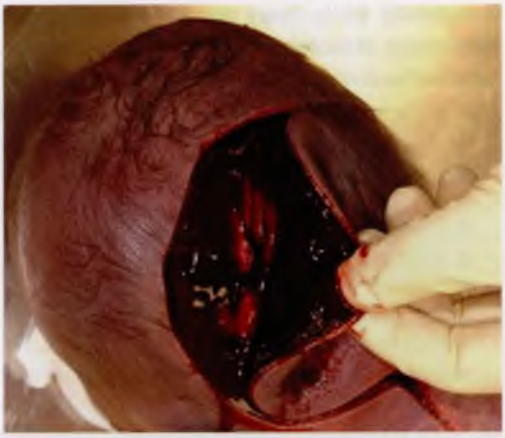

Figure 2 Massive subgaleal (subaponeurotic) haemorrhage in a term baby following vacuum extraction; view of posterior head with partially reflected scalp. Courtesy of Dr Mudher Al-Adnani, Guy's and St Thomas' NHS Foundation Trust.

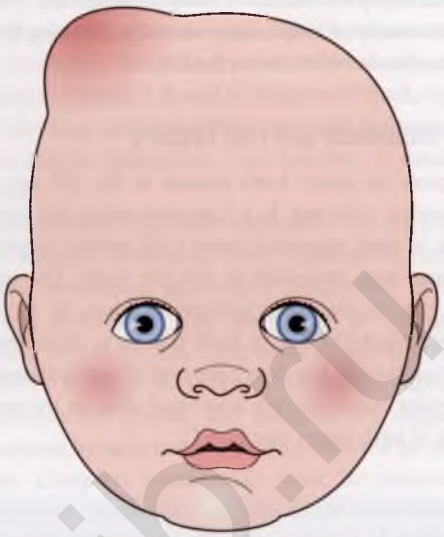

Figure 3 Cephalohaematoma.

at the back of the head within 12–72 hours after the delivery, and is not restricted by the suture lines. The mass may expand slowly, resulting in an ongoing blood loss. The subgaleal space is capable of holding up to 50 per cent of a newborn baby's blood. Therefore, the baby may become progressively anaemic and hypotensive, and possibly die. This condition is associated with a high mortality rate of up to 12–14 per cent. Early recognition of this injury is crucial for survival.

Cephalohaematoma is a subperiosteal collection of blood caused by the rupture of vessels beneath the periosteum. It is normally limited to the surface of one cranial bone, usually the parietal or occipital bone (Figs 1 and 3). The swelling is not visible at birth, and there is no discoloration of the overlying scalp. Occasionally it can be associated with underlying skull fracture. Most cephalohaematomas will resolve within a few weeks without any complications. Sometimes they may be calcified. Palpation of an organised cephalohaematoma gives an impression of 'scalloping' at the margins. Complications of cephalohaematoma include jaundice due to breakdown of haemoglobin, blood loss, deformity of the skull, infection, sepsis, and rarely osteomyelitis.

Erythema, ecchymosis, cuts and abrasions or subcutaneous fat necrosis may occur following instrumental deliveries or vaginal breech delivery. Ecchymosis (subcutaneous collection of blood following rupture of small blood vessels) is common in premature babies. Cuts and abrasions may result during caesarean section due to cutting the baby with the scalpel blade. Subcutaneous fat necrosis may occur on the pressure points on the face, trunk, extremities, and buttocks. It is normally not detected at birth and may take a few days or weeks to develop. It presents as an irregular, hard, subcutaneous plaque with purple discoloration. Treatment is normally not required, and it will resolve in a few weeks. Hypercalcaemia is a rare complication of subcutaneous fat necrosis that may need further intervention.

Ocular injuries such as subconjunctival and retinal haemorrhages are common minor injuries. Petechial spots over the face and neck are also common. These are secondary to a sudden rise in intrathoracic pressure during passage of the chest through the birth canal. No treatment is required. Serious ocular injuries, including hyphaema, vitreous haemorrhage, and damage to the Descemet's membrane of the cornea, are rare and are associated with forceps delivery.

Intracranial haemorrhage

The term *intracranial haemorrhage* includes subdural, subarachnoid, epidural, intraventricular, and less commonly intracerebral haemorrhages (Figs 1 and 4). Intracranial haemorrhages are associated with such operative delivery as forceps and vacuum-assisted deliveries. In subdural, subarachnoid, and epidural haemorrhage, the baby typically

Figure 4 Massive intraventricular haemorrhage in a preterm infant at 28 weeks' gestation; medial aspect of left cerebral hemisphere showing blood within the lateral and third ventricles. Courtesy of Dr Martin Weber, Guy's and St Thomas' NHS Foundation Trust.

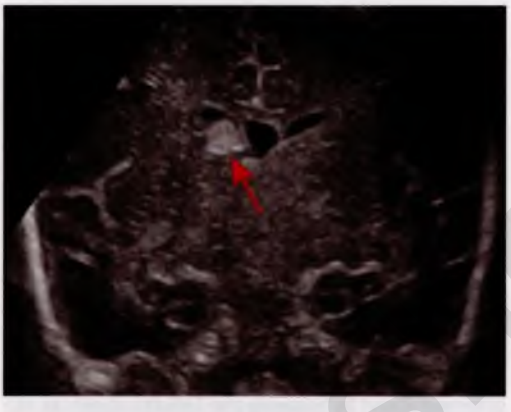

Figure 5 Right subependymal haemorrhage on cranial ultrasound, coronal view.

presents at 24–48 hours of age with neurological symptoms of seizure, hypotonia, and apnoea. A computed tomography (CT) or magnetic resonance imaging (MRI) scan will show the underlying lesion. The management of the condition will depend on the size of the haemorrhage and any signs of raised intracranial pressure. The condition may resolve with conservative treatment. If there are signs of raised intracranial pressure, neurosurgical input is required. Intraventricular haemorrhage is usually associated with premature delivery. In the absence of a clotting problem or hypoxic injury, the condition is usually mild (subependymal haemorrhage: see Fig. 5) and the prognostic outcome is good.

Peripheral nerve injuries

The incidence of brachial plexus injury is about 1.5 per 1000 live births.[5] The majority of cases are Erb's palsy. Certain conditions are associated with a greater risk of injury. Shoulder dystocia has a 100 times greater risk, an exceptionally large baby (>4.5 kg) 14 times greater risk, and forceps delivery 9 times greater risk of injury.

Erb's palsy – The injury is on the fifth and sixth cervical nerves. It causes asymmetrical movement of the arms. The movement of the affected arm is reduced, with weak or no shoulder abduction, and the arm adducted and internally rotated (Fig. 6). The elbow is pronated and extended with the wrists flexed, adopting a waiter's tip position. The Moro and biceps reflexes are absent, but the grasp reflex is usually retained. Five per cent of patients with Erb's palsy may have ipsilateral phrenic nerve palsy.

Klumpke's palsy – This is rare, and affects the seventh and eighth cervical and first thoracic nerve. It results in paralysis with weakness of the hand and loss of grasp reflex. Horner syndrome (ipsilateral ptosis and myosis) may be seen if the thoracic nerve is damaged.

The majority of cases of Erb's and Klumpke's palsy resolve spontaneously in 2–4 months. Treatment in the initial stage is physiotherapy is to prevent muscle wasting. If the recovery is slow or incomplete after 3 months, a referral should be made to the regional peripheral nerve surgical unit.

Phrenic nerve palsy – The phrenic nerve consists of the cervical nerve roots C3–C5. It controls the movement of the diaphragm. Damage to the phrenic nerve is often accompanied by brachial nerve injury. The neonate may present with cyanosis and laboured and irregular breathing. Chest X-rays may show a raised diaphragm. An ultrasound scan can be used to assess the movement of the diaphragm.

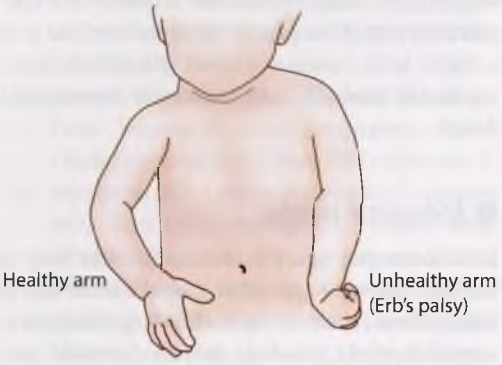

Figure 6 Erb's palsy.

The management plan is to support the breathing and feeding. The condition usually resolves spontaneously by three months.

Facial nerve palsy is usually peripheral in nature. It results from pressure over the facial nerve. Typically the mandibular branch of the facial nerve is affected. The trauma can occur in utero from efforts during labour or from use of forceps during assisted delivery. Traumatic facial nerve palsy needs to be distinguished from facial nerve agenesis. Peripheral facial palsy involves the whole side of the face, including the forehead. When the infant cries, movement appears on the unaffected side of the face and hence the mouth is drawn to that side. The forehead is smooth on the affected side and the eye cannot be closed. In central facial palsy, the forehead remains unaffected (see Bell's palsy in pregnancy).

Most infants with peripheral palsy begin to recover within a few weeks. Artificial eye drops may be required if the eyes cannot be closed. Consultation with a paediatric neurologist or neurosurgeon is indicated if no improvement is observed within 2 weeks.

Spinal cord injuries

Spinal cord injury is rare; the incidence is thought to be 1 in 60,000 births.[6] A neonate may sustain injury to the spinal cord during delivery when the spine is hyperextended (traction) or rotated. Traction is more significant in breech deliveries and causes injury to the lower cervical–upper thoracic vertebrae. Rotation or torsion is significant in vertex deliveries causing damage to the fourth cervical vertebra. Forceps-assisted delivery and breech vaginal delivery are risk factors. Other neurological injuries include spinal epidural haematoma, vertebral fractures or dislocations, and disruption or total transection of the cord. The outcome is poor with a high mortality rate if the part of the spine involved is at a higher level. Lesion at a lower spinal level causes significant morbidity and permanent neurological deficit.

Abdominal injuries

Intra-abdominal injury is uncommon. The liver is the only internal organ other than the brain that is vulnerable to injury during birth. A large baby, intrauterine asphyxia, bleeding disorders, extreme prematurity, breech presentation and hepatomegaly are predisposing factors. Common lesions are rupture of the liver and subcapsular haematoma. Symptoms of shock may be delayed. Early detection by means of ultrasonographic diagnosis and institution of prompt supportive therapy may be life saving. Splenic rupture may occur rarely, alone, or in association with liver rupture.

Adrenal haemorrhage occurs in some cases, especially after breech deliveries. Its cause is usually undetermined, but trauma, stress, anoxia, or severe sepsis may be contributory, with 90 per cent being unilateral. Presenting features are profound shock and cyanosis, though not all adrenal haemorrhages are fatal.

Fractures

Fractures are most often observed following breech delivery and/or shoulder dystocia in macrosomic babies with a birth weight over 4.5 kg.

The clavicle is the most frequently fractured bone in the neonate during birth. The incidence is unpredictable and sometimes it is an unavoidable complication of normal birth. If the fracture is displaced (complete), crepitus may be felt on palpation of the clavicle, with oedema in the surrounding tissue. The movement of the ipsilateral arm is reduced. X-rays will confirm the fracture. The prognosis is excellent, with healing occurring by 10 days. The arm is immobilised by pinning the infant's sleeve to the shirt. Other injuries should be checked for, and there may be co-existing brachial plexus injury. A non-displaced fracture may not have any clinical signs. The diagnosis is often delayed when an X-ray shows callus formation on the clavicle.

Long bone fracture of the humerus or femur should be suspected when a 'pop' or 'snap' of arms or legs is noticed during the delivery. The limb will become swollen later and movement reduced. Crepitus may be felt and the baby may dislike palpation of the fractured limb. For humerus fracture, the Moro reflex will be asymmetrical and often reduced on the affected side. The diagnosis is confirmed by an X-ray. Risk factors for humeral fractures are shoulder dystocia, macrosomia, caesarean section, breech delivery, and low birth weight. Humeral shaft fracture is usually treated with a splint and the arm is strapped to the chest. Healing occurs in 2–4 weeks. For femoral fractures, good results can be obtained with traction suspension of the lower extremities, even if the fracture is unilateral. Healing is

Table 1 Clinical stages of severity of hypoxic injury

Sarnat stage	Clinical features	Likelihood of neuro-developmental handicap	Likelihood of death
Stage 1 (Mild)	Irritability, excessive crying, muscle tone may be slightly increased, neurological examination normalises in 3–4 days	Low	Low
Stage 2 (Moderate)	Lethargy, hypotonia, poor feeding and sucking reflexes, seizures occur within 24 hours, full recovery possible within 1–2 weeks	Moderate	Low
Stage 3 (Severe)	Seizures occur early and are difficult to control with treatment, coma, breathing irregular and often requires ventilator support, hypotonia, neonatal reflexes are absent (Moro, sucking, swallowing), pupils may be dilated, fixed or poorly reactive to light	Inevitable	High

usually accompanied by excess callus formation, and orthopaedic consultation is recommended.

Dislocations and epiphyseal separations

Dislocations rarely result from birth trauma. The upper femoral epiphysis may be separated during breech extraction. The affected leg shows swelling, limitation of active movement, and painful passive movement. The prognosis is usually good.

Hypoxic ischaemic injury

Hypoxic ischaemic encephalopathy (HIE) is the term used to describe hypoxic injury to the neonatal brain. The incidence of HIE is estimated at 1 to 8 per 1000 live births in a developed country. The incidence is much higher in developing countries, however (e.g., 26.2 per 1000 live births in a Nigerian study).[7] It is difficult to estimate the incidence accurately owing to the lack of universally agreed definitions and selection bias in referral centres. In terms of mortality rates, birth asphyxia accounted for 23 per cent of the 4 million neonatal deaths (during the first 28 days of life) worldwide in 2000.[8] The risk of dying due to birth asphyxia is 8 times higher for babies in a country with a high neonatal mortality rate. The risk of death or severe neurological impairment following hypoxia-ischaemia is estimated at about 1 per 1000 live births in a resource-rich country, and 5–10 per 1000 live birth in a resource-poor country.[9]

The aetiology of HIE is multi-factorial. Antenatal and intrapartum risk factors are present in the majority of cases. Complications of perinatal asphyxia include learning difficulties, global developmental delay, deafness, epilepsy and death. The degree of the neonatal hypoxic injury is divided into 3 categories (see Table 1), HIE stage 1 being the mildest and HIE stage 3 being the most severe.

HIE should be suspected in a newborn baby if the following are observed:

- Apgar score 0–3 at 5 minutes or less than 5 at 10 minutes;
- poor cord gas, arterial pH < 7.0, or the first neonatal blood gas pH < 7.0;
- lack of spontaneous breathing at birth, requiring mechanical ventilation.

A baby with suspected HIE should be admitted to the neonatal intensive care unit. The treatment is supportive and directed towards the underlying cause, such as sepsis. 'Total body cooling' or induction of moderate hypothermia is indicated for babies with moderate to severe HIE. Induction of moderate hypothermia for 72 hours in infants with perinatal asphyxia has been shown to improve the neurological outcome in survivors. However, total body cooling does not significantly reduce the combined rate of death or severe disability.[10]

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BLEEDING DISORDERS IN PREGNANCY, INCLUDING THROMBOCYTOPENIA

Naim Akhtar

The fine physiological haemostatic balance between haemostasis and fibrinolysis is shifted in pregnancy to favour pro-coagulation (Box 1). As a consequence, Virchow's triad of coagulation, vessel wall damage, and flow rate is affected, making venous thromboembolic disease a potential problem. Bleeding may result from the resulting disequilibrium and subsequent anticoagulation therapy.

Bleeding in pregnancy may result predominantly from a coagulation defect or deficiency (coagulopathy), or a reduction or functional defect in platelets (thrombocytopathies). Both may arise from inherent tendencies or may be acquired (Box 2).

Box 1 Physiological coagulation changes in pregnancy

- Predominantly pro-haemostatic changes (shortened clotting times)
  - increased fibrinogen concentration
  - increased factor VIII and other coagulation factors
- Increased plasminogen activator inhibitor concentration (reduced systemic fibrinolytic capacity)
- Reduced protein S concentration
- Increased protein C concentration

Box 2 Bleeding disorders in pregnancy

Coagulation disorders

Congenital and inherited

- Haemophilia A (Factor VIII deficiency)
- Haemophilia B (Factor IX deficiency)
- Haemophilia C (Factor XI deficiency)
- Von Willebrand's disease
- Rarer factor deficiencies (Factors XIII, X)

Acquired

- Disseminated intravascular coagulopathy (DIC)
- Coagulopathy associated with severe sepsis
- Coagulopathy associated with acute promyelocytic leukaemia
- Coagulopathy associated with massive blood loss
- Coagulopathy associated with renal and hepatic disease
- Acquired inhibitors of coagulation – antiphospholipid syndromes
- Acquired inhibitors of coagulation – Factor VIII antibodies
- Thrombotic thrombocytopenic purpura (TTP)
- Other thrombotic microangiopathies

Thrombocytopathies (platelet disorders)

Congenital and inherited

- Inherited thrombocytopenia and functional defects
- Drugs/chemicals (ethanol, thiazides, oestrogens)
- Isoimmune (neonatal alloimmune) thrombocytopenia
- Bone marrow infiltration (mucopolysaccharidosis)
- Congenital infections (cytomegalovirus, toxoplasmosis, rubella)

Acquired

- Gestational thrombocytopenia
- Immune thrombocytopenia
- Associated with pregnancy-induced hypertension
- Drug induced (heparin, quinine, zidovudine, sulphonamides)
- Antiphospholipid syndromes
- Associated with human immunodeficiency virus infection
- Other secondary causes (DIC, TTP, hypersplenism)

Coagulation disorders

The inherited coagulation bleeding disorders are all relatively uncommon and can be classified as follows.

Common (20–100 cases per million):

- haemophilia A, an X-linked Factor VIII-deficient or -defective condition;
- haemophilia B, an X-linked Factor IX-deficient or -defective condition;
- von Willebrand's disease (vWD), an autosomal dominant or recessive condition resulting in deficient or defective von Willebrand factor (vWF).

Rare (up to 1 case per million):

- haemophilia C, an autosomal dominant or recessive condition resulting in Factor XI deficiency, common in Ashkenazi Jews;
- autosomal recessive conditions resulting in deficiencies of Factors X, V, VII, II, XIII, combined V + VIII, afibrinogenaemia, and dysfibrinogenaemia.

In haemophilia A, females are carriers and 50 per cent will have sufficiently low levels of Factor VIII to require replacement therapy to cover surgery, including caesarean section. True haemophilia A is rare (in a child of a carrier and an affected male, or in Turner's syndrome).

However, the most common reason for a female to have Factor VIII deficiency is vWD. vWD is easily distinguished by the demonstration of reduction in vWF antigen immunologically and by a prolonged bleeding time (failure of vWF in assisting platelets to adhere to cut surfaces). Up to 20 per cent of women with menorrhagia have undiagnosed vWD. However, during pregnancy, vWF rises to normal or low normal range, except in the rare severe type 3 disease.

The rarer congenital bleeding disorders have a higher incidence where consanguineous marriages are frequent (Muslims, India). These conditions are generally heterogeneous and have a relatively mild presentation.

Factor XI deficiency is prevalent in Ashkenazi Jews, with a heterozygosity as high as 8 per cent, but they are mildly affected. In studies with Iranian non-Jews, no correlation was found between clinical bleeding and moderate/severe deficiency (Factor XI <5 per cent), and mild deficiency (6–30 per cent). Both groups had a mild bleeding diathesis, with 25 per cent having muscle haematomas and haemarthrosis, and 50 per cent oral or postoperative bleeding. Women requiring caesarean section should be covered with Factor XI concentrate or fresh-frozen plasma.

Factor XIII deficiency is associated with a severe bleeding tendency, affecting mucosal and skeletal surfaces (mouth bleeding, epistaxis, haematomas, haemarthrosis). Up to 20 per cent of women of reproductive age will have an intraperitoneal bleed, with some requiring hysterectomy. A total of 50 per cent of pregnant women will have had at least one miscarriage.

Factor X deficiency is associated with haematomas and haemarthrosis in two-thirds of patients, and some with gastrointestinal bleeding.

The acquired coagulopathies are more common in pregnancy and may complicate many high-risk pregnancies, and are particularly associated with obstetric calamities such as amniotic fluid embolism and abruptio placentae. The coagulopathy is defined on the basis of prolonged coagulation times, consumptive thrombocytopenia, and increased fibrinolysis (Table 1). This helps to distinguish other causes of a thrombotic microangiopathy (Table 2).

In a clinical assessment of a patient that reveals continual oozing from sites of venous access and mucosal surfaces (bleeding from gums, epistaxis), the differential diagnosis of the main causes include:

- disseminated intravascular coagulopathy;
- coagulopathy associated with severe sepsis;
- massive blood loss;
- hepatic dysfunction or disease;
- renal disease;
- acquired inhibitors of coagulation.

Disseminated intravascular coagulopathy (DIC) is common in obstetrical practice, with multiple contributing factors (Box 3). Direct activation of coagulation causes DIC in amniotic fluid embolism, and also via leakage of thromboplastin into the maternal circulation in placental abruption.

Table 1 Simple laboratory screening tests in acquired coagulation disorders

Test	Description
Coagulation	
Prothrombin time (PT)	Prolonged PT, APTT (perform 50:50 mix with normal plasma to correct for factor deficiencies)
Activated partial thromboplastin time (APTT)	
Thrombin time (TT)	Prolonged TT (perform reptilase to exclude heparin effect)
Fibrinogen assay	Reduced fibrinogen
Platelets	
Absolute count	Blood film inspection for clumps, confirm reduction and morphology
Function	Bleeding time (skin template or PFA 100)
Fibrinolysis	
Fibrin degradation products (FDPs)	Increased FDPs
Accelerated clot lysis	Enhanced euglobulin clot lysis time

PFA, platelet function analyser.

Table 2 Differential diagnosis of thrombotic microangiopathies

Condition	Specific tests
Disseminated intravascular coagulopathy	Raised fibrin degradation products, D-dimers, reduced fibrinogen, prolonged PT/APTT
Pre-eclampsia/HELLP	Raised transaminases
SLE/scleroderma/ vasculitis/APS	Positive ANA, anticardiolipin antibodies, lupus anticoagulant
Evans' syndrome (haemolysis and ITP)	Positive direct Coombs' test
Haemagglutinin inhibition test	Platelet-associated and heparin antibodies
TTP/HUS	ADAMTS-13 absent

ADAMTS-13, a disintegrin and metalloproteinase with thrombospondin motif 13; ANA, antibody to nuclear antigen; APS, antiphospholipid antibody syndrome; APTT, activated partial thromboplastin time; FDPs, fibrin degradation products; HELLP, haemolysis, elevated liver enzymes, low platelets; HUS, haemolytic uraemic syndrome; ITP, immune thrombocytopenic purpura; PT, prothrombin time; SLE, systemic lupus erythematosus; TTP, thrombotic thrombocytopenic purpura.

In patients with a thrombotic microangiopathy, the haematologist should be asked to help distinguish several related causes on the basis of simple coagulation tests, blood film examination, and specific confirmatory tests. The differential diagnosis and important distinguishing features are enumerated in Table 2.

Box 3 Contributing factors of disseminated intravascular coagulopathy in obstetrical practice

- Sepsis/severe infection
- Birth trauma/surgical intervention
- Obstetrical calamities (amniotic fluid embolism, abruptio placentae)
- Toxic/immunological reactions (transfusion reactions, recreational drugs)
- Massive blood loss with inadequate replacement therapy
- Co-morbidities (diabetes, heart failure, renal/liver disease, sickle cell disease, underlying malignancy)

Thrombotic thrombocytopenic purpura (TTP) is an uncommon but potentially devastating condition, which may arise in pregnancy and the postpartum period. The consistent features are thrombocytopenia, microangiopathic haemolytic anaemia, and ischaemic symptoms due to widespread formation of thrombi in the terminal circulation of several organs resulting in neurological and renal manifestations.

Thrombotic thrombocytopenic purpura is rare (2–10 per million); it had a high mortality (80–90 per cent) until the introduction of plasma exchange, but it is still around 10–20 per cent. The condition is now known to be due to ADAMTS13 deficiency. ADAMTS13 (a disintegrin and metalloprotease with thrombospondin-13 repeats) is a plasma ion-dependent metalloproteinase (which cleaves endothelial-bound ultralarge vWF multimers). Failure to cleave vWF multimers leads to persistence in plasma and endothelial cells of ultralarge multimers, which tend to aggregate platelets. ADAMTS13 is, therefore, absent in TTP, but mild to moderate deficiency of ADAMTS13 has been found in pregnancy, liver disease, HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, inflammatory states, the postoperative period, and autoimmune diseases.

Thrombocytopathies (platelet disorders)

The clinical manifestations of a reduction in platelets or functional abnormality are characterised by:

- spontaneous or immediate bleeding after trauma;
- mucosal bleeding;

- petechiae or purpura;
- haemarthrosis or deep haematomas (rarely occur).

The congenital and inherited thrombocytopathies are uncommon (Box 4) but worthy of inclusion.

In neonatal alloimmune thrombocytopenia the maternal platelet count is normal, complicating 1 in 1000 to 2000 live births, with half of the cases presenting in primigravids. Haemorrhagic manifestations (petechiae, ecchymoses) are common, but 10–20 per cent of infants will have an intracranial haemorrhage in utero. Half of the cases are due to sensitisation and the development of alloantibody to the paternal human platelet antigen-1a (HPA-1a), also known as platelet antigen 1 (Pl-A1), present on the infant's platelets but lacking in the mother. The infant will be born severely haemorrhagic and thrombocytopenic (50 per cent of cases with a platelet count <20), and the treatment is to infuse HPA-1a-negative platelets or, if unavailable, the mother's harvested platelets to the infant. The recurrence rate is high: up to 100 per cent depending on the zygosity of the father. Infants in subsequent pregnancies will be equally or more severely affected.

Thrombocytopenia in pregnancy is relatively common, but it is important to be clear about definitions and terminology (Box 5). The main causes are listed in Box 6. Blood film examination will exclude pseudothrombocytopenia due to consumption, platelet clumps or in vitro aggregation. However, the common differential diagnosis is between the following:

- gestational thrombocytopenia;
- immune thrombocytopenia (ITP);
- associated with pregnancy-induced hypertension (PIH).

Box 4 Congenital and inherited platelet disorders

Congenital

Drugs/chemicals

- Maternal ingestion of ethanol, thiazides, oestrogens

Isoimmune

- Neonatal alloimmune thrombocytopenia (NATN)

Bone marrow infiltration

- Congenital leukaemia, mucopolysaccharidosis

Infections

- Maternal toxoplasmosis, cytomegalovirus, rubella, herpes simplex virus, hepatitis

Inherited

Thrombocytopenia with:

- Reduced platelet size (Wiskott–Aldrich syndrome)
- Normal platelet size (TAR [thrombocytopenia, absent radii] amegakaryocytosis)
- Increased platelet size (May–Hegglin anomaly)

Thrombocytopathies

Disorders of:

- Platelet adhesion (Bernard–Soulier syndrome)
- Platelet aggregation (Glanzmann's thrombasthenia)

Box 5 Thrombocytopenia in pregnancy

Definition and terminology

- Mild thrombocytopenia (100–150)
- Moderate (50–100)
- Severe (<50)

Differential diagnosis

- Increased platelet destruction – immune, abnormal platelet activation, consumption
- Decreased platelet production – leukaemia, aplastic anaemia, folate deficiency

Box 6 Causes of thrombocytopenia in pregnancy

- Gestational thrombocytopenia
- Pregnancy-induced hypertension
- HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome
- Pseudothrombocytopenia
- Human immunodeficiency virus infection
- Immune thrombocytopenic purpura
- Antiphospholipid syndromes
- Hypersplenism
- Disseminated intravascular coagulation
- Thrombotic thrombocytopenic purpura
- Haemolytic uraemic syndrome
- Congenital thrombocytopenia
- Drug-induced (heparin, quinine, quinidine, zidovudine, sulphonamides)

Gestational thrombocytopenia is common (8 per cent of pregnancies) and mild (invariably with a platelet count over 70, usually over 100). There are no clinical manifestations or bleeding, and it is usually picked up incidentally on routine full blood count. The platelet count returns to normal 2–12 weeks after delivery. There is therefore an extremely low risk of fetal or neonatal thrombocytopenia. The aetiology remains uncertain, but is perhaps related to accelerated platelet consumption.

Immune thrombocytopenia complicated between 1 in 1000 and 10,000 pregnancies, resulting from the presence of an immunoglobulin G (IgG) antiplatelet antibody and immune-mediated platelet destruction. However, with the variable detection of the platelet-associated antibody, the diagnosis remains one of exclusion, namely:

- persistent thrombocytopenia <100;
- normal or increased megakaryocytes on bone marrow examination;
- exclusion of other systemic disorders or splenomegaly.

The symptoms are usually mild both for the mother (easy bruising, gingival bleeding) and infant (minor bleeding associated with thrombocytopenia; approximately 10 per cent will have platelets <50). Serious bleeding occurs in about 3 per cent of affected infants, with intracranial haemorrhage in less than 1 per cent. The infant platelet count nadir will be several days after delivery.

There is incomplete correlation between maternal and fetal thrombocytopenia and outcome. However, the maternal platelet count is used as a surrogate marker, and corticosteroid therapy is indicated (1 mg/kg/d) when the platelet count is below 80 or falling rapidly. Nearer term, intravenous immunoglobulin is used (0.4 g/kg/d) for a more rapid response. The exact mechanism of action of these therapies is unknown, but involves immune suppression and blockade to some degree.

Pregnancy-induced hypertension accounts for 21 per cent of maternal thrombocytopenia in pregnancy, is usually moderate and rarely below 20. In 10 per cent of cases, it is associated with a microangiopathic blood picture and haemolysis and elevated liver enzymes – the HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome. The cause is unknown but is likely to be multifactorial; the management is expectant with replacement therapy of blood products and early delivery, where indicated.

BLEEDING IN CHILDHOOD (VAGINAL)

Madhavi Kalidindi

Vaginal bleeding in childhood is a rare but serious condition and should always be evaluated promptly. The main causes of vaginal bleeding in children are listed in Box 1 and Figure 1.

A foreign body is most commonly responsible for vaginal bleeding in paediatric patients. Bleeding in the presence of a foul-smelling discharge is suggestive of a foreign body in the vagina. Ultrasonography is often helpful, but vaginoscopy confirms diagnosis and also allows removal of the foreign body under direct vision using a very narrow hysteroscope under GA. The irrigating fluid may flush the foreign body out.

Vulvovaginitis: Poor hygiene often contributes to recurrent vulvovaginitis, and appropriate advice is necessary regarding personal hygiene. External application of bland emollient barriers may be helpful. Vulvovaginitis may be caused by respiratory, oral,

Box 1 Common causes of vaginal bleeding in childhood

- Foreign body
- Vulvovaginitis
- Trauma, which may or may not be associated with sexual abuse
- Tumour / neoplasms
  - Haemangioma of vulva
  - Benign papilloma of vagina
  - Functional ovarian cyst
  - Sarcoma botryoides / embryonal rhabdomyosarcoma
  - Germ cell tumours – endodermal sinus tumours / yolk sac tumours
  - Granulosa cell tumour of the ovary
- Hormonal
  - Precocious puberty
  - Exposure to exogenous oestrogen / sex steroids
- Dermatological
  - Lichen sclerosus
- Urogenital
  - Urethral prolapse
  - Haemorrhagic cystitis
- Bleeding diathesis

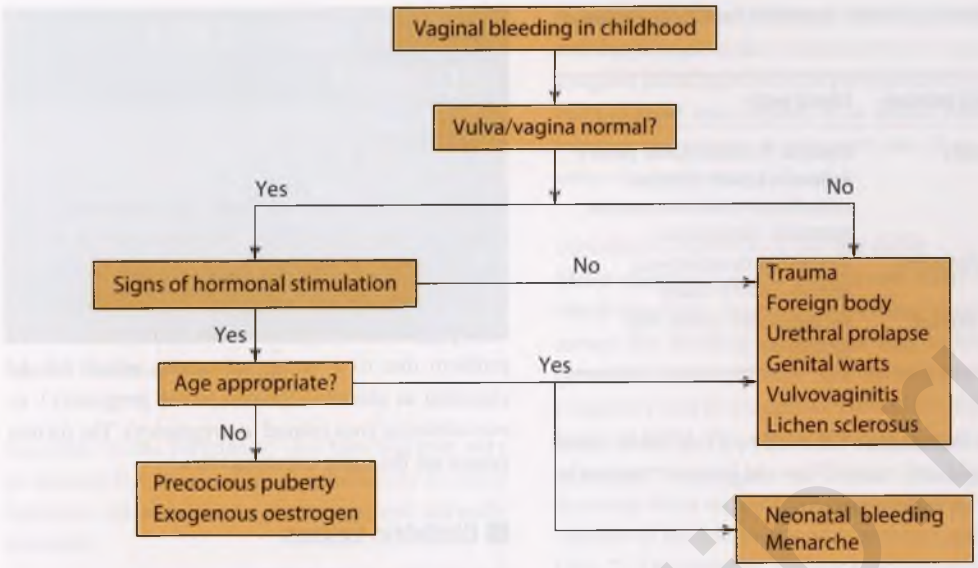

Figure 1 Algorithm for vaginal bleeding in childhood.

or faecal pathogens causing purulent serosanguinous drainage or cause vulvar irritation or excoriation of the skin.

Trauma: Most injuries to the genital area are accidental, blunt, and non-penetrating. Blunt injury may cause formation of a haematoma. A small vulvar haematoma can be managed by local pressure and analgesics.

The possibility of sexual abuse should be considered in every case where vaginal trauma is suspected. Penetrating injury warrants very careful examination and urgent communication with the hospital's paediatric team is of paramount importance if sexual abuse is suspected. It may be necessary to involve other agencies (police and social services). A good clinical practice is to organise a joint examination by a paediatrician trained in child sexual abuse and a forensic specialist for suspected sexual abuse so that the maximum information can be gathered with minimum discomfort to the child.

Hormonal: Vaginal bleeding could be the first manifestation of precocious puberty in a young girl. This is discussed in detail in Puberty.

Haemorrhagic cystitis: Adenovirus infection and drug toxicity (cyclophosphamide) are two common causes of haemorrhagic cystitis. It usually presents with sterile haematuria, dysuria, frequency, and urgency. Viral infection is self-limiting, while the drug toxicity resolves after withdrawal of treatment.

Urethral prolapse, although uncommon, is a known cause of painless vaginal bleeding or urinary symptoms. This is characterised by the circular eversion of the urethral mucosa at the meatus, forming a smooth, dusky red or purplish annular mass, with a characteristic doughnut shape and central lumen between the labia majora. Typically it happens in girls aged 2–10 years. Often this responds to topical oestrogen.

Benign and malignant tumours of the vulva may present as vaginal bleeding. Capillary venous malformation of the labia majora has been reported as a cause of vaginal bleeding in children. The differential diagnoses include capillary haemangioma and other vascular malformation. The malformation can be locally excised.

Sarcoma botryoides is a vaginal carcinoma that occurs primarily in girls under the age of 2 years (90 per cent are under the age of 5). Mesonephric carcinoma commonly affects girls above the age of 3 years. Clear cell adenocarcinoma is often associated with antenatal exposure to diethylstilbestrol. Malignant germ cell tumours account for 3 per cent of childhood cancers and endodermal sinus tumour, also called yolk sac tumour, is the most common type. Suspicion of any of these conditions warrants urgent referral to a paediatric oncologist for confirmation of diagnosis, treatment, and counselling.

Blood dyscrasias responsible for vaginal bleeding in a child are listed in Table 1. A detailed history and

Table 1 Bleeding disorders responsible for vaginal bleeding in childhood

Underlying pathology	Clinical entity
Low platelets	Idiopathic thrombocytopenic purpura, leukaemia, aplastic anaemia, chemotherapy-related bone marrow depression, hypersplenism
Platelet dysfunction	Glanzmann's thrombasthenia, Bernard–Soulier's disease
Clotting disorders	Von Willebrand's disease, liver dysfunction

systemic examination followed by a full blood count and coagulation screen are diagnostic. Treatment depends on the primary cause.

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BLEEDING DURING EARLY PREGNANCY

Mala Arora

Bleeding in the first trimester of pregnancy may occur in one-fifth of all pregnancies, of which nearly half miscarry.[1] The incidence of spontaneous abortion/miscarriage is estimated at 15–22 per cent of all pregnancies. It is thus a commonly encountered problem due to a variety of causes, which can be classified as obstetric (related to the pregnancy), or non-obstetric (not related to pregnancy). The former causes are the more common ones.

Obstetric causes

Bleeding with viable embryo

This can be ascertained only by performing an ultrasound scan. It is generally believed that bleeding from the uterine cavity in early pregnancy is associated with fetal demise.

However, in some patients there may bleeding at the time of the missed menstrual period for the first couple of months of the pregnancy owing to shedding of the decidua parietalis.

It has also been clinically observed that embryos with karyotypical abnormalities, e.g. trisomies, monosomies, or Robertsonian translocations, can present as an early threatened miscarriage; the pregnancy may continue, however, but there is an increased incidence of intrauterine growth restriction, hydrops fetalis, and stillbirth.

In rare instances of bicornuate uterus, there may cyclical bleeding from the non-pregnant horn.

Low implantation of the gestational sac

The site of implantation occurs in the fundus or body of the uterus in the majority of pregnancies. However, sometimes it may implant in the lower segment and, as the lower uterine segment stretches to accommodate the growing sac, there may be bleeding. In this case the pregnancy may develop a placenta praevia, and subsequent haemorrhage may occur later in the pregnancy.

Retrochorionic bleeding

In patients with early pregnancy bleeding there may be ultrasound evidence of retrochorionic collection of blood (Fig. 1). This is analogous to abruptio

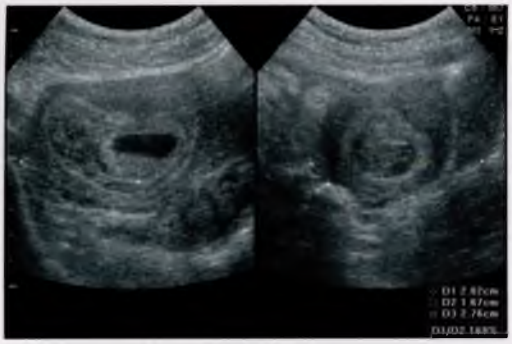

Figure 1 Retroplacental haematoma.

placentae in late pregnancy. This bleeding may vary in amount but may resolve spontaneously in many instances, allowing the pregnancy proceed normally thereafter.

Multifetal gestation

In pregnancies induced by artificial reproductive techniques (ART) there may be multifetal gestation of the higher order, such as quintuplets or sextuplets. This may result in bleeding due to distension of the lower segment. In the UK, this is regulated by the HFEA (Human Fertilisation and Embryology Authority).

Bleeding with a non-viable embryo

This can be due to a variety of causes, as described below.

Missed miscarriage

This occurs when fetal growth is arrested in early pregnancy, usually within the first 8 weeks, but the products have not been expelled. The cause of fetal demise could be intrinsic to the embryo, such as karyotypical abnormalities or extrinsic in its environment. The first manifestation of this condition may be bleeding or discharge in early pregnancy. The bleeding may be painless initially but is later accompanied by uterine cramps. In some cases, the symptoms of early pregnancy resolve without any bleeding. Occasionally, a routine ultrasound scan will diagnose a missed miscarriage before the bleeding becomes obvious.

Ectopic pregnancy

The main symptom of an ectopic or tubal pregnancy is a period of amenorrhoea or menstrual upset with pain which may be accompanied by vaginal bleeding in many cases. The bleeding is due to shedding of the decidua formed in the uterine cavity. In women with irregular bleeding where the periods have previously been normal and regular, it is worth considering whether the woman is pregnant and, if so, exactly where the pregnancy is located.

Gestational trophoblastic disease (GTD)

Molar pregnancy is the commonest form of GTD, which manifests classically as bleeding in early pregnancy. The bleeding in this case may be heavy and persistent, often painless. The other symptoms of pregnancy may be exaggerated due to the high serum levels of HCG. The uterus is larger than the period of amenorrhea and has a soft boggy feel. Ultrasound scan may show an absence of gestational sac, and the interior of the uterus has a 'snowstorm' appearance (Fig. 2). Occasionally, a viable embryo may be present with gestational trophoblastic disease (Fig. 3).

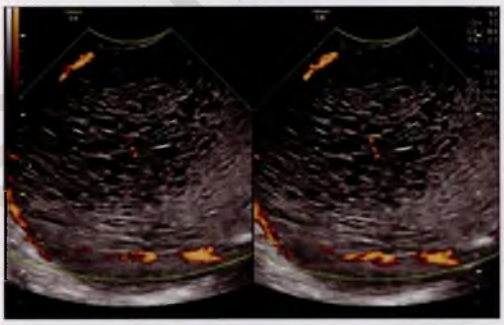

Figure 2 Molar pregnancy (courtesy The Ultrasound Lab, New Delhi, India).

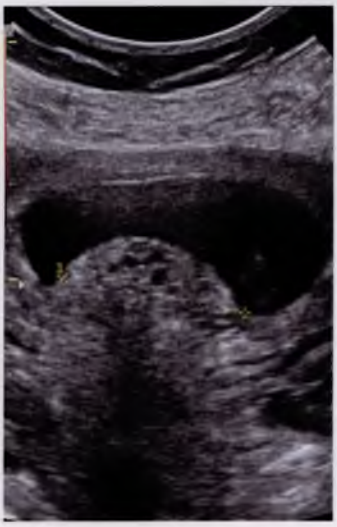

Figure 3 Gestational trophoblastic disease with a viable embryo.

The cause is genetic. At the time of fertilisation, the genetic component of the oocyte is lost and both genetic components are derived from the paternal germ line. The chromosomal composition is 46XX.

Vanishing twin syndrome

Pregnancy may start as a twin gestation but then, for some reason, one of the twins may stop growing at an early stage. The non-viable sac is then absorbed gradually but may result in bleeding during this period. In this case the bleeding consists of altered brown blood, and may or may not be accompanied by cramps.

Vasa praevia

The presence of a blood vessel on the underside of the gestational sac will lead to bleeding from that vessel as the gestational sac grows. This bleeding is more commonly seen in the second and third trimester, but occasionally can occur in the first trimester. (See Bleeding in late pregnancy.)

Non-obstetric causes

These are listed in Box 1.

Box 1 Non-obstetric causes of bleeding *per vaginam*

Cervical
- Cervical polyps
- Cervical ectropion
- Cervical pregnancy
- Cervical cancer

Vaginal
- Trichomonas vaginitis
- Bacterial vaginosis
- Foreign bodies in the vagina
- Vaginal tumours

Bleeding disorders
- Thrombocytopenia
- Haemophilia
- Von Willebrand disease

Drug induced
- Heparin
- Aspirin
- Warfarin

Cervical

Bleeding from the cervix can be due to the following. (See also Cervical swelling.)

Cervical polyps

These are benign lesions that can be fibrous or myomatous in nature. They may be small or large, and are seen protruding through the cervical os. Very often they can be easily avulsed in the outpatient setting and sent for histopathological examination.

Cervical ectropion

Prior to puberty the squamocolumnar junction is within the endocervical canal. As a result of puberty, the pill, or pregnancy, the columnar epithelium everts and comes to face the vagina. This will cause metaplasia, in that the columnar epithelium will change to squamous cells. The area can become inflamed and develop cervicitis. The cervix appears reddened, as the columnar epithelium is one cell thick and thus translucent, giving the impression of vascularity beneath. Likewise it can be easily traumatised and can develop contact bleeding (smear or coitus). If significant, it can be treated with cautery or cryotherapy. This should probably be avoided in pregnancy unless absolutely essential. Colposcopy may be indicated if there is any suspicion of malignancy.

Cervical pregnancy

The cervix is a rare site for ectopic pregnancy. This can be a cause of bleeding and may also be difficult to treat or remove surgically owing to the possibility of haemorrhage.

Cervical cancer

This may be a squamous cell carcinoma or adenocarcinoma. The age of presentation of cervical cancer is in the reproductive age group. Hence it can occasionally present for the first time in pregnancy.

Vaginal

Bleeding from the vagina can be due to the following:

- vaginitis, most commonly due to vaginal thrush, which is common in early pregnancy;
- *Trichomonas vaginalis*, which may cause vaginitis, and which presents as bleeding;

- bacterial vaginosis, which is a mixed infection of the vagina by organisms of low virulence, such as *Peptostreptococcus* and *Ureaplasma urealyticum*;
- foreign bodies in the vagina, the commonest being forgotten tampons, which may also present with a blood-mixed discharge;
- vaginal polyps and malignancy are rare causes of vaginal bleeding during pregnancy.

Bleeding disorders

Bleeding disorders, such as thrombocytopenia, haemophilia, and von Willebrand disease, may cause bleeding, although haemophilia is rare in women. However, Christmas disease does occur in women.

Drug induced

The use of heparin, aspirin, or warfarin during pregnancy may lead to spontaneous bleeding.

Bleeding from other sites

Bleeding haemorrhoids are often confused with vaginal bleeding. Similarly, lesions on the vulva, such as haemangiomas that bleed, may present as vaginal bleeding.

Diagnosis and investigations

Bleeding in early pregnancy is most often from the uterus in the form of threatened miscarriage: a careful history of the amount of bleeding and any accompanying pain should be elicited. Prior to the advent of ultrasound, a prediction of viability was made based on signs and symptoms.[2] Today, a transvaginal ultrasound scan should be performed in all cases. It has been elucidated that clinical judgement is not a valid substitute for ultrasonographic assessment;[3] a transvaginal scan has become the gold standard for diagnosing the cause of early pregnancy bleeding. It will diagnose all obstetric causes of bleeding. However, it is not able to predict an abnormal karyotype in early pregnancy,[4] and will only give a snapshot in time and may have limited predictive value.

Gentle speculum examination should be performed if the cause is suspected to be local.

Cervical (Pap) smears are usually avoided in pregnancy, but can be performed opportunistically if the woman has a poor attendance record. If no local cause is detected, the patient's coagulation profile should be evaluated.

In all cases, a blood group should be obtained and consideration given to administering anti-D, if the bleeding is excessive or if any operative procedure needs to be undertaken, e.g. evacuation of retained products of conception.

Explanation of terminology of miscarriages (abortions; Fig. 4)

- *Threatened miscarriage* is defined as the presence of bleeding with an intrauterine gestational sac when the cervical os is closed. The embryo may be viable, in which case the pregnancy will continue, or it may be non-viable as in a missed abortion.
- *Inevitable miscarriage* is defined as bleeding in early pregnancy with an intrauterine gestational sac and an

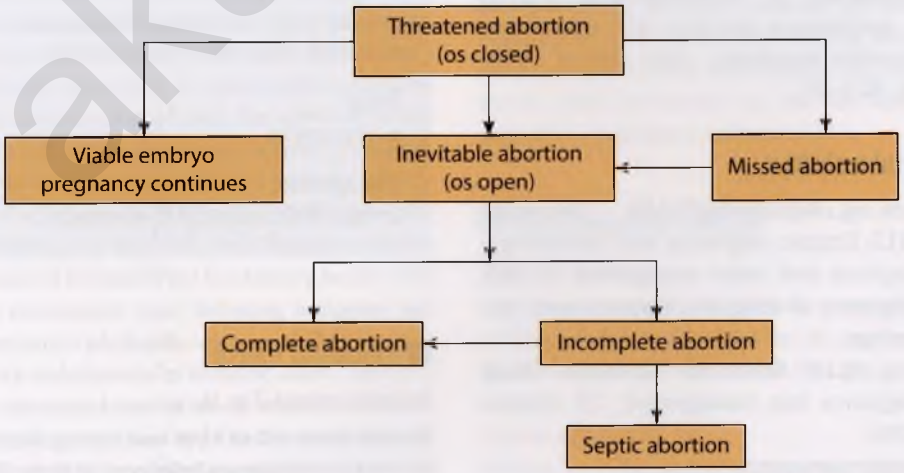

Figure 4 Bleeding in pregnancy.

open cervical os. In this case, the pregnancy will abort and there may be associated pain.

- *Incomplete miscarriage* is defined as bleeding with the presence of retained products of conception within the uterine cavity.
- *Spontaneous miscarriage:* complete expulsion of the products of conception from the uterine cavity is defined as 'spontaneous complete abortion'.
- *Induced medical miscarriage:* growth of a pregnancy disrupted by administration of tablets of mifepristone (antiprogesterone) or misoprostol (prostaglandin).
- *Induced surgical miscarriage:* pregnancy terminated by dilatation and curettage or suction evacuation.
- *Medical termination of pregnancy* is synonymous with induced medical termination and may occur up to 9 weeks' gestation.
- *Septic miscarriage* is defined as incomplete abortion with intrauterine infection of retained products of conception.

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Useful websites

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BLEEDING IN LATE PREGNANCY (ANTEPARTUM HAEMORRHAGE)

C Jayalath and Dilip Visvanathan

Antepartum haemorrhage (APH) is defined as bleeding from or in the genital tract after 24 weeks of pregnancy and prior to the delivery of the baby (Box 1). APH complicates 2–5 per cent of pregnancies and is a leading cause of maternal mortality, morbidity, and perinatal mortality worldwide, especially in women who live in areas of conflict or in rural areas with a poor transport infrastructure. Twenty per cent of very preterm babies are born in association with APH, as the subsequent impaired placental perfusion and fetal hypoxia can cause severe neurological injury or even fetal death. Every woman who presents with an APH must therefore be appropriately triaged to prevent and minimise both maternal and fetal complications. Any bleeding in pregnancy is a cause of anxiety and stress for the mother and their carer.

Box 1 Classification of the causes of APH

Placental causes
- Placenta praevia
- Abruption of placenta

Non-placental causes

Maternal
- Local causes coincidental to the pregnancy
- A bloody 'show' with the onset of labour

Fetal
- Vasa praevia

Unexplained
- Where the cause cannot be identified

Placental causes

Placenta praevia (Fig. 1)

The incidence is 2 to 5 per cent of pregnancies after 24 weeks, reducing to 1 per cent at term. The placenta implants in the lower part of the uterus either

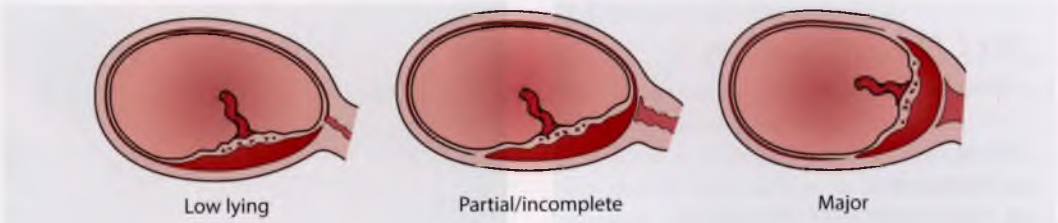

Figure 1 Diagram of placenta praevia.

in whole or in part. This will account for 30 per cent of cases of bleeding in late pregnancy. Risk factors for placenta praevia include previous caesarean section, previous termination of pregnancy, multiparity, advanced maternal age, multiple pregnancy, deficient endometrium due to a uterine scar, endometritis, and a previous history of manual removal of placenta.

An ultrasound scan performed at 20 weeks will detect whether the placenta praevia is reaching or covering the internal cervical os. A low-lying placenta usually appears to move upwards as the lower segment develops below it from 30 weeks of pregnancy onwards. All women in the UK have an anomaly scan at around 20 weeks' gestation. At this scan the location of the placenta is confirmed. If the leading edge of the placenta has completely covered the os, a major placenta praevia at term is more likely. In this situation and where there is an overlying scar, a repeat ultrasound scan at 32 weeks' gestation would enable confirmation of the diagnosis, thereby allowing for planning of the mode and timing of delivery. The sensitivity of transabdominal ultrasound scans is less accurate especially for posterior placenta praevia, whereas a transvaginal ultrasound is more effective in delineating the lower edge of the placenta. An anterior placenta praevia in a woman with a previous caesarean section should alert the clinician to the possibility of a placenta accreta. Doppler ultrasound can be used to detect extra uterine vascular anastomoses. Magnetic resonance imaging (MRI) is helpful in establishing the diagnosis. Early diagnosis enables the woman to be transferred to a tertiary facility with a multi-professional team including urologists and interventional radiologists who are skilled in uterine artery embolisation in obstetric cases. Third trimester ultrasound scan at 30–32 weeks is indicated in high-risk women and at 34 weeks where there is a likelihood that the placenta would be clear of the lower segment.

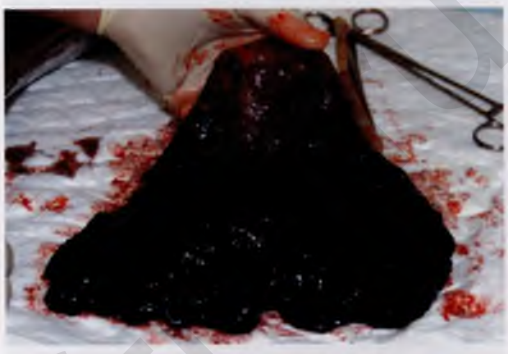

Figure 2 Abruption: a large retroplacental clot attached found at emergency caesarean section at 30 weeks' gestation.

Placental abruption (Fig. 2)

Abruption is the premature separation of the placenta and occurs in 1 per cent of pregnancies. This condition accounts for 20 per cent of cases of bleeding in late pregnancy. The best predictive factor for abruption is a history of a previous abruption, with a 4 per cent risk for one to a 20–25 per cent risk for two previous abruptions. Other risk factors for abruption include pre-eclampsia, fetal growth restriction, polyhydramnios, advanced maternal age, premature rupture of membranes, low BMI, smoking, recreational drug use (amphetamine and cocaine), and abdominal trauma (both accidental, e.g. seat belt injury, and deliberate, e.g. domestic violence).

Non-placental causes

Maternal causes

A systematic way of looking at local causes of bleeding in later pregnancy is to consider the anatomy from the vulva up to the placental site (Box 2).

Uterine rupture (Fig. 3)

Uterine rupture is a rare but important cause of late APH due to the risk of fetal and possible maternal

Box 2 Non-placental causes of bleeding in late pregnancy

Vulval
- Vulval varices
- Trauma to vulva at the site of piercings
- Rupture of a vulval abscess
- Trauma to rapidly growing or extensive genital warts

Urethral
- Urethral polyps
- Urethral warts
- Paraurethral abscess rupture
- Urethral rupture, e.g. self-catheterising in paraplegic women

Vaginal
- Infections
- Trichomoniasis
- Candidiasis

Cervical
- Cervical ectropion
- Infected nabothian follicle
- Passage of cervical mucus plug or blood
- Polyp
- Cervical warts
- Carcinoma cervix – squamous and adenocarcinoma

Uterine
- Uterine rupture

Anal (need to be excluded)
- Haemorrhoids
- Anorectal carcinoma – unusual in this age group
- Ulcerative colitis, pre-existing IBD

death. It should be considered in all women but especially in those with the following risk factors:

- previous caesarean section especially with a classical scar;
- myomectomy;
- uterine perforation from evacuation of retained products of conception;
- transcervical resection procedures;
- A thinned-out myometrium from grand multiparity and obstructed labour in a multiparous woman are causes of uterine rupture in the absence of a scar.

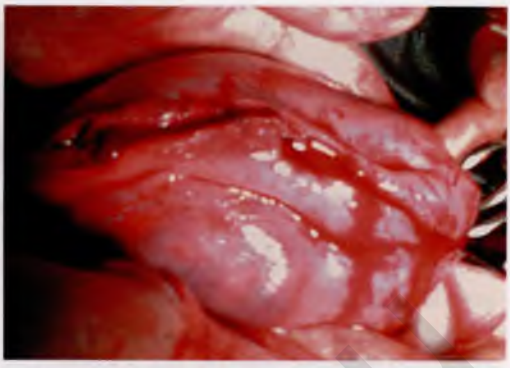

Figure 3 Spontaneous uterine rupture, in this case in an *in vitro* fertilisation twin pregnancy at 35 weeks' gestation.

- Spontaneous rupture of the uterus in a nulliparous woman with no risk factors has also been described but is fortunately rare.
- Induction of labour with prostaglandins with subsequent stimulation with Syntocinon increases the risk. Therefore, care must be taken if both agents are used.

The classical presentation of uterine rupture is the triad of continuous pain over the uterus, a fall off of the uterine contractions, and an abnormal cardiotocograph (CTG). The earliest sign is an abnormal CTG, and therefore all these women must have continuous electronic fetal monitoring in labour. Early diagnosis and recourse to emergency lower segment caesarean section (LSCS) is imperative to prevent fetal loss and even maternal death.

Traumatic causes

During pregnancy the genital tract increases in vascularity, and so trauma to any par of the genital tract can cause significant bleeding. Causes include:

- laceration following fall;
- sexual assault;
- foreign body;
- traumatic use of sex toys, from circumferential injury at the introitus to a tear at the vaginal fornices due to deep penetrative injury; the latter can cause profound bleeding.

Fetal causes

Vasa praevia (Fig. 4)

Fetal blood vessels can pass through the membranes without any underlying support from placental tissue or from the cord. When these vessels are below the presenting part in the region of the internal os the term *vasa praevia* is used. Vasa praevia can occur

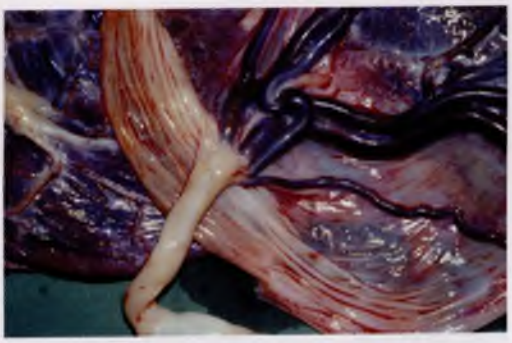

Figure 4 Blood vessel in the membranes of the amniotic sac. If this occurred over the cervix, it would be a vasa praevia.

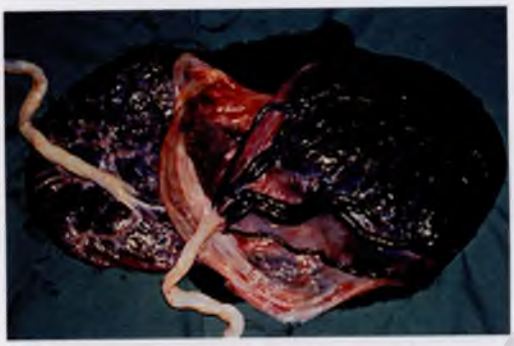

Figure 5 Placenta from twin pregnancy with velamentous insertion of cord on the right hand placenta.

with the presence of a succenturiate lobe where there is velamentous insertion (Type 1: Fig. 5) or when the vessels run between a placenta with one or more accessory lobes (Type 2). These vessels may rupture with either spontaneous or artificial rupture of membranes, causing significant fetal haemorrhage and even death. Fortunately the incidence is rare, occurring once every 2000–3000 pregnancies. The symptoms are usually fresh vaginal bleeding at the time of membrane rupture and CTG abnormalities, which include fetal decelerations, bradycardia, or a sinusoidal trace. The attendant fetal mortality rate can be as high as 60 per cent.[1]

Unexplained APH

When a cause for bleeding cannot be established it is labelled an unexplained APH. It can be due to multiple mild abruptions (separations) at the periphery of the placenta. Unexplained APH is associated with preterm delivery, stillbirth, small for gestational age, and babies who are more likely to be admitted to neonatal intensive care units.

Clinical assessment in APH

Effective clinical assessment is important, as urgent intervention may be required to reduce maternal and fetal compromise. Clinical assessment may need to be undertaken while the history is being taken. It has been shown that blood loss in APH is often underestimated, as much of the blood may be concealed within the uterus. The earliest signs of hypovolaemia are a rise in respiratory rate, a delay in capillary refill time, and an abnormality of the cardiotocograph. Hypotension may be a late sign in young healthy women who compensate well initially. Women with these signs should be stabilised and immediately transferred to a consultant-led unit or any facility where an emergency delivery and transfusion of the mother can be performed. All units should have a massive obstetric haemorrhage protocol which includes contacting the haematologist on call for advice regarding the use of blood products.

In women who are stable, the history should include the nature and amount of bleeding, the presence of pain, contractions, ruptured membranes, placental localisation at the last ultrasound scan, the result of the last cervical smear, and the rhesus status. Bleeding at the time of ruptured membranes may suggest vasa praevia. Sudden onset of painless, bright red vaginal bleeding may suggest placenta praevia. Women with placenta praevia may have a few episodes of warning bleeds before a major bleed, and admission for observation needs to be considered. Sudden onset of a severe continuous abdominal pain associated with darker bleeding may suggest placental abruption. Loss of fetal movements may suggest a placental cause. If the bleeding is associated with a thick mucoid plug, this may be a heavy show associated with the onset of labour. A history of domestic violence should be explored where there is an APH following trauma.

Examination

ABC of resuscitation should be performed and baseline readings recorded on the maternal early warning observation (MEOW) chart. A soft, non-tender abdomen with a high unengaged presenting part or abnormal lie is suggestive of placenta praevia. A tense or 'woody', tender uterus may indicate placental abruption. The uterus may be markedly tender all over or localised to where the placental abruption has occurred.

If the woman has not been booked in the index pregnancy, an ultrasound scan must precede a digital or a speculum vaginal examination to exclude a major placenta praevia, as examination may aggravate the bleeding. A speculum examination may help diagnose local causes of vaginal bleeding as well as help assess cervical dilatation.

Investigations to find the cause

Ultrasonography

Placenta praevia. Ultrasound is useful in diagnosing placenta praevia in the unbooked woman. As mentioned earlier a transvaginal ultrasound is more accurate than a transabdominal ultrasound. Transvaginal scans are especially useful in posterior placenta praevia. Doppler studies can help identify a placenta accreta.

Placental abruption. Ultrasound may not be helpful in an early abruption where the diagnosis is usually a clinical one.

Vasa praevia. If suspected (e.g. with a succenturiate lobe), a transvaginal ultrasound Doppler study can diagnose vasa praevia in the antenatal period. However, in a woman presenting with APH the diagnosis is clinical.

Investigations to assess the severity

After insertion of a wide bore cannula, a full blood count plus a blood group and save is important in order to obtain a baseline haemoglobin and platelet count. If there is massive obstetric haemorrhage, then 4–6 units of blood are cross matched and a baseline coagulation profile should be arranged. The massive obstetric protocol should be activated, with urgent anaesthetic and obstetric input at the consultant level.

Investigations to enable further management

Ideally, a Kleihauer test should be performed in rhesus-negative women to quantify fetomaternal haemorrhage so that the appropriate dose of anti-D may be calculated. It is not a sensitive test for the diagnosis of placental abruption. There is no evidence that there is any utility in doing this test in rhesus-positive women.

Placental abruption may be the clinical presentation of a woman with severe pre-eclampsia. The hypotension following blood loss may mask the hypertension. A catheter specimen of urine should be routinely checked for protein. It is important to consider this in all women with abruption and the protocol for the management of severe pre-eclampsia activated accordingly.

The age-old adage 'antepartum haemorrhage weakens, but it is the ensuing post-partum haemorrhage that kills' is still relevant. It is important that the massive obstetric haemorrhage protocol is activated, appropriate blood products are used with haemotological advice, and active management of the third stage of labour and early detection and treatment of a consumptive coagulopathy are done to prevent this from happening.

Useful website

http://www.rcog.org.uk – Green-top Guideline. No 63, November 2011.

BLEEDING, POSTMENOPAUSAL

Sabrina O'Dwyer

Definition

Postmenopausal bleeding (PMB) is defined as any vaginal bleeding that occurs after a 12-month duration of amenorrhoea resulting from menopause. This is by definition a retrospective diagnosis of amenorrhoea of 1-year duration due to failure of ovarian function. Confirmation of menopause by raised follicle-stimulating hormone (FSH) levels >30 U/mL is not necessary.

Any vaginal bleeding that occurs after 6 months of amenorrhoea from presumed menopause should be treated as suspicious. Investigations should be directed to determine the cause of bleeding depending on the age of the woman. It is important to remember that while the overall incidence of endometrial carcinoma in women with PMB is 10 per cent,[1] if the woman is over 50 years old, this risk is <1 per cent, and if she is over 80, the risk is 25 per cent. If she is obese, the risk is increased to 18 per cent, and to 21 per cent if diabetic. The risk is even higher if she is both obese and diabetic.[2] Finally, the risk of endometrial cancer in users of tamoxifen (as a treatment of breast cancer) is four-fold when used for five years or more.[1]

Common causes

These are summarised in Box 1 and considered in more detail below.

Box 1 Causes of postmenopausal bleeding

- Atrophic vaginitis
- Atrophic endometritis
- Uterine polyp – endometrial/fibroid
- Endometrial hyperplasia
- Endometrial neoplasia/carcinoma
- Intake of exogenous unopposed oestrogens
- Miscellaneous causes from the genital tract, such as:
  - Cervical neoplasia/dysplasia
  - Vulval neoplasia/dysplasia
  - Cervical polyp
  - Adnexal masses – benign or malignant
  - Trauma – vulvovaginal, perineal, pelvic
  - Chronic endometritis, e.g. tubercular
  - Uterine sarcoma
  - Pregnancy-associated bleeding
  - Foreign body (e.g. ring pessary)
- Systemic bleeding disorders and anticoagulation usage
- Non-vaginal causes often mistaken for vaginal bleeding, including:
  - Urethral caruncle
  - Cystitis
  - Urinary bladder polyp
  - Urinary bladder neoplasia
  - Anal haemorrhoids
  - Anal fissure
  - Rectal polyp
  - Carcinoma of rectum or anus

Atrophic vaginitis

Atrophic vaginitis is caused by non-specific vaginal irritation and extreme thinning of vaginal epithelium as a result of oestrogen deficiency. Because of atrophic changes, even the slightest of trauma from intercourse or dabbing oneself dry may result in bleeding. Apart from postmenopausal bleeding, it may also be associated with dyspareunia, vaginal pruritus, dryness, and pain. It is a common condition, which affects up to 45 per cent of postmenopausal women.

This condition is easily treated and prevented by the local application of oestrogen creams. As topical oestrogens have limited systemic absorption, they can be used in an unopposed nature in women with a uterus for a limited time span. Large trials have established that the various low-dose vaginal oestrogen preparations, used for 1 year unopposed, are not associated with endometrial hyperplasia or carcinoma.[3]

In women with a previous history of breast cancer, the risk of recurrence with the use of local low-dose oestrogen preparations is undefined. Consequently, most clinicians would use these preparations with caution and after counselling about the theoretical increased risk of oestrogen levels that can contribute to breast cancer recurrence.

Finally, systemic hormone replacement therapy (HRT) may be considered (combined with progesterone for women who have not undergone hysterectomy previously) if vaginal atrophy is associated with other menopausal symptoms, especially vasomotor ones.

Atrophic endometritis

Endometrial inflammation and thinning that occurs as a result of oestrogen deficiency is known as atrophic endometritis (Fig. 1). It may result in postmenopausal spotting or even bleeding, particularly in hypertensive women.

This is a diagnosis of exclusion, arrived at after the more sinister pathological causes of postmenopausal bleeding within the uterus have been excluded. Treatment, in the form of HRT, can be considered depending on severity of symptoms.

Uterine polyps

Uterine polyps are a common cause of postmenopausal bleeding. Endometrial polyps are usually inflammatory, but may occasionally have hyperplastic or neoplastic changes of the covering endometrium (Fig. 2). Uterine polyps can also be of fibroid origin and are much more common in a fibroid uterus, though they rarely become sarcomatous.

Intrauterine polyps may be identified on transvaginal ultrasound or seen just as thickened endometrium.

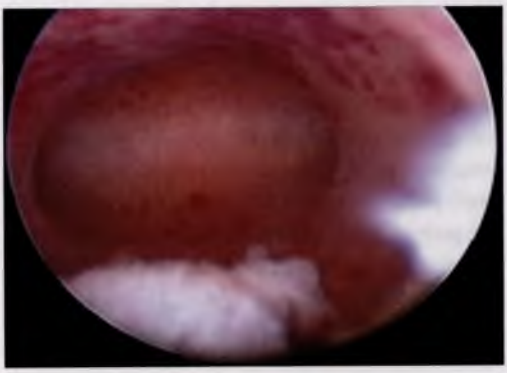

Figure 1 Hysteroscopic view of atrophic endometrial cavity.

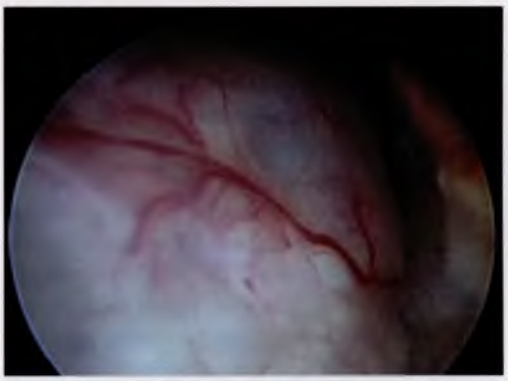

Figure 2 Hysteroscopic view of benign endometrial polyp.

Saline sonohysterography is a particularly useful diagnostic tool for identifying intrauterine polyps. However, hysteroscopy is able not only to confirm the presence of polyps, it can also be used to simultaneously remove them. Blind dilatation and curettage are no longer carried out, as a polyp can easily be missed, especially if it is on a mobile pedicle.

Endometrial hyperplasia

The term *hyperplasia* means 'thickened lining'. The classification of endometrial hyperplasia has been simplified as follows:

- simple hyperplasia (risk of malignancy 1 per cent);
- complex hyperplasia (risk of malignancy 3 per cent);
- simple hyperplasia with atypia (risk of malignancy 8 per cent);
- complex hyperplasia with atypia (risk of malignancy 22–30 per cent).

Hyperplasia without atypia can be treated with progestogen therapy (tablets or via the levonorgestrel intrauterine system) for 3 months followed by a repeat biopsy. If by then the hyperplasia has reverted to normal and the patient is asymptomatic, the progestogen therapy can be discontinued; with the levonorgestrel intra-uterine system, the device can remain in situ for the 5-year duration should the patient wish. If the hyperplasia without atypia persists, progestogen should be continued, with repeated sampling every 6 months to ensure atypia does not develop. Hysterectomy can also be discussed with the patient as an option if the woman's family is complete, particularly if she continues to suffer from troublesome bleeding.

If the hyperplasia has atypia, the patient should also be offered a hysterectomy because of its malignant potential. As a general rule, one would usually have a low threshold for surgical management, as the condition may well recur. Factors aiding the decision to undertake a hysterectomy will be presence of symptoms, the age, and the general medical condition of the postmenopausal woman.

It should be borne in mind that, in postmenopausal women, levels of circulating oestrogens are low. The development of hyperplasia may be reflective of continuous oestrogen stimulation with either exogenous or endogenous oestrogens. In patients with unexplained endogenous oestrogen production (e.g. non-obese patients), the possibility of a small undetected ovarian granulosa cell tumour must be investigated by assessing oestradiol and inhibin-A levels. A hysterectomy may be warranted in such patients with even simple hyperplasias without atypia after adequate counselling.

Endometrial neoplasia

Endometrial neoplasia (Fig. 3) and its grade are diagnosed on histopathological examination of endometrial tissue. It has to be managed after appropriately investigating and assessing the extent of disease. (See Uterine swellings for details.)

Intake of exogenous oestrogens

After the release of the 'Women's Health Initiative' and the 'Million Women Study' results in 2003, the use of hormone replacement therapy decreased significantly. Prior to this, one of the commonest causes of postmenopausal bleeding was problems with exogenous oestrogen use. Missed doses of medication and failure to follow the schedule of advised HRT often resulted in bleeding episodes. In women on low-dose HRT, associated gastrointestinal problems, either acute or chronic, may result in partial failure of absorption of HRT, leading to waxing and waning

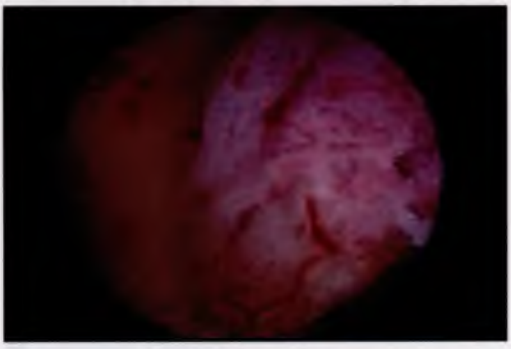

Figure 3 Hysteroscopic view of a polyp with prominent blood vessels. Histology revealed a well-differentiated endometrial cancer within the polyp.

oestrogen levels and episodes of breakthrough postmenopausal spotting. In developing countries, with rampant problems of chronic giardiasis or amoebiasis, this may be a relevant consideration.

In women on treatment with a continuous combined HRT regimen, irregular bleeding that persists after the initial 6 months or that develops after amenorrhoea is established should be investigated. Additionally, withdrawal bleeding that occurs after sequential cyclic oestrogen-progestogen therapy beyond the expected time of withdrawal, as well as any breakthrough bleeding, should also be investigated.

Patients on tamoxifen therapy, with its paradoxical oestrogen-like action on the endometrium, behave similarly to patients on unopposed oestrogen therapy. They are thus at risk of developing endometrial hyperplasia, polyps, or even neoplasia and need to be managed accordingly with a low threshold to undertake hysteroscopy and endometrial biopsy, depending on symptoms.

Miscellaneous causes of bleeding from the genital tract

Cervical lesions, including severe cervicitis, cervical polyps, and carcinoma (squamous or adenomatous) of the cervix may also cause postmenopausal bleeding. It is usually postcoital but may also occur spontaneously without evident history of local trauma. These lesions are usually visible on a careful speculum examination, which must always be performed in women who present with postmenopausal bleeding. It is only in patients with endocervical lesions that inspection of the cervix fails to reveal the problem. A cervical smear test should be considered according to NHSCSP guidelines if the patient has not had a recent smear and is within the age range.

Adnexal tumours of ovarian and fallopian tube origin – benign or malignant – may also present with postmenopausal bleeding by virtue of functional ovarian tumours producing oestrogens, or the association of the pelvic congestion and increased vascularity with non-functional tumours.

Chronic endometritis of tuberculosis has also been known to cause postmenopausal bleeding. This is of particular relevance in countries with a high incidence of tuberculosis.

Rarely, a uterine sarcoma and other uterine tumours (mixed Müllerian types) may present with postmenopausal bleeding.

Systemic bleeding disorders

Rarely, even postmenopausal women may have a systemic cause for vaginal bleeding superimposed against a backdrop of severe atrophic endometritis. The common causes of these may be:

- thrombocytopenia;
- leukaemia;
- pancytopenia from immunosuppression, chemotherapy, or bone marrow suppression;
- anticoagulation (iatrogenic), especially when a high international normalised ratio (INR) is a therapeutic requirement, or when the INR is labile;
- secondary coagulopathy from liver disease.

Other congenital bleeding disorders, such as haemophilia and von Willebrand disease, are usually diagnosed well before the menopause.

A high index of suspicion is required to diagnose these conditions as a cause of postmenopausal bleeding. Diagnosis and treatment should be directed at the cause.

Non-vaginal bleeding

Non-vaginal bleeding could often be mistaken by women to be vaginal in origin. Surrounding structures and problems that need to be considered from the urogenital part of the perineum are a bleeding urethral caruncle, haematuria from acute or chronic cystitis, bladder polyp, and even neoplasia. This bleeding is usually painless, although occasionally is associated with local perineal or pelvic pain.

Similarly, rectal bleeding can be mistaken for bleeding of vaginal origin. Anorectal piles, fissures, and malignancy may be other offending causes to be considered as the source of bleeding.

Investigation

Investigation is aimed at primarily excluding endometrial cancer, the most common gynaecological malignancy. Most postmenopausal women with endometrial cancer will present initially with PMB, and often present at an early stage where there is a good chance of curative treatment via hysterectomy. Timely diagnosis is therefore important, and women with PMB should be seen in the gynaecology outpatient clinic within 2 weeks of being referred.

While a traditional consultation would consist of a history followed by examination prior to investigation, in the case of PMB one might argue that a transvaginal ultrasound (TVS) for endometrial thickness

may be useful prior to conducting an intimate examination. TVS is relatively non-invasive and is often well tolerated even in older patients, compared to a standard pelvic examination.

A summary flow chart for the investigation of PMB is shown in Fig. 4.

Transvaginal ultrasonography

Along with being able to detect adnexal masses, uterine polyps, and other pathologies that may be responsible for PMB, the endometrial thickness (ET) is of particular interest when evaluating a woman's risk of endometrial hyperplasia or neoplasia. Women with a thin endometrium (<5 mm) are unlikely to have endometrial cancer, and thus endometrial sampling is not recommended in such cases.[1,4,5]

Knowledge of the ET can then guide the course of the pelvic examination, to include endometrial sampling if appropriate in the outpatient setting if the ET is >5 mm. If the endometrial lining is <5 mm, then examination should focus on detection of other causes of bleeding (e.g. cervical, vulval).

If ultrasonography is not possible, or if bleeding persists in spite of initial ET of <5 mm, then endometrial biopsy should be performed.

Blind outpatient endometrial biopsy

Pipelle (Pipelle de Cornier, Paris, France) and Vabra (Berkeley Medivices, Inc., Richmond, CA, USA) devices are less invasive than the traditional dilatation and curettage, and biopsy can be easily performed in the outpatient setting. Detection rates for

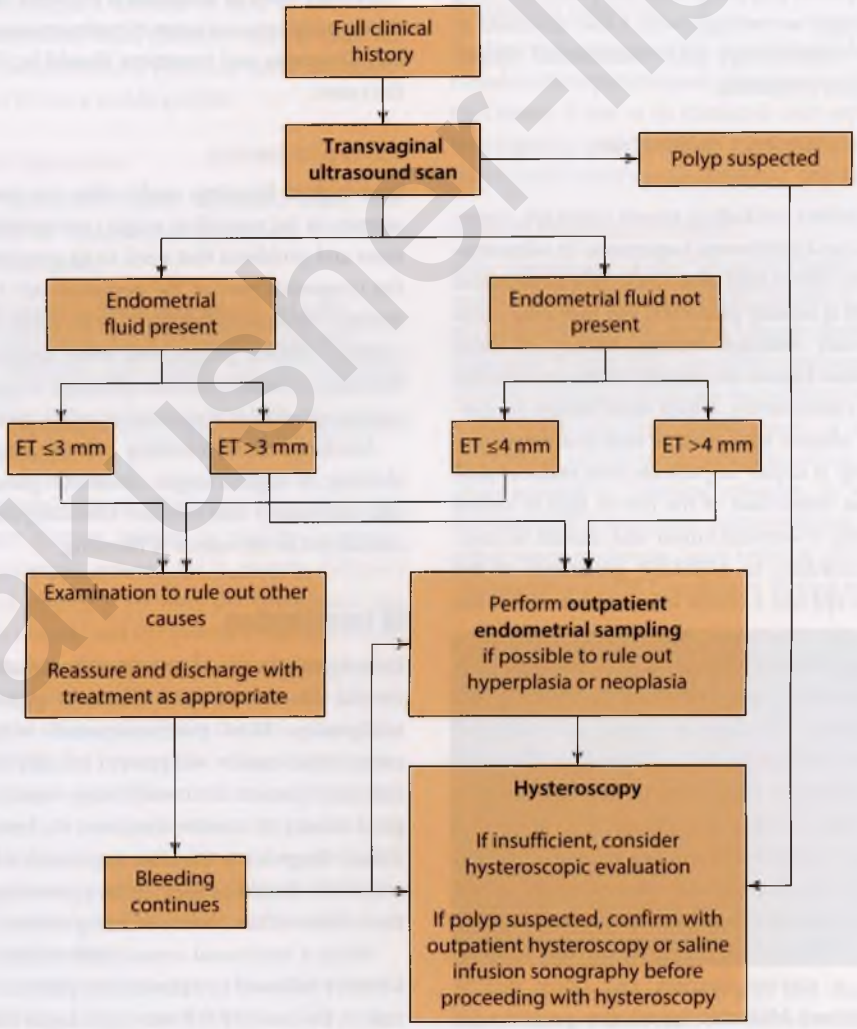

Figure 4 Summary flow chart for the investigation of postmenopausal bleeding. ET, endometrial thickness.

endometrial hyperplasia and neoplasia are 99.6 per cent and 97.1 per cent, respectively.[6]

At times these methods can yield insufficient sampling, and hysteroscopy will be necessary.

Hysteroscopy

Hysteroscopy can be conducted in the outpatient setting with or without local anaesthesia. Direct visualisation of the endometrial cavity enables the diagnosis of endometrial polyps or submucous fibroids. Most patients tolerate the procedure well, particularly with the use of 'no touch' techniques. However, general anaesthesia in the operating theatre is still used for some patients who do not tolerate the procedure or who request a general anaesthetic.

Diagnostic accuracy of hysteroscopy for endometrial cancer is high, owing to the abnormal appearance of the endometrium. However, pre-malignant change such as hyperplasia may not be so easy to detect visually, and biopsy via curettage is the recommended gold standard for arriving at a tissue diagnosis.[7]

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BLEEDING, RECTAL, DURING PREGNANCY

Kirana Arambage and Dilip Visvanathan

Rectal bleeding usually occurs from diseases involving the colon, rectum, and anus (Box 1). Bleeding from the upper gastrointestinal tract, the oesophagus and stomach, and from the small intestine usually presents as malaena. However, massive upper gastrointestinal bleeding can present as dark red blood loss per rectum owing to a rapid transit time.[1] Rectal bleeding may be obvious as a result of acute blood loss. Patients with a chronic blood loss may present with an iron deficiency anaemia blood detectable only on faecal occult blood testing. This section will address rectal bleeding secondary to acute haemorrhage from the lower gastrointestinal tract.

Box 1 Causes of rectal bleeding in pregnancy

Anorectal conditions
- Haemorrhoids
- Anal fissure
- Solitary rectal ulcer syndrome (mucosal prolapse)

Large bowel conditions
- Inflammatory bowel disease
- Adenomatous polyps
- Carcinoma
- Arteriovenous malformation
- Meckel's diverticulum

History and evaluation

A detailed history from the patient may give clues to the cause of the colorectal bleeding. Bright red blood

separate from the stool suggests an anorectal cause. Diarrhoea and mucus mixed with darker blood suggests colitis or a lesion in the large bowel. A history of alteration in bowel habits, namely constipation and diarrhoea with abdominal discomfort, may suggest malignancy, whereas faecal urgency, acute bleeding, and abdominal pain are more suggestive of colitis. A digital examination and proctosigmoidoscopy can help diagnose an anorectal condition. A colonoscopy, though difficult in the bleeding patient, will help at least identify the segment involved. Mesenteric angiography may be helpful in diagnosis if radiological expertise is present. In the event of a woman who presents with acute rectal bleeding and haemodynamic compromise, surgical evaluation at the time of emergency treatment may be required. If a lower gastrointestinal cause cannot be found, then investigation of the upper gastrointestinal tract by upper gastrointestinal (GI) endoscopy is recommended.[1]

Anorectal disease

Haemorrhoids and anal fissures are the commonest anorectal conditions that present during pregnancy and may cause significant distress. The real incidence of these lesions is unknown[2] and they tend to be inadequately investigated and treated.

Haemorrhoids

Haemorrhoids in pregnancy are due to increased circulating volume, increased venous congestion caused by compression of the superior rectal veins by the pregnant uterus, and the relaxing effect of progesterone on the smooth muscle in the walls of the veins.[3]

Haemorrhoids can present with bleeding, prolapse, mucoid discharge, pruritus, and rectal discomfort. It is important to exclude other causes of these symptoms such as inflammatory bowel disease, anal fissure, and carcinoma of the colon, rectum, or anus. Sigmoidoscopy and colonoscopy can be performed safely in pregnancy.

Treatment during pregnancy is directed mainly at relieving symptoms, especially pain control. Conservative management includes dietary modifications, increased fluid intake, stool softeners, and analgesics. For many women, symptoms will resolve spontaneously soon after birth. Definitive treatments are therefore deferred to some time after delivery.

Rubber band ligation can be safely performed in pregnancy for internal haemorrhoids. If the haemorrhoids are severely prolapsed or have associated ulceration, severe bleeding, fissure, or fistula and symptoms fail to respond to conservative measures, haemorrhoidectomy should be considered.[4,5]

Anal fissure

Anal fissure is a painful condition that affects a sizeable majority of the population. Selecting a method of treating the condition that could achieve optimal clinical results with the least pain and inconvenience to the patient has always posed a challenge to the surgeons. While acute fissures can be managed with medical therapy alone, chronic fissures do need some form of manipulation or surgery to relieve internal sphincter spasm.[6]

Trauma

Rectal bleeding may occur secondary to trauma. In a woman who has had a fourth-degree perineal tear, especially with a buttonhole injury, involvement of the inferior rectal artery can cause profound rectal bleeding. Prompt diagnosis and involvement of the colorectal surgeon allows for optimal results.

Inflammatory bowel disease

Most pregnant women with a history of inflammatory bowel disease have uneventful pregnancies, and exacerbations of disease can be controlled with medical therapy. It is rare for inflammatory bowel disease to present for the first time in pregnancy. When relapses of Crohn's disease do occur during pregnancy, they usually present in the first trimester. Most patients are already on some form of medical therapy. Surgery in pregnancy can be carried out, especially if there is a suspected abscess causing peritonism.[7,8]

Many patients with a history of ulcerative colitis managed with ileal pouch anal anastomosis will be able to become pregnant. Long-term outcomes of pregnancy and vaginal delivery in such patients are positive.[9]

Colorectal cancer

Colon cancer during pregnancy is very rare and the majority of cases of colorectal carcinomas in pregnant women arise in the rectum. The diagnosis frequently is delayed because symptoms of colorectal cancer, such as rectal bleeding, nausea and vomiting, and constipation are usually attributed to symptoms of pregnancy. Digital rectal examination, tests for occult blood, and flexible sigmoidoscopy followed by colonoscopy should be performed for complaints consistent with or suggestive of colonic disease.[1,10]

Treatment of colorectal cancer follows the same general guidelines as for non-pregnant patients. Primary surgical treatment should be performed whenever it is indicated. Later in pregnancy, it is preferable to delay surgery to allow fetal maturation and delivery. With respect to colon cancer, many authors recommend primary surgical treatment during the first half of the pregnancy because delaying treatment until after delivery may result in tumour spread. Therefore, in the first half of pregnancy, primary resection and anastomosis are advised.[11] Rectal cancer presenting in pregnancy is managed somewhat differently from colon cancer. During the first 20 weeks of pregnancy, patients wishing to carry their pregnancies to term may elect to have primary resection followed by chemotherapy after delivery. If the patient chooses to terminate the pregnancy, she may be managed as a non-pregnant patient after therapeutic termination.[12]

During pregnancy, a variety of colorectal conditions merit special consideration for reasons related to the safety and timeliness of the operation while preserving fetal viability and fertility. In benign conditions, there is more latitude to adopt a conservative approach. In the patient with malignancy, delaying surgical, chemotherapy or radiation therapy carries an unknown risk to the patient.[1] The patient's personal views regarding future fertility should be addressed. A multidisciplinary team approach is recommended with close collaboration between the obstetrician, surgeon, oncologist, neonatologist, and paediatrician.

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BLOCKED NOSE IN PREGNANCY

Eva Papesch and Mike Papesch

Nasal obstruction in pregnancy has many causes (Box 1). Women who already have nasal obstruction prior to becoming pregnant may suffer considerable exacerbation of their blocked nose. In women who have not had symptoms of rhinitis prior to conception, the most common causes are 'rhinitis of pregnancy' and rhinitis medicamentosa.

'Rhinitis of pregnancy' (ROP) occurs in up to 30 per cent of pregnant women.[1–3] It is defined as nasal congestion present for 6 weeks or more during pregnancy, without other signs of respiratory tract infection and with no known allergic cause, disappearing within 2 weeks after delivery.[4] Eustachian tube dysfunction may persist for up to 2 months after delivery. Up to half of women affected by rhinitis in

Box 1 Nasal obstruction: causes

Congenital
- Choanal atresia, septal deviation

Traumatic
- Septal deviation

Infection
- Acute/chronic viral/bacterial/fungal rhinitis/sinusitis

Neoplastic
- Benign: nasal polyps, inverted papilloma, pyogenic granuloma
- Malignant: adenocarcinoma

Allergy
- Allergic rhinitis

Autoimmune
- Wegener's granulomatosis, sarcoidosis, atrophic rhinitis

Iatrogenic
- Surgical, drug induced

Foreign body

Hormonal
- Rhinitis of pregnancy

Pharmacological
- Rhinitis medica mentosa
- Preservative benzalkonium

Vasomotor[6]
- Secondary to odours, alcohol, emotion, temperature change, pressure change, bright light, spicy food, gastro-oesophageal reflux disease

Occupational

one pregnancy have ROP in subsequent pregnancies. It may also occur in women who have not suffered ROP in previous pregnancies.[5] It is caused by oedema and increased blood volume in the nasal mucosa. Symptoms include sneezing, rhinorrhoea, nasal itch, blocked nose and mouth breathing, snoring and ear problems (eustachian tube dysfunction, acute otitis media, ear popping). ROP renders women more susceptible to obstruction and infection from common 'cold' viruses. Sinusitis has been reported to be six times more common in pregnant than non-pregnant women.[6]

Rhinitis medicamentosa (RM) can occur as a complication of the treatment of ROP and manifests as increased nasal mucosal swelling and blockage. It is caused by the continual use (beyond 1 week) of topical nasal vasoconstrictors such as xylometazoline or pseudoephedrine.[7] Benzalkonium chloride (BKC), a preservative used in sprays to prevent bacterial contamination, may increase the risk of developing RM by also inducing mucosal swelling.[8]

Aetiology

Rhinitis of pregnancy (ROP) is related to altered hormonal levels although the exact mechanism leading to blockage is poorly understood. It is similarly seen in nasal blockage associated with the menstrual cycle. Topically applied oestrogens have produced congestion of the nasal mucosa and increased nasal resistance. However, increased levels of oestradiol and progesterone were not found in a study of pregnant women with nasal congestion compared with a control group of women without nasal congestion,[2] and the regular use of the combined oral contraceptive pill has not been associated with increasing symptoms.[9]

The following mechanisms have been proposed for ROP.

Oestrogen

Oestrogen has a definite influence on nasal mucosa, causing swelling by a direct cholinergic effect through increased local acetylcholine production.[9] However, nasal congestion is not seen with peak oestrogen levels in the menstrual cycle, and ROP does not affect all pregnant women. Oestrogen levels have been found to be the same in women who have ROP and those who do not, and indeed some women with allergic rhinitis improve during pregnancy.

Progesterone

Nasal vascular pooling may occur as a result of progesterone-linked nasal vascular smooth muscle relaxation. Increased vasoactive intestinal peptide (VIP), stimulated by progesterone and oxytocin, leads to increased nasal congestion (animal studies). Fibroblasts in the nasal mucosa are influenced by progesterone, subsequently affecting the extracellular matrix.[1] Serum levels of progesterone are similar in women with and without ROP, suggesting this is *not* the cause.

Oestrogen and progesterone

Both can increase neurotransmitters such as substance P, causing nasal stuffiness.[1]

Cortisol

Cortisol increases during pregnancy, but the end organ effects of this increased cortisol may be blocked by competitive antagonism at the steroid receptor level exerted by other pregnancy hormones, such as progesterone, deoxycorticosterone, and aldosterone. This would lead to nasal congestion.[10]

Allergy

Allergic response to placental or fetal proteins leads to increased parasympathetic activity, with subsequent increased nasal mucosal glandular secretion and vascular congestion.[11] There does not appear to be any relationship to previous allergic rhinitis,[6] and there is no consistent IgE change in pregnancy.[10]

Blood volume

Elevated (40 per cent) blood volume and increased interstitial fluid volume in the third trimester increases nasal vascular pooling, mucosal swelling, and nasal resistance.[10]

Placental growth hormone

Placental growth hormone (PGH) has been suggested as a cause of rhinitis of pregnancy, and in one study the serum levels of PGH were significantly higher in women with ROP.[11]

Smoking

Incidence is higher in smokers, due to the direct irritation of cigarette smoke.[6]

Management

History

The relevant points include the length of history, the side of obstruction, any previous injury or surgery, exacerbating and relieving factors, associated symptoms consistent with sinusitis, history of atopy, and response to previous treatments.

Examination

Examination of the front of the nose with a speculum allows assessment of the anterior nasal septum and the turbinates, and can exclude any anterior nasal polyps. Prominent turbinates are often confused with nasal polyps. The distinguishing features are that polyps are pale (not red) and insensate to touch. Rigid or flexible nasendoscopy (after decongesting the nose with co-phenylcaine) allows complete examination of the nasal cavity as well as assessment of the postnasal space.

Investigation

Radioallergosorbent test (RAST) is an allergen-specific IgE antibody test and is used to screen for common environmental allergens (pollens, cat, etc). Skin prick allergy testing is not recommended in pregnancy because of the (albeit extremely low) risk of systemic reactions.[2,10]

Computed tomography (CT) scanning is the gold standard for assessing sinus disease, but is not recommended in pregnancy due to high-dose irradiation. Magnetic resonance imaging (MRI) can be considered in the management of complications of sinusitis.[12,13]

Ultrasound is a safe form of investigation for the evaluation of the frontal and maxillary sinuses in pregnant women, as it avoids ionising radiation. However, its sensitivity and specificity compared with CT is poor and it has little to offer in the clinical management of ROP.[14]

Treatment

General

Allergen avoidance, if applicable, can be helpful.[15] The avoidance of cigarette smoke and other non-specific irritants is also important. Exercise appropriate to physical condition and gestational age may reduce symptoms.[6,16,17] Saline nasal rinses such as Sterimar® or Neilmed Sinus Rinse® may provide some symptomatic relief and are completely safe.[6,10,17] Many recipes for homemade rinses are available – for example, ½ teaspoon salt, ½ teaspoon bicarbonate of soda, and ½ pint of warm, clean water mixed together and rinsed through the nose with a rinse bottle while standing over a sink. Sleeping with the head elevated may reduce nasal congestion (books under the head of the bed are better than extra pillows).[6] Alar dilators and nasal strips are also of some benefit.

Medical treatment

Medication should be given only when benefits outweighs the risks. Many drugs are advised against during pregnancy simply because studies have not been

undertaken to prove safety.[18] Topical treatments are preferred. The classification for potential of drug teratogenicity used by the United States Food and Drug Administration (FDA) is shown in Table 1.[19] When known, the classification is used in this text.

Table 1 US Food and Drug Administration use-in-pregnancy ratings[3]

Category	Interpretation
A	Controlled studies show no risk. Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.
B	No evidence of risk in humans. Either animal findings show risk, but human findings do not; or, if no adequate human studies have been done, animal findings are negative.
C	Risk cannot be ruled out. Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However potential benefits may justify the potential risk.
D	Positive evidence or risk. Investigational or post marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.
X	Contraindicated in pregnancy. Studies in animals or humans, or investigational or post marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

A summary of drugs used in pregnancy and their safety is shown in Table 2.

Topical treatments (first-line treatments)

Good compliance and correct positioning when administering treatment is very important. Nasal drops are best administered in the reclined head back position. Topical nasal sprays should be directed: 1) upwards and backward; and 2) directly backward, to provide the best application to the nasal cavity. Patients frequently complain of dryness of the nasal septum and crusting and bleeding of the nose with the use of sprays. Directing the sprays away from the nasal septum and the use of Vaseline or moisturiser creams can help prevent this.

Topical sodium cromoglycate (Class B) (Rynacrom®) is an over the counter mast cell stabiliser with an excellent safety profile and can be effective and safe in managing allergic rhinitis, in or out of pregnancy. However, it has to be given four times a day and has not been shown to be effective in ROP.[17,19,20]

Topical antihistamines: The risks of azelastine (Rhinolast®) use are unknown (Class C). No studies were found on its efficacy in ROP; however, other studies have shown an effect in non-allergic vasomotor rhinitis. There is no evidence to date to support a link between topical use and adverse pregnancy outcomes.[21,22]

Topical ipratropium bromide (Class B) (Rinatec®) is useful for symptomatic control of non-allergic

Table 2 Drugs and their safety in pregnancy

Drug	1st Trimester	2nd Trimester	3rd Trimester	Efficacy in ROP
Topical saline: Sterimar, Neilmed sinus rinse	Safe			Effective
Topical sodium cromoglycate	Safe			No effect
Topical steroids: fluticasone, mometasone	Safe			No effect
Topical ipratropium bromide	Safe			Hypothetical
Topical antihistamines	Risks unknown			Unknown
Topical decongestants	Unsafe (placental insufficiency and hypertension of pregnancy)			Effective
Oral steroids	Risk of cleft lip/palate in first trimester Only use in severe medical conditions			No Effect
Oral antihistamines	Caution advised		Avoid	Hypothetical
	Risk of teratogenicity		Risk of neonatal seizures/withdrawal	Hypothetical
Oral leukotriene receptor antagonists	No controlled studies in pregnancy			Unknown
Oral decongestants	Avoid: risk of gastroschisis	Pseudoephedrine can be used Avoid in hypertension of pregnancy		Effective
Immunotherapy	Not recommended to start during pregnancy. Can continue (reduced dosage) if therapy already initiated.			Unknown

rhinitis, though no specific studies could be found on its efficacy in pregnancy. It is safe to use in pregnancy.[23]

Topical nasal steroids are very safe in pregnancy, although in a small randomised control trial of 53 patients, they were not shown to have been of benefit in ROP.[24] They are, however, effective in the control of known allergic rhinitis. Inhaled corticosteroids used in pregnancy are not teratogenic, do not affect fetal growth or birth weight and have no effect on maternal cortisol levels.[17,19,25–28] Budesonide (Rhinocort Aqua®) has a Class B rating (all others are Class C).

Topical decongestants such as xylometazoline (Otrivine®) (Class unknown) give good temporary relief in pregnancy rhinitis. However, pregnancy-related vasodilation and congestion of the nose is relatively resistant to topical vasoconstrictors and overuse is common, leading to the development of RM.[29] Decongestants are rapidly absorbed, and there is concern that local vasoconstriction may cause placental insufficiency or exacerbate hypertension of pregnancy. Topical phenylephrine is associated with eye and ear malformations and club foot. Oxymetazoline (Class C) has no significant systemic absorption and has fewer sympathomimetic effects than other topical preparations.

Systemic treatment

Corticosteroids: Systemic use is generally not recommended, and no effect on ROP has been proven. There are a few case reports of cleft lip or palate when steroids have been used in the first trimester of pregnancy.[17,28,30] However, they are used when indicated in acute asthma; and when given in the third trimester to prevent infant respiratory distress, they have not resulted in drug-related abnormalities.[19,31]

Antihistamines: Even though these drugs have been used safely in pregnancy, there are concerns regarding teratogenicity.[32] They therefore should not be used in the first trimester.[33] They should also be avoided in late pregnancy (risk of neonatal seizures) and in women with fetal growth retardation as they carry a risk of retrolental fibroplasias in the fetus. If used at high dosage at term, the infant should be observed for neonatal withdrawal syndrome (tremor, clonic movements of the arms, poor feeding, and diarrhoea).[34,35] We have not found studies specifically evaluating the use of oral antihistamines in ROP, but theoretically they may be of value, as one of the proposed causes of ROP is an allergic response to placental or fetal proteins.[11] Chlorpheniramine has a Class B rating despite reports of eye and ear malformations and inguinal hernia.[10] Tripelenamine (Class B) has not been shown to be teratogenic and is preferred during pregnancy.[10,36,37] If not tolerated, cetirzine (Class B) and loratadine (Class B) may be used.[17,20,22,38]

Leukotriene receptor antagonists: No controlled studies have been done to assess the use in pregnancy.[31] Montelukast is classified as FDA Class B, based on animal studies.

Oral decongestants: These should be avoided in the first trimester as a large epidemiological study has linked their use with the development of endocardial cushion defects, ear deformities, pyloric-stenosis, and gastroschisis.[39] Oral decongestants should also be avoided in labour and in women with hypertension of pregnancy.[33] While pseudoephedrine (Class C) may be used in the second and third trimester, it is to be avoided in the first trimester.[17,20] Phenylpropanolamine (PPA) given orally at 50 mg twice daily has been shown to be effective and safe in ROP specifically, with no effect on blood pressure.[40] However, in the United States, the FDA has removed phenylpropanolamine from all drug products, because of the risk of haemorrhagic stroke in young women and men.[41]

Immunotherapy should not be commenced in pregnancy, but it can be continued if it is providing benefit and is not causing systemic reactions.[10,17,27] During pregnancy the maintenance dose should be reduced and routine antigen build up should be avoided.[30]

Antibiotics

These should be used for specific infections associated with nasal obstruction, such as acute bacterial sinusitis. Penicillins (amoxicillin), cephalosporins, and marcolides (erythromycin) are commonly used and are safe. Renal and liver function as well as serum drug levels can be monitored if there are concerns.

The following should be avoided:

- sulphonamides: haemolytic anaemia and hyperbilirubinaemia;
- tetracycline: teeth discoloration and impaired bone growth;
- trimethoprim: hyperbilirubinaemia;
- aminoglycosides: renal and neural arch anomalies (first trimester), ototoxicity and nephrotoxicity (third trimester);
- chloramphenicol: grey baby syndrome in pregnancy, owing to lack of the necessary liver enzymes to metabolise this drug; chloramphenicol accumulates in the baby, causing hypotension, cyanosis and often death.

Surgical treatment

Ideally, surgery is postponed until after delivery or later in the pregnancy. Surgical options include:

- *Inferior turbinate reduction*: diathermy reduction of inferior turbinates.
- *Nasal polypectomy*: intranasal polypectomy under local anaesthetic can be considered if severe nasal symptoms are present.
- *Endoscopic sinus surgery*: this can be undertaken for more extensive polypectomy and sinus clearance.

However, the relative risk of a general anaesthetic needs to be considered.

Summary

Nasal blockage in pregnancy is common. The usual causes of nasal obstruction as well as ROP need to be considered. ROP affects up to 32 per cent of pregnant women. Aetiologies include elevated VIP, substance P, and PGH, leading to increased nasal congestion. An allergic response to placental or fetal proteins may cause nasal congestion. Elevated blood volume in the third trimester of pregnancy also contributes to nasal blockage. Smoking exacerbates this rhinitis.

Rhinitis of pregnancy can lead to blocked nose, rhinorrhoea, and sinusitis. It can also lead to mouth breathing, snoring, and obstructive sleep apnoea (linked to hypertension, pre-eclampsia, and intrauterine growth retardation.[6]

General treatment measures include allergen avoidance, avoidance of cigarette smoke and other non-specific nasal irritants. Physical exercise is helpful in reducing symptoms. Saline nasal rinses such as Sterimar or Neilmed Sinus Rinse may also be useful. Sleeping with the head elevated may reduce nasal congestion.

Recommended topical medications include sparing use of decongestants and possibly ipratropium bromide. Topical decongestants often lead to rebound nasal congestion, may exacerbate hypertension and cause placental insufficiency. Whilst topical nasal steroids have not been shown to be of benefit in ROP, they are so in established allergic rhinitis.

Oral decongestants are not to be used in the first trimester and should be avoided in women with hypertension of pregnancy.

Immunotherapy can be continued, but should not start, during pregnancy. Further investigation and treatment, such as CT scanning and surgery, are ideally delayed until after delivery.

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BREAST LUMPS IN PREGNANCY

Peter Frecker

Nowadays women are asked to be 'breast aware' so that they present early with breast cancer, that is to say, as soon as they perceive any change in their breast (Box 1).

Box 1 Differential diagnosis of breast lumps in pregnancy

- Physiological
- Prominent breast lobule
- Montgomery's tubercle
- Accessory breast tail
- Incidental
- Lipoma
- Sebaceous cyst
- Neurofibroma
- Haemangioma
- Lymph nodes
- Fibroadenoma
- Cyst
- Conditions related to pregnancy
- Lactating nodule
- Galactocoele
- Abscess
- Malignancy
- Carcinoma

During pregnancy, changes to the breast can be marked, and some women may seek advice for what to the examining physician are considered normal physiological developments. These changes include:

- breast lobules becoming more prominent;
- enlarged Montgomery's tubercle;
- thickening of an area of the breast;
- accessory breast tissue in the axilla, a common anatomical anomaly, which will enlarge naturally during pregnancy; it may cause a little discomfort and be perceived as a serious problem.

Pregnant women may become more conscious of their breasts and present with lesions that have been there for a long time, including lipomas, sebaceous cysts, neurofibromas, or haemangiomas. Lymph nodes adjacent to the axillary tail of the breast can fluctuate in size, and it must not be forgotten that one is occasionally situated within that part of the breast, the intramammary node. Many of these concerns can be allayed by experienced midwives.

Lactating nodule

This is also known as adenosis of pregnancy, and the difference between this and the very common fibrocystic disease of the breast, which is unrelated to pregnancy, is blurred. The breast undergoes huge proliferation in pregnancy, and many women may note one particular area to be more thickened than the rest, an asymmetrical swelling, or an actual well-defined lump, such that imaging and biopsy may be contemplated. In this last case, the ultrasonographer may recognise it as a solid lump, but of similar echogenicity to the surrounding breast tissue, and the pathologist will describe it as normal breast tissue of pregnancy. Hopefully, as with other benign breast lumps seen in pregnancy, resort to excision biopsy can be avoided.

Fibrocystic disease

Although fibrocystic disease of the breast does not occur because of pregnancy, the condition is included for completeness. It has been labelled 'benign breast change syndrome', the symptoms of which include cyclical pain and thickening of the breast, typically in the upper outer quadrant. It should be emphasised that this is a very common problem and that the diagnosis begins with 'benign' and no 'disease' is mentioned. The pathologists looking at pieces of such breasts histologically might call it 'fibrocystic disease' because of its cyclical proliferative features and the sclerotic features that are perceived to be the basis of the mild inflammation. However, this term is very similar to fibroadenoma, which is also common but a quite different condition; hence, it is falling out of use.

Fibroadenoma

Fibroadenomas are common benign breast lumps seen in teenagers and women in their twenties, and there is a rise in incidence in women in their forties. Typically they appear mobile within the breast, are of a rubbery consistency on palpation, have a slightly irregular or bosselated surface, and frequently are

multiple. Excision is unnecessary as long as imaging and biopsy support the benign diagnosis. The natural history of these lumps is that they enlarge over a period of months and then remain unchanged, even for years, but eventually shrink and possibly appear as a calcified spot on mammograms in later life. In pregnancy they may appear as a new diagnosis, enlarge to cause concern, or infarct. This last condition may demand a surgical excision, which is susceptible to wound complication.

Cyst and galactocoele

A simple breast cyst can be large compared to the multiple tiny cysts of fibrocystic disease. It may present as a lump of sudden onset. They are often found to be multiple when the breast is scanned and are most common in women in their thirties and forties, being an age group of pregnancy more common these days than for our ancestors. We assume that the explanation for not seeing this in pregnancy nearly as frequently as in the non-pregnant population is that the simple cyst is essentially a degenerative change in the breast, in direct contrast to what is happening as a consequence of pregnancy. Galactocoeles are more common in pregnancy and present as the same spherical shape with a smooth surface as does the simple cyst. The diagnosis, for both, is confirmed by needle puncture and aspiration.

Abscess

Abscesses are more common in the lactating woman than the pregnant one. Usually they do not present a diagnostic problem, owing to their general systemic upset, localised pain, tenderness and redness of the overlying skin, and, usually, the sign of fluctuance. The main difficulty is in determining whether it is an abscess, or (the not much less painful) mastitis. Yet even if an abscess is mistaken for mastitis and nothing is done other than to prescribe antibiotics, the abscess may become partially treated in any case and become better defined, so that one is left with a clear decision to aspirate or drain it in an operation.

Carcinoma (Fig. 1)

This is a disastrous diagnosis for any young woman, but in pregnancy it is doubly difficult. If the

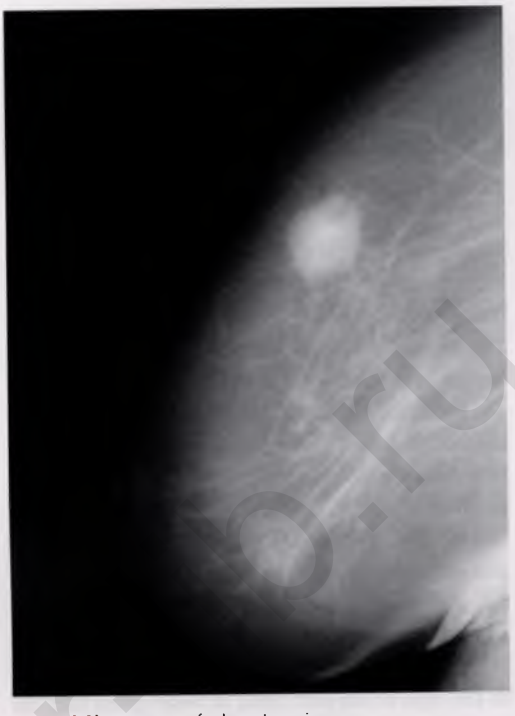

Figure 1 Mammogram of a breast carcinoma.

appropriate scan is requested or biopsy made in good time, the prognosis is no worse than that for a similar lesion occurring in a woman of similar age who is not pregnant. The problem is that the irregular hard lump might be seen as being something to do with the pregnancy, or mastitis, and the diagnosis could be missed. It should therefore be considered mandatory to take a careful account as to what has happened to the breast and then to examine both breasts and both axillae thoroughly. In this way, failure or delay in diagnosis may be avoided. Referral to a breast specialist should be triggered by the following findings:

- slight asymmetry of the breasts;
- a subtle dimpling of the skin;
- apparent inflammation but without the commensurate tenderness;
- nipple retraction;
- an ill-defined lump.

Useful website

www.breastcancercare.org.uk

BREAST TENDERNESS IN PREGNANCY AND THE PUERPERIUM

Peter Frecker

Breast pain, of mild degree, is a very common symptom during pregnancy and in the puerperium. As a consequence, the clinician of first contact can usually be confident in reassuring the woman as to its benign cause and with strategies for coping with it. The breast surgeon, therefore, sees many women with the benign breast change syndrome (BBC) but few with breast pain due to the changes of pregnancy and lactation. BBC is, by definition, not seen in pregnancy, but we recognise that the cycle of proliferative and degenerative changes with a mild inflammation has some parallels with what happens in pregnancy, where it is all proliferative.

Some heavy-breasted woman may need advice as to the type of support (bra) to wear given that the pain, whatever the cause, is exacerbated by poor support of the breast. Others may need to be told about engorgement of the breast and how to breast-feed the baby.

Sepsis

Mastitis is manifested by redness, swelling, and oedema of the breast, together with fever and tachycardia in severe cases. This is treated with antibiotics. The woman should be encouraged to continue breast-feeding the baby, perhaps expressing and discarding the milk from the infected side. If an abscess develops, the pain is more intense and exquisite tenderness may develop over the infected area (Fig. 1). This can be managed by either serial aspiration, with antibiotics, or by surgical drainage under a general anaesthetic. It can be difficult for the mother to continue to feed the baby during such an episode.

An ultrasound scan of the breast may be helpful in distinguishing between mastitis and abscess. A needle can be inserted, speculatively, to see whether or not there is pus present. The mother, who may have other young children, requires help and continued attention from health professionals during this difficult time.

Diabetic women can pose extra complications; for example, it may be that they harbour an unusual

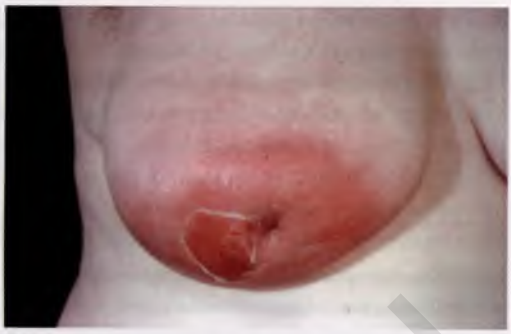

Figure 1 Breast abscess. Reproduced with kind permission from Richard Sainsbury.

organism that leads to necrosis of the skin over a part of the breast. Diabetic granulomatous mastopathy is a rare non-specific inflammatory condition, characterised by pain and lumps and mimicking carcinoma. The diagnosis is made histologically usually by a core biopsy that can be performed in an outpatient clinic.

Carcinoma

Breast cancer normally presents as a painless lump. However, the breast in pregnancy and during lactation is difficult to assess clinically, and there may be breast pain and tenderness in addition to a carcinoma or actually caused by the malignancy, as in inflammatory carcinoma. The assessment of the breast with the usual means of imaging is also difficult, and, if suspicion remains, investigations must be pursued. (See Box 2 in Breast/nipple discharge in pregnancy.)

Useful website

www.nhs.uk – Breast changes during and after pregnancy.

BREAST/NIPPLE DISCHARGE IN PREGNANCY

Peter Frecker

Physiological

The function of the breast is to produce milk, and as preparation for lactation occurs during the pregnancy, discharge is to be expected. The breast specialist sees

many young women with a trivial nipple discharge who are not pregnant and, in the absence of a definitive diagnosis (e.g. hyperprolactinaemia), would classify this symptom as a variant of normal. This discharge is from several ducts, typically bilateral, and clear or slightly coloured. The differential diagnosis is outlined in Box 1.

Box 1 Causes of breast/nipple discharge in pregnancy

- Intrinsic to pregnancy (physiological)
- Skin disorders – eczema
- Benign breast problems
  - duct ectasia
  - intraductal papilloma
- Malignancy
  - Paget's disease of the nipple (carcinoma presenting at the nipple)
  - ductal carcinoma in situ (may occur concurrently with an invasive malignancy of the breast)

Duct ectasia

There is no particular association with pregnancy, but this condition occurs in approximately 1 in 15 women at some time in their lives and is usually of no more than a nuisance. However, acute severe sepsis around the nipple/areola complex can occur and become a chronic problem in some women.

Ectasia is a term used to describe dilatation or distension of a hollow organ. The primary problem is a non-specific inflammatory condition labelled *periductal mastitis*, which can be complicated by secondary bacterial infection and enlargement, or ectasia, of ducts. The condition is seen typically in women in their 30s and 40s, and there is an association with smoking. The discharge is from multiple ducts, usually bilateral, can be of various colours, and, on occasions, be tinged with blood.

Some of the women with this problem may have nipple inversion as a consequence, or a possible cause, of the problem. This inversion may interfere with the woman's ability to breast-feed. Rarely, a fistula will develop, or occur following a procedure to drain an abscess, between a duct and an opening on the areola, or beyond. The patient may complain of staining on the bra only, but close inspection will reveal the opening of the mammillary fistula eccentric to the nipple.

Blood

A persistent blood-stained discharge, unilaterally, raises the possibility of ductal carcinoma in situ (DCIS) or actual invasive carcinoma. It is important to ascertain the exact nature of the discharge. It can be almost black in duct ectasia, while in DCIS it is usually bright red and persistent.

A phenomenon that is seen rarely, and for which there is no good explanation among primiparous women, is copious discharge of blood, bilaterally, towards the end of pregnancy and in the puerperium. Investigation is required, but very often no serious pathology is found.

A further cause of a blood-stained nipple discharge unilaterally is intraductal papilloma (Fig. 1). This is a benign polypoid lesion, which may be visualised on the wall of a duct close to the nipple, on a scan.

The woman presenting with discharge of blood needs to be examined with these diagnoses in mind. If a mass is found on examination, this should be investigated in the usual way (Box 2). If there is no associated mass, then some form of imaging is required. Ultrasound scanning can be diagnostic and mammograms, with protection of the fetus as necessary, can be undertaken. If these investigations are normal, then any diagnostic biopsies, for final confirmation of a benign pathology, can usually be delayed until after parturition. Applying some of the discharge to slides for cytology may provide further reassurance in the interim.

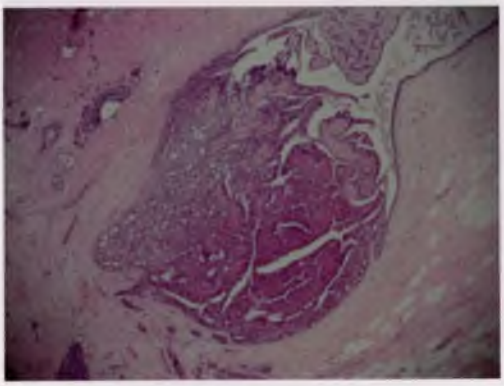

Figure 1 Histological picture showing an intraductal papilloma.

Box 2 Breast/nipple discharge: establishing a diagnosis

- History
- Clinical examination
- Cytology of the discharge
- Ultrasound scan and/or mammogram
- If there is a mass lesion:
  - fine-needle aspiration for cytology
  - core biopsy
  - excision biopsy

Nipple discharge of blood requires referral to a breast specialist. Rarely, both intraductal papilloma and DCIS can present with persistent, clear discharge.

Paget's disease

This is carcinoma presenting at the nipple (Fig. 2). The usual presentation is of an unhealed ulcer, the erosive lesion not having been noticed, and in some cases the complaint may be of a slight discharge, with or without blood. Close examination leads the clinician to imaging and nipple biopsy. The main differential diagnosis is eczema, the distinguishing features being that this much more common benign problem is usually bilateral and affects the periareolar area rather than the nipple itself. It is usually associated with itching and florid inflammation. The patient with eczema may also present complaining of nipple discharge because she has noticed staining on the bra, which is actually due to serum 'leaking' from the rash, and has not made the link between that and the irritation.

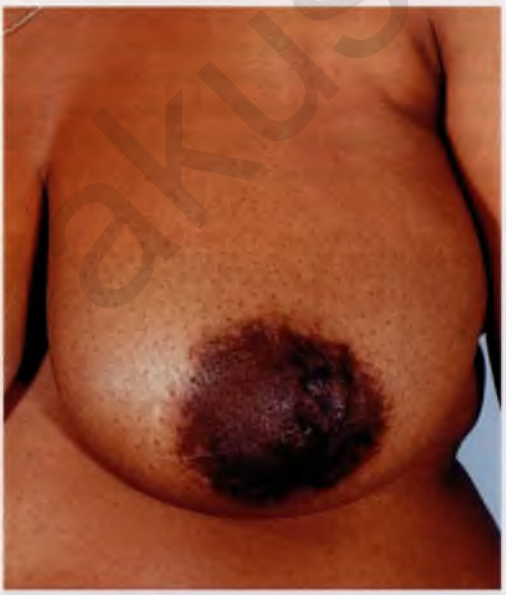

Figure 2 Paget's disease of the nipple.

BREATHLESSNESS IN PREGNANCY: CARDIAC CAUSES

Abhishek Joshi and Sandy Gupta

Introduction

Breathlessness is a common complaint in pregnancy, and is most often caused by maternal physiological changes. There are other simple, non-cardiac, causes for shortness of breath in pregnant women, such as iron deficiency anaemia and exacerbation of underlying respiratory conditions. However, shortness of breath in association with any of the following conditions should arouse suspicions of an underlying cardiac pathology:

- orthopnoea – breathlessness when lying flat;
- paroxysmal nocturnal dyspnoea – sudden onset of breathlessness at night;
- dysrhythmia – erratic heart rhythm;
- newly identified heart murmur.

Cardiomyopathies and congenital heart disease constitute two of the main life-threatening conditions for the mother and her baby[1,2] (Fig. 1). Acquired heart disease, such as rheumatic heart disease in pregnancy, is uncommon in the UK but may be a relevant in some populations.

Cardiomyopathies

Cardiomyopathy in pregnancy mainly comprises three types: peripartum, dilated, and hypertrophic. While dilated and hypertrophic cardiomyopathies may affect anyone and present at any time, including during pregnancy, peripartum cardiomyopathy occurs more often in women of Afro–Caribbean origin and during the last trimester of pregnancy or in the first 6 weeks postpartum.

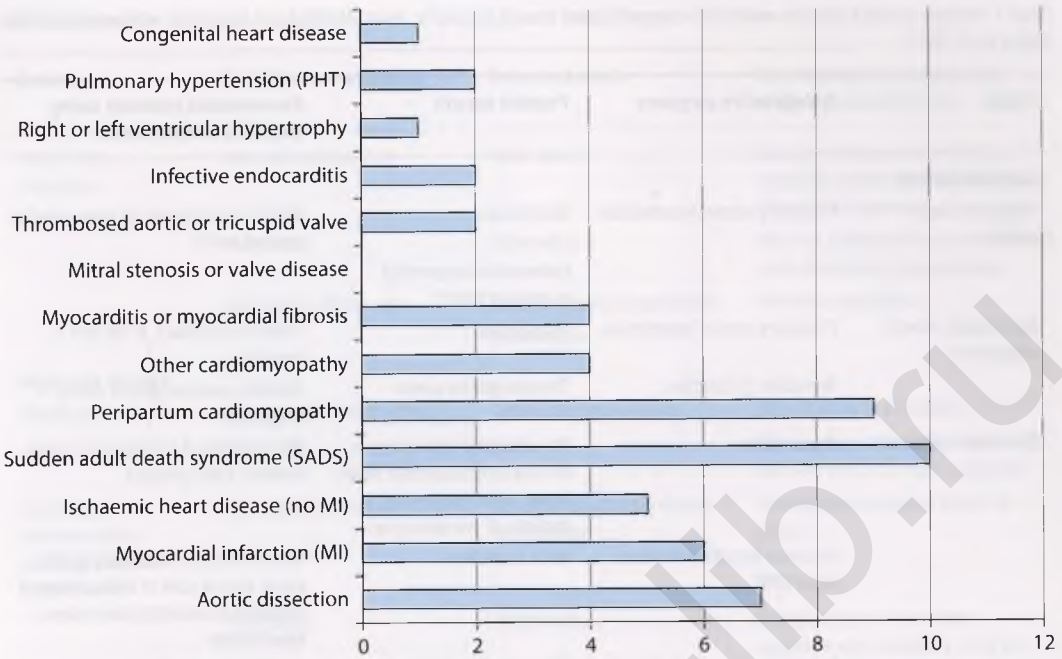

Figure 1 Frequency of causes of maternal death in UK 2006–2008.[1]

Peripartum cardiomyopathy (PPCM)

This is a non-hereditary cause of cardiomyopathy. It is rare, but with great geographical variation in incidence (from 1:300 to 1:4000 pregnancies).[3] There are a number of disparate diagnostic criteria (see Table 1). Predisposing factors appear to be family history of the disease, multiparity, multiple child births, teen pregnancy or advanced age of mother, ethnicity, smoking, diabetes, hypertension, pre-eclampsia, and prolonged use of beta-blockers. Data for prognosis in Europe is sparse, but worldwide prognosis appears to vary geographically. Between 20 and 40 per cent of women return to normal cardiac function, although mortality can be as high as 28 per cent after 2 years.

The pathophysiology of PPCM is not fully elucidated, but recent work has suggested that the nursing hormone prolactin may play a role.[3] Oxidative stress in the context of pregnancy appears to lead to the production of 16-kilodalton prolactin, which has been described as having direct cardiotoxic effects in animal models. Further work has focussed on the anti-angiogenic effect of the postpartum placenta. Other putative mechanisms of PPCM include viral illnesses and inflammatory and autoimmune causes.

Symptoms of breathlessness, orthopnoea, and paroxysmal nocturnal dyspnoea, along with abdominal pain from hepatic congestion, dizziness, and palpitations, usually develop in the 4 months after delivery, although 10 per cent may present in the final month of gravidum. Clinical signs may vary, but are usually consistent with congestive cardiac failure.

Electrocardiography is usually abnormal, with almost all (96 per cent) of patients exhibiting abnormal ST-T segments, and with two thirds showing left ventricular hypertrophy by voltage criteria. Serum brain naturetic peptide (BNP) is elevated. Echocardiography is mandatory to identify cardiac dysfunction. More recently, cardiac magnetic resonance imaging (CMR) has been used in determining chamber size and cardiac function and in identifying other aetiologies.

Recovery of cardiac function is common in patients with PPCM, and treatment focuses initially on supportive measures. Treatment of heart failure after delivery should follow usual therapeutic guidelines. Pharmacological management during pregnancy should take into account recommendations for avoiding fetal harm. For severe, critically ill patients, mechanical support with left ventricular assist devices and progression to cardiac transplant

Table 1 Pregnancy-related risks for women with congenital heart disease by specific lesion (Modified and reproduced with permission from Uebing *et al.* 2006)[6]

Lesion	Exclude before pregnancy	Potential hazards	Recommended treatment during pregnancy and peripartum
Low-risk lesions			
Ventricular septal defects	Pulmonary arterial hypertension	Arrhythmias	Antibiotic prophylaxis for unoperated or residual defect
		Endocarditis (unoperated or residual defect)	
Atrial septal defects unoperated)	Pulmonary arterial hypertension	Arrhythmias	Thromboprophylaxis, if bed rest is required
	Ventricular dysfunction	Thromboembolic events	Consider low-dose aspirin during pregnancy
Coarctation (repaired)	Recoarctation	Pre-eclampsia (coarctation is the only congenital heart lesion known as an independent predictor of pre-eclampsia)	Beta-blockers, if necessary, to control systemic blood pressure
	Aneurysm formation at site of repair (MRI)	Aortic dissection	Consider elective caesarean section before term in case of aortic aneurysm formation or uncontrollable systemic hypertension
	Associated lesion, such as bicuspid aortic valve (with or without aortic stenosis or aortic regurgitation), ascending aortopathy	Congestive heart failure	Antibiotic prophylaxis
	Systemic hypertension Ventricular dysfunction	Endarteritis	
Tetralogy of Fallot	Severe right ventricular outflow tract obstruction	Arrhythmias	
	Severe pulmonary regurgitation	Right ventricular failure	Consider preterm delivery in the rare case of right ventricular failure
	Right ventricular dysfunction DiGeorge syndrome	Endocarditis	Antibiotic prophylaxis
Moderate-risk lesions			
Mitral stenosis	Severe stenosis	Atrial fibrillation	Beta-blockers
	Pulmonary venous hypertension	Thromboembolic events	Low-dose aspirin
		Pulmonary oedema	Consider bed rest during third trimester with additional thromboprophylaxis
			Antibiotic prophylaxis
Aortic stenosis	Severe stenosis (peak pressure gradient on Doppler ultrasonography >80 mmHg, ST segment depression, symptoms)	Arrhythmias	Bed rest during third trimester with thromboprophylaxis
	Left ventricular dysfunction	Angina	Consider balloon aortic valvotomy (for severe symptomatic valvar stenosis) or preterm caesarean section if cardiac decompensation ensues (bypass surgery carries 20% risk of fetal death)
		Endocarditis	Antibiotic prophylaxis
		Left ventricular failure	
		Endocarditis	

Table 1 Continued

Lesion	Exclude before pregnancy	Potential hazards	Recommended treatment during pregnancy and peripartum
Fontan-type circulation	Ventricular dysfunction	Heart failure	Consider anticoagulation with low-molecular-weight heparin and aspirin throughout pregnancy
	Arrhythmias	Arrhythmias	Maintain sufficient filling pressures and avoid dehydration during delivery
	Heart failure (NYHA >II)	Thromboembolic complications Endocarditis	Antibiotic prophylaxis
High-risk lesions			
Marfan syndrome	Aortic root dilatation >4cm	Type A dissection of aorta	Beta-blockers in all patients Elective caesarean section when aortic root >45 mm (≈35 weeks' gestation)
Eisenmenger syndrome; other pulmonary arterial hypertension	Ventricular dysfunction	30–50% risk of death related to pregnancy	Therapeutic termination should be offered
	Arrhythmias	Arrhythmias	If pregnancy continues, close cardiovascular monitoring, early bed rest and pulmonary vasodilator therapy with supplemental oxygen should be considered
		Heart failure	Close monitoring necessary for 10 days postpartum
		Endocarditis for Eisenmenger syndrome	

MRI, magnetic resonance imaging; NYHA, New York Heart Association

may be considered, although there are no reliable data on their use in PPCM. Recent studies supporting the use of bromocriptine to reduce the action of prolactin in its suggested role in PPCM have shown some promising results, but the therapy will require further evaluation.

If ejection fraction (EF) does not normalise, further pregnancies should be discouraged. PPCM carries a recurrence risk of 30–50 per cent, even in women with normalisation of cardiac function.

Dilated cardiomyopathy (DCM)

DCM is symptomatic heart failure with left ventricular dilatation and systolic dysfunction; it has no identifiable cause. It is distinguished from PPCM by the timing of onset, and may pre-exist but be unmasked by pregnancy. It is poorly tolerated in pregnancy, and often deteriorates. The risk of maternal death is 7 per cent if the patient is in the New York Heart Association (NYHA) functional classification >II. An EF of <40 per cent (normal range: >55 per cent) is classed 'high risk' and should be managed in a tertiary centre. An EF of <20 per cent carries a high risk of maternal death, and termination of pregnancy should be discussed.[4]

Hypertrophic cardiomyopathy (HCM)

Women with HCM usually tolerate pregnancy well, as the left ventricle seems to adapt in a physiological way.[5] This is especially advantageous in this condition, where the left ventricular cavity dimensions tend to be small. Women with a murmur and an increased gradient across the left ventricular outflow tract may present for the first time in pregnancy.

Maternal death is uncommon, and there is no evidence to suggest the risk of sudden death is increased by pregnancy.[1] However, considerable distress may be caused by the diagnosis and by the genetic implications. The diagnostic echocardiogram, electrocardiogram (ECG), exercise testing and ambulatory ECG monitoring, and genetic

counselling are carried out as in the non-pregnant patient.

Women with severe diastolic dysfunction may be at risk of pulmonary congestion or even florid pulmonary oedema. Beta-blockers should be continued and a small dose of diuretic may help, but rest is recommended in conjunction with the beta-blocker in order to prevent tachycardia.

Atrial fibrillation in women with HCM is frequently managed with low-molecular-weight heparin and beta-blockade. Cardioversion may be considered if rate control fails, after excluding thrombus in the left atrial appendage with a transoesophageal echocardiogram.

Finally, the genetic risk should be discussed, including the phenomenon of anticipation, which determines an earlier onset and more severe form in succeeding generations in some families.

Normal vaginal delivery with good analgesia and a low threshold for forceps assistance is the safest mode of delivery for the mother with any form of cardiomyopathy, since it is associated with reduced blood loss and less rapid haemodynamic changes in comparison with caesarean section.

Congenital heart disease

Congenital heart disease is the most common birth defect in the world – about 1 per cent of newborns around the world have congenital heart disease. In the UK, approximately 250,000 adults have congenital heart disease, divided equally between the sexes. Some have simple defects, such as small atrial or ventricular septal defects that may remain clinically silent until diagnosed on routine examination, whereas others have complex abnormalities that require surgical intervention for survival.

Fifty years ago, 90 per cent of this population would not have reached adulthood. Advances in cardiology and cardiac surgery have led to more than 85 per cent of these infants surviving into childbearing age, and the number is growing by approximately 1600 new cases every year. These women are at heightened risk of maternal and fetal complications should they conceive. The medical profession should, therefore, be aware of the clinical presentations, diagnosis, and management of the following conditions. The congenital cardiac lesions in pregnancy can be broadly classified based on the related risks for the pregnant women into low-, moderate- and high-risk lesions (Box 1).[6] The ensuing discussion will focus on the clinical manifestation and diagnosis of individual congenital cardiac lesions. The management of pregnancy and labour depends on the risk category of the patient (Table 1).

Box 1 Classification of congenital heart disease by risk in pregnancy

Low-risk lesions
- Ventricular septal defect
- Atrial septal defects (unoperated)
- Coarctation repaired
- Tetralogy of Fallot repaired

Moderate-risk lesions
- Mitral stenosis
- Aortic stenosis
- Fontan-type circulation

High-risk lesions
- Marfan syndrome
- Eisenmenger syndrome

Low-risk conditions

Ventricular septal defect

A small ventricular septal defect (VSD) with normal right-sided pressures confers no added risk in pregnancy. Paradoxical embolism is not common in VSD with a large pressure gradient across the defect. Large defects causing pulmonary vascular disease are discussed under pulmonary hypertension and Eisenmenger syndrome/complex. In general, these are low-risk lesions, although pre-eclampsia may be more prevalent in women with VSD.

Unoperated atrial septal defect

Unoperated atrial septal defects (ASDs) are well tolerated in the presence of a normal pulmonary vascular resistance. The pre-existing tendency to atrial arrhythmia may increase with the rise in cardiac output in pregnancy. The combination of a potential right-to-left shunt and the hypercoagulable state of pregnancy increases the risk of paradoxical embolism, especially with rises in intrathoracic pressure during labour. This also applies to patent foramen ovale. Prophylactic anticoagulation

with low-molecular-weight heparin is recommended during periods of immobility.

Repaired coarctation of the aorta

In current-day practice almost all patients born with coarctation of the aorta have the condition corrected by early childhood. Pregnancy poses little risk in repaired coarctation as long as there is no aneurysm at the site of repair. This should be confirmed by magnetic resonance imaging (MRI) or computed tomography (CT) before conception.

Repaired tetralogy of Fallot

Tetralogy of Fallot is the most common cyanotic congenital heart disease and was among the first complex congenital defects to be successfully repaired surgically. Most patients with tetralogy of Fallot reaching adulthood have had their anomaly repaired, and are currently asymptomatic and leading a near-normal life. Pregnancy is well tolerated in this group of women; however, severe pulmonary insufficiency may ensue and may cause decompensation during pregnancy. This emphasises the need to assess women with congenital heart disease – even with a 'successful' repair – on a regular basis to ensure that any cardiac lesions that might limit cardiac reserve enough to complicate pregnancy can be corrected before conception.

Moderate-risk conditions

Fontan-type circulation

The various forms of Fontan operation (Fig. 2) create two separate circulations in series in the presence of a functionally univentricular heart. These patients are therefore not cyanosed, but experience a long-term low-output state and are at risk of ventricular failure and atrial arrhythmia. They are generally anticoagulated with warfarin, which should be converted to full-dose, low-molecular-weight heparin for the duration of pregnancy. Maternal outcome depends on functional capacity and ventricular function, which is more likely to be adequate if the single ventricle is morphologically left. Patients with oxygen saturation <85 per cent at rest, depressed ventricular function, and/or moderate to severe atrioventricular (AV) regurgitation or with protein-losing enteropathy should be counselled against pregnancy. Without these factors, if the woman accepts a risk of first-trimester fetal loss twice that of the general

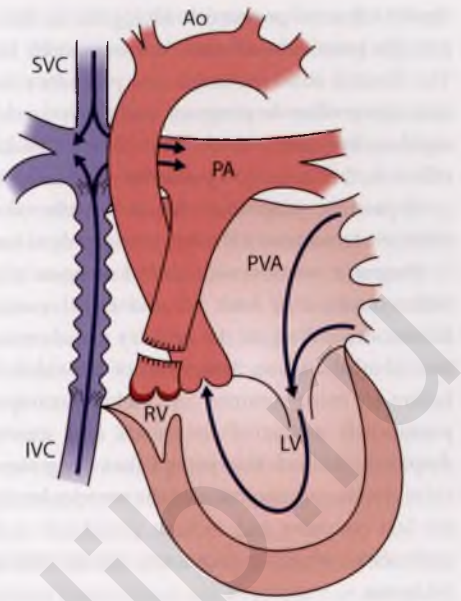

Figure 2 The total cavopulmonary connection variant of the Fontan operation for a single functional ventricle. The superior vena cava (SVC) and inferior vena cava (IVC, via a conduit) are connected directly to the right pulmonary artery and the main pulmonary artery ligated. The ventricle supports the systemic circulation and there is no mixing. A rudimentary second ventricle can be seen. Ao, aorta; LV, left ventricle; PA, pulmonary artery; PVA, pulmonary venous atrium; RV, right ventricle.

population, then there is no reason to advise against pregnancy, as was typically done in the past.[7]

Mitral stenosis

The commonest chronic rheumatic valvular lesion in pregnancy in the UK is mitral stenosis, particularly in the immigrant population from the Indian subcontinent, China, Eastern Europe, and East African countries. Since rheumatic mitral stenosis can remain silent up until the third decade, symptoms may often first appear during pregnancy. Congenital fusion of the commissures, or 'parachute mitral valve', and left atrial myxoma are other causes of mitral stenosis during pregnancy.

Haemodynamic abnormalities in a pregnant woman with mitral stenosis include elevated left atrial, pulmonary venous, and arterial pressures, which is a function of valve area and flow across the valve. The maternal complications include pulmonary oedema, pulmonary hypertension, and right ventricular failure. Tachycardia that may be precipitated by exercise, fever, or emotional stress may decrease the diastolic left ventricular filling time and further

elevate left atrial pressure, reducing the cardiac output. The potential end result is biventricular failure. The elevated atrial pressures, and pregnancy per se, may also predispose pregnant women to developing atrial arrhythmias, which may have unfavourable effects further leading to pulmonary oedema.

If possible, pregnancy should be deferred until definitive treatment of the stenosis is undertaken.

Pregnant women with mitral stenosis present with symptoms of both left and right ventricular failure, depending on the severity and duration of the valvular disease. Symptoms of left-sided heart failure are more common and include orthopnoea, paroxysmal nocturnal dyspnoea, and exertional dyspnoea. Unless the patient has long-standing valve disease, symptoms of right ventricular failure are less common and include peripheral oedema and ascites, which in pregnancy can be difficult to recognise.

Careful examination by listening specifically for an opening snap and a diastolic rumbling murmur with presystolic accentuation, which are characteristic auscultatory findings in mitral stenosis, may be rewarding. The presence of elevated jugular venous pressure, hepatomegaly, a loud pulmonary component of the second heart sound, and right ventricular heave on examination also support a diagnosis of mitral stenosis. Many pregnant women with mitral stenosis may present with atrial fibrillation or cardiac failure.[4]

Transthoracic echocardiography is the diagnostic modality of choice for evaluation of mitral stenosis in pregnant women. It may confirm the diagnosis and help determine the severity of the stenosis. In addition, the echocardiogram allows assessment of pulmonary pressures, right ventricular function, mitral regurgitation, other valves, and the configuration of the subvalvular apparatus, which is important in determining the success of percutaneous mitral balloon valvuloplasty. Invasive diagnostic testing, such as right heart catheterisation, is seldom warranted.

When symptoms occur, or pulmonary artery pressures exceed 50 mmHg, the patient's activity should be limited and beta-blockers used to reduce heart rate. Low-dose diuretics may help if symptoms persist. Patients with paroxysmal or persistent atrial fibrillation, severe left ventricular dysfunction, ventricular thrombus, or prior embolus should be anticoagulated.

In patients with raised pulmonary artery pressures and severe symptoms despite optimal medical management, percutaneous mitral commissurotomy may be indicated after 20 weeks of pregnancy.

Aortic stenosis

Symptomatic aortic valve disease is less common than mitral valve disease in pregnant women. In the UK, congenital aortic stenosis secondary to a bicuspid aortic valve appears to be the predominant cause. In contrast, rheumatic heart disease is the most common cause in developing countries and the ethnic population in the UK. During pregnancy, women with bicuspid aortic valves are at risk for aortic dissection related to the hormonal effects on connective tissue.

The pressure gradient across the aortic valve is responsible for the haemodynamic changes in aortic stenosis. The increase in left ventricular systolic pressure needed to maintain sufficient pressure in arterial circulation leads to increased stress on the ventricular wall. To compensate for this, left ventricular hypertrophy develops, which can result in diastolic dysfunction, fibrosis, diminished coronary flow reserve, and late systolic failure.

An increase in stroke volume and a fall in peripheral resistance are largely responsible for the increase in the gradient across the aortic valve. The clinical consequences of the increased aortic gradient depend on the degree of pre-existing left ventricular hypertrophy and left ventricular systolic function. When compensatory changes in the left ventricle are inadequate to meet the demands imposed by the need for increased cardiac output late in pregnancy, symptoms develop. This usually occurs with moderate to severe aortic stenosis.

Clinical presentation and symptoms depend on the degree of aortic stenosis. Women with aortic valve areas >1.0 cm^2 tolerate pregnancy well and are asymptomatic. Women with more severe aortic stenosis may have symptoms of left-sided heart failure, which may manifest primarily as exertional dyspnoea. Blackout and near-fainting pre-syncope are rare, and pulmonary oedema is even more unusual.

As symptoms of aortic stenosis may resemble those of normal pregnancy, clinicians may be misled. Physical findings vary with the severity of the disease. The left ventricular impulse is sustained and displaced laterally. A systolic ejection murmur is heard along the right sternal border and radiates toward the carotid arteries and a systolic ejection click may be heard. A fourth heart sound may be present, suggesting abnormal diastolic function. The presence of slow rising pulse and narrow pulse

pressure (difference between systolic and diastolic blood pressure) suggests haemodynamically significant aortic stenosis.

Diagnosis can be confirmed with echocardiography. The aortic gradient and valve area can be calculated by Doppler flow studies. In addition, echocardiography can detect left ventricular hypertrophy. Estimation of EF and left ventricular dimensions may be useful in predicting outcome during pregnancy, labour, and delivery. Exercise testing in asymptomatic women confirms freedom from symptoms, blood pressure response, and the propensity to arrhythmia. Women with an EF <55 per cent are at high risk for developing heart failure during pregnancy. Cardiac catheterisation is indicated if the clinical picture is consistent with severe aortic stenosis, if non-invasive data are inconclusive, and if percutaneous balloon valvuloplasty is required. Fetal echocardiography is indicated if the mother has congenital aortic stenosis, since the risk that the fetus has similar anomalies is about 15 per cent.

Asymptomatic patients without left ventricular dilatation or hypertrophy and with normal exercise tolerance are safe to proceed with pregnancy. Those with symptoms, impaired left ventricular function, or a pathological exercise test should be counselled against pregnancy until definitive treatment.

Pregnancy in the presence of symptomatic aortic stenosis carries a 10 per cent risk of heart failure and a 25 per cent risk of adverse pregnancy outcomes. Treatment is initially with rest and traditional management of heart failure symptoms. Patients who are increasingly symptomatic, especially in the second half of pregnancy, may undergo percutaneous valvuloplasty.

In severe, symptomatic patients, or those with heart failure, elective caesarean section under general anaesthetic is preferred. Otherwise, vaginal delivery avoids the complications of peripheral vasodilation in the context of a fixed cardiac output.

High-risk lesions

Marfan syndrome

Marfan syndrome in pregnant women with normal aortic root carries a 1 per cent risk of aortic dissection; this risk is tenfold with an aortic root diameter >4 cm. The main maternal risk in Marfan syndrome is type A aortic dissection, repair of which carries a 22 per cent maternal mortality. Patients with family history, cardiac involvement, and aortic root >4 cm diameter or a rapidly dilating aorta are at high risk of dissection and should be advised against pregnancy.[8]

Those who elect to proceed with pregnancy should be treated with beta-blockers and undergo elective caesarean section.

Aortic dissection can occur without pre-existing disease in pregnancy, probably because of the hormonal changes and increased cardiovascular stress of pregnancy. Bicuspid aortic valve with dilated aortic root may also be a risk factor for aortic dissection in pregnancy, with similar histological findings to that of Marfan syndrome.

Patients with Marfan syndrome may also experience mitral valve regurgitation, and subsequent heart failure and supraventricular tachycardias.

Pulmonary hypertension and Eisenmenger syndrome

Pulmonary hypertension can be primary or caused by disease of the lung or left heart. Pulmonary hypertension caused by congenital heart disease and shunts is called Eisenmenger syndrome. Pulmonary hypertension of any cause carries a high risk of maternal death (up to 50 per cent in some studies).[9] Maternal death is due to pulmonary hypertensive crises, refractory right heart failure, or pulmonary thrombosis.

Women should be advised against pregnancy.[4] Laparoscopic sterilisation may be considered but not without significant risk. The progesterone subdermal implant is at least as effective as sterilisation without any added cardiovascular risk. In the event of pregnancy, therapeutic termination should be offered in a tertiary centre. Women who elect to continue should be referred to a specialist centre.

Antenatal care

The level of antenatal care and monitoring should be determined prior to conception or as soon as pregnancy is confirmed. The main management recommendations for individual cardiac lesions are summarised in Table 1.

General obstetricians based in a district general hospital in the UK on average only ever see a few patients with moderate to severe congenital heart disease; therefore, these patients should be referred to a specialist centre for counselling. Moderate- to high-risk patients should ideally be managed in a tertiary multidisciplinary setup with 24-hour access to a cardiologist, anaesthetist, obstetrician, and neonatologist. Low-risk patients may continue with their antenatal care locally, taking into consideration specialist

recommendations (Table 1). The patient should be involved in the decision-making process and understand the 'minimal risk' approach. Some patients may benefit from hospitalisation during the third trimester of pregnancy for bed rest, closer cardiovascular monitoring, and for oxygen therapy (in patients with cyanotic heart disease). Patients admitted for bed rest should receive appropriate thromboprophylaxis with low-molecular-weight heparin.

Anticoagulation in pregnancy and labour

Women with congenital heart disease are at heightened risk of thromboembolic events secondary to chronic or recurrent arrhythmia, sluggish blood flow, or metallic heart-valve prostheses. The risk of thromboembolism is elevated 6-fold during pregnancy and 11-fold in the puerperium;[10] therefore, achieving adequate anticoagulation is important. However, this is not without risk, and is associated with substantial maternal and fetal complications. Warfarin, an effective oral anticoagulant, crosses the placenta and thus carries major risks for the fetus. In contrast, heparin does not cross the placenta and is, therefore, safe.

However, it is reported to be less effective for thromboprophylaxis, particularly in women with metallic valve prosthesis. Any advice on anticoagulant treatment during pregnancy must weigh the risks and benefits for both mother and fetus, and decisions regarding treatment should be made jointly with parents.

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BREATHLESSNESS IN PREGNANCY: RESPIRATORY CAUSES

Simon Quantrill

Introduction

Breathlessness in pregnancy is usually due to physiological changes and less commonly to other conditions. The incidence of these conditions in pregnancy is difficult to estimate owing to a lack of relevant studies. Breathlessness, which is the sensation of difficulty in breathing, should be distinguished from tachypnoea, which is an increased respiratory rate. Respiratory rate is crucial to assessing the severity of illness and is often poorly noted by clinicians. Cyanosis is unreliable as a marker of hypoxia, particularly in pregnancy, where there is likely to be a degree of anaemia.

Causes of breathlessness

Table 1 lists those causes of breathlessness in pregnancy most likely to be encountered or which are well recognised as specific complications of pregnancy, but are rare, such as amniotic fluid embolism. When assessing the breathless pregnant patient, the approach should be similar to that undertaken in the non-pregnant patient, as most potential causes are the same. It is helpful to divide these causes into physiological, upper airways, respiratory, chest wall, cardiac (see Breathlessness in pregnancy: cardiac causes), and metabolic.

Physiological

Physiological breathlessness usually starts in the first or second trimester and increases in incidence as gestation progresses. It occurs in 60–70 per cent of pregnant women and is thus the norm. The main diagnostic problem is in distinguishing between a physiological cause and a more serious condition, such as those listed in Table 1. Physiological breathlessness of pregnancy is usually relatively mild, rarely severe, and actually improves or at least does not worsen as term approaches. Breathlessness at rest is uncommon, and activities of daily living and exercise tolerance are not usually affected.

Many studies have been conducted on changes of lung function during pregnancy, with conflicting results. These changes occur as a result of homeostasis owing to the increasing need for oxygenation of the growing fetus. The most significant and well-documented alteration is of increased minute ventilation by 20–40 per cent (tidal volume x respiratory rate) owing to a higher tidal volume. Respiratory rate is not significantly altered or only very slightly increased, so most of this higher tidal volume can be ascribed to greater inspiratory effort. This in turn is what leads to the sensation of breathlessness through activation of chest wall proprioceptors and may explain why patients sometimes complain of 'difficulty getting air in'.

Table 1 Non-cardiac causes of breathlessness in pregnancy

Site	Conditions
Physiological	Physiological breathlessness of pregnancy
	Dysfunctional breathing
Upper airways	Vocal cord dysfunction, nasal obstruction, anaphylaxis
Respiratory	*Obstructive airways disease*: asthma, cystic fibrosis, bronchiectasis, COPD, obliterative bronchiolitis, allergic bronchopulmonary aspergillosis & collapsed lung due to carcinoid tumour, lung cancer or a mucus plug:
	Parenchymal and interstitial lung disease: pneumonia, aspiration pneumonitis, ALI/ARDS, extensive tuberculosis, pulmonary metastases, sarcoidosis, drug-induced, lymphangioleiomyomatosis, lymphangitis carcinomatosa, extrinsic allergic alveolitis, fibrosing alveolitis, COPD, simple pulmonary eosinophilia, COP, usual interstitial pneumonia/non-specific pneumonia, pulmonary haemorrhage, vasculitis, e.g. Wegener's granulomatosis, Churg–Strauss syndrome, drug induced
	Vascular: pulmonary embolism, amniotic fluid embolism, pulmonary hypertension (primary and secondary), sickle cell crisis
	Pleural: pleural effusion, empyema, pneumothorax, ascites, pneumomediastinum
Chest wall	Obesity
	Kyphoscoliosis
	Ankylosing spondylitis
	Obesity hypoventilation syndrome / overlap syndrome
	Neuromuscular disease, e.g. multiple sclerosis, polio, myasthenia gravis, diaphragmatic paralysis
	Trauma: rib fractures
Metabolic	Anaemia
	Thyrotoxicosis
	Acute or chronic renal failure
	Metabolic acidosis/diabetic ketoacidosis
	Systemic sepsis

ALI, acute lung injury; ARDS, adult respiratory distress syndrome; COP, cryptogenic organising pneumonia; COPD, chronic obstructive pulmonary disease.

Chest X-ray and lung function tests are essential for excluding other causes of breathlessness, but there is no specific diagnostic test for physiological dyspnoea of pregnancy. The diagnosis is, therefore, made on clinical grounds together with a normal chest X-ray and lung function tests.

Dysfunctional breathing is common in young women and hence would be expected to occur commonly in pregnancy. Patients typically complain of breathlessness, which appears to be out of proportion to the clinical findings and their ability to perform activities of daily living. It occurs at rest and while talking as well as during exercise. Frequently there are unusual descriptions of dyspnoea including 'difficulty in taking a full breath' or 'a feeling of blockage in the chest'. Physical examination, as for physiological breathlessness of pregnancy, is normal apart from a possible increased respiratory rate.

The term *dysfunctional breathing* covers a number of phenotypes (clinical manifestations) of which hyperventilation is one of the best known. Although these conditions are clearly not life threatening, they may cause considerable distress to sufferers, who may also have underlying psychological problems or psychiatric illness.

Upper airways

Nasal obstruction (see Blocked nose in pregnancy) due to rhinitis may occur in up to 30 per cent of pregnant women, as a result of mucosal oedema, hyperaemia, capillary congestion, and mucus hypersecretion, which are caused by increased oestrogen levels. This occurs mostly in the third trimester and may lead to a sensation of breathlessness, particularly if severe. Vocal cord dysfunction could also be grouped under dysfunctional breathing and leads to similar descriptions of breathlessness. However, this condition frequently manifests as attacks of breathlessness and may simulate asthma, with which it often coexists. Around 10 per cent of all acute asthma admissions may in fact be due to vocal cord dysfunction. It can be diagnosed by clinical history, simple spirometry, which shows a narrowed inspiratory flow–volume loop, and laryngoscopy, which demonstrates adduction of the vocal cords on inspiration and sometimes expiration. Examination may reveal frank stridor or inspiratory wheeze on auscultation of the chest, transmitted from the vocal cords, but is usually normal between attacks.

Respiratory

Obstructive airways disease

Asthma is by far the most common obstructive airways disease likely to be encountered in pregnancy, occurring in 0.4–7 per cent of women. The diagnosis may be made for the first time in pregnancy, and the clue if often an unexplained or recurrent chest infection. It is characterised by intermittent breathlessness and wheeze, worse on exertion, which responds rapidly to inhaled beta- agonists. Examination reveals widespread expiratory wheeze when uncontrolled or during exacerbations. Diagnosis can be confirmed by peak flow monitoring over a 2-week period, typically revealing overall reduced peak flows and significant variability. There is frequently diurnal variation, with symptoms worsening at night or in the early morning. Uncontrolled asthma is defined by any of the following features: persistent troublesome symptoms, nocturnal symptoms, frequent use of inhaled beta-agonists, exacerbations, and limitation of physical activity.

There is some evidence that asthmatic symptoms worsen in one-third of patients, improve in one-third and are unchanged in the remaining third during pregnancy. However, it is also known that more than one-third of women reduce the use of their inhaled corticosteroids during pregnancy, which leads to an increased need to use the emergency department for this condition. Non-steroidal anti-inflammatory drug (NSAID) usage may trigger or worsen asthma.

Allergic bronchopulmonary aspergillosis (ABPA) is a complication of asthma and a form of pulmonary eosinophilia which results in pulmonary shadows typically in the upper lobes, mucus plugging, and lung or lobar collapse. Diagnosis is made by blood tests (high specific IgE to aspergillus, positive aspergillus IgG serology, blood eosinophilia higher than is usual in asthmatics) and chest X-ray.

Cystic fibrosis and *bronchiectasis are* characterised by frequent chest infections and increased cough with viscous, discoloured sputum. Breathlessness occurs if the disease is moderate or severe. Haemoptysis and chest pain may occur during exacerbations, and there is a greater frequency of pneumothorax, especially in cystic fibrosis. Malabsorption with steatorrhoea is common with cystic fibrosis, and sinusitis is common to both conditions.

Auscultation usually reveals inspiratory crackles over the affected areas. The diagnosis can be confirmed by chest X-ray, but high-resolution

computerised tomography (HRCT) scanning may be necessary for some cases of cystic fibrosis and is the investigation of choice for suspected bronchiectasis. This investigation may be necessary in pregnancy, but may be deferred if the immediate clinical management is unlikely to be significantly altered by the result.

Chronic obstructive pulmonary disease (COPD) can develop only with a smoking history of a minimum of 20 pack-years (number of cigarettes smoked per day multiplied by number of years smoked, divided by 20), and so is most likely to occur in pregnant women who are older than 35 years of age. The main symptom is breathlessness on exertion with reduced exercise tolerance. It may be accompanied by a cough with morning sputum production (chronic bronchitis). Examination may reveal reduced breath sounds generally or wheeze during exacerbations. Although confined to older women, this condition is very common, accounting for more admissions to hospital than any other respiratory disease. It often goes undetected as lung function (FEV1, see Lung function section below) can decline significantly before symptoms develop. Spirometry is, therefore, the cornerstone of diagnosis, while chest X-ray may be normal or reveal only hyperexpanded lungs.

Obliterative bronchiolitis is a relatively uncommon condition that is difficult to diagnose. Clinical and radiological features may be indistinguishable from asthma, with small airways obstruction, and there may be a history of childhood respiratory illness.

Parenchymal and interstitial lung disease

Pneumonia does not occur more frequently in pregnancy and usually presents as an acute illness with a short history of breathlessness, cough, and fever. There may be sputum production, pleuritic chest pain, and a preceding history of sore throat, cold, or influenza-like symptoms. Occasionally, e.g. with mycoplasma pneumonia, the illness may be of several weeks' duration. Examination may reveal increased respiratory rate, auscultatory crackles, or bronchial breathing. Diagnosis is confirmed by chest X-ray, which shows consolidation (Fig. 1). Pneumocystis pneumonia, which most often complicates human immunodeficiency virus (HIV) disease, usually presents with a several week history of dry cough and worsening breathlessness. Chest X-ray in this condition usually reveals bilateral interstitial infiltrates, although it may be normal. Bronchoscopy

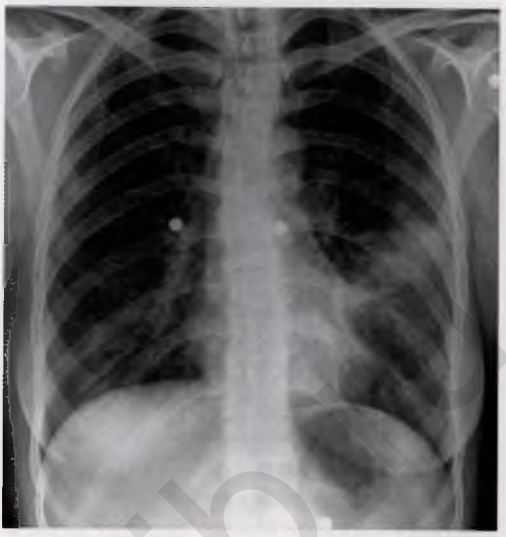

Figure 1 Pneumonia of the lingula lobe.

is often necessary to obtain specimens for cytological analysis.

Aspiration pneumonitis is more common during pregnancy due to the propensity for gastro-oesophageal reflux, and can occur during labour or during induction of general anaesthesia. The result may be a clinical condition indistinguishable from pneumonia resulting in respiratory failure owing to acute lung injury or adult respiratory distress syndrome (ARDS).

Acute lung injury or ARDS occurs in 0.2–0.3 per cent of pregnancies and may be caused by pneumonia, aspiration pneumonitis, eclampsia, or amniotic fluid embolism in pregnancy, with which the patient will have presented initially. The diagnosis is suggested by a deteriorating clinical condition and worsening of chest X-ray consolidation throughout both lung fields.

Tuberculosis (TB) may lead to breathlessness when there is extensive bilateral involvement of lung parenchyma. There may be a history of cough, sputum, weight loss, haemoptysis and night sweats, frequently with underlying risk factors, such as ethnicity or family history. Sputum should be examined for acid-fast bacilli and a chest X-ray performed, which will show extensive consolidation (if the patient presented with breathlessness), often with cavitation. If there is no sputum production, then bronchoscopy is necessary to collect bronchial washings. Old TB frequently leads to airflow obstruction indistinguishable from asthma or COPD.

Pulmonary metastases, such as from choriocarcinoma, are rare and easily diagnosed by chest X-ray, which shows one or more nodules of varying size. Symptoms usually occur when metastases are extensive, and include breathlessness, cough, and haemoptysis, but chest auscultation will often be normal. Choriocarcinoma may also cause pleural effusions when pleural metastases are present.

Sarcoidosis is common in young women, especially of Afro–Caribbean origin in which it is often more severe. It may cause breathlessness if there are pulmonary infiltrates or, rarely, extensive mediastinal lymphadenopathy compressing the main bronchi. In such cases there may also be cough, weight loss, and other organ involvement, such as skin or eyes. Auscultation of the chest may be normal or reveal inspiratory crackles or wheeze. There may be palpable lymphadenopathy and skin lesions. The diagnosis is suggested by chest X-ray in conjunction with the clinical picture. Serum angiotensin-converting enzyme may be raised but is not specific enough to confirm the diagnosis and a biopsy is usually undertaken, e.g. of bronchial mucosa by bronchoscopy, or of mediastinal lymph glands by endobronchial ultrasound (EBUS).

Drug-induced interstitial lung disease may be caused, for example, by nitrofurantoin or amiodarone. Nitrofurantoin, which is used for long-term treatment of recurrent urinary tract infections, can cause acute and chronic forms of interstitial lung disease with severe life-threatening hypoxia. Amiodarone, which is used in the treatment of cardiac arrhythmias, can cause an acute pneumonitis (incidence 0.1–0.5 per cent with a dose of 200 mg daily) and subsequent pulmonary fibrosis (incidence 0.1 per cent). It is more common with increasing dose and duration of therapy. These conditions usually present with breathlessness and dry cough. Auscultation of the chest may reveal fine bibasal inspiratory crackles.

Lymphangioleiomyomatosis is a rare condition, but it occurs exclusively in young women of reproductive age and should, therefore, be considered in the differential diagnosis of breathlessness in pregnancy. Clinical manifestations include interstitial lung disease, recurrent pneumothoraces, which may be bilateral, and an association with tuberous sclerosis, which is often apparent. Chest auscultation may be normal or reveal fine inspiratory crackles. There is some evidence that lymphangioleiomyomatosis worsens during pregnancy. Diagnosis may be suspected clinically and with chest X-ray, but HRCT scanning is needed for confirmation.

Lymphangitis carcinomatosa occurs in advanced metastatic breast cancer, and can cause severe breathlessness and dry cough. As with drug-induced interstitial lung disease, there may be profound hypoxia.

Extrinsic allergic alveolitis is relatively uncommon and often associated with an identifiable trigger antigen, such as inhalation of thermophilic *Actinomycetes* spores in mouldy hay (farmer's lung). Progressive breathlessness, wheeze, and cough occur with pulmonary infiltrates on chest X-ray, often in the upper lobes.

Usual interstitial pneumonia (UIP) and *non-specific interstitial pneumonia* (NSIP) (formerly known as 'fibrosing alveolitis') usually occur later in life, but may be associated with autoimmune diseases, which occur more frequently in young women, such as rheumatoid disease, scleroderma, and systemic lupus erythematosus, and should, therefore, be considered in the differential diagnosis of breathlessness in pregnancy. Other rarer forms of interstitial lung disease include acute interstitial pneumonia and respiratory bronchiolitis interstitial lung disease. Progressive breathlessness and cough are typical, with bilateral, fine, mid-late inspiratory crackles on auscultation. Finger clubbing may be present, but is often absent in earlier and milder disease. Chest X-ray usually shows peripheral bibasal interstitial shadowing, but HRCT scanning is necessary to define the type of disease and likely response to treatment. Lung function testing, as with the other interstitial lung diseases, reveals a reduced transfer factor (diffusion capacity).

Cryptogenic organising pneumonia, a condition more common than might be assumed, may also be associated with the above autoimmune diseases, and may present more acutely with breathlessness, cough, and hypoxia. The parenchymal shadowing is often more patchy than in UIP and NSIP. The chronic nature of some of the above conditions may not necessarily be compatible with pregnancy, although some may have a relatively acute onset.

Vascular

Pulmonary embolus remains an important cause of breathlessness that needs to be excluded. The risk of *pulmonary embolism* (PE) in pregnancy is higher with increasing age, body mass index, caesarean section, family history of thromboembolism, thrombophilia, previous thromboembolism, and pre-eclampsia. Pregnancy itself is also a major risk factor for venous

thromboembolism, and PE remains one of the most common causes of maternal death in the UK. PE may present with breathlessness and chest pain, but also may be asymptomatic: 40 per cent of patients with a proximal deep vein thrombosis and no chest symptoms will have a positive ventilation/perfusion (V/Q) scan. There may be tachycardia and hypotension in more severe cases, and usually a degree of hypoxia. Chest examination will usually be normal except for an increased respiratory rate. Chest X-ray is important in excluding other possible causes of breathlessness, and diagnosis is confirmed by V/Q scanning. Computerised tomographic pulmonary angiography (CTPA) may be needed for diagnosis when the V/Q scan is inconclusive.

Amniotic fluid embolism is rare, occurring in 0.01–0.001 per cent of pregnancies, and presents with sudden onset of breathlessness during labour or within 30 minutes of delivery. There is cardiovascular shock as well as disseminated intravascular coagulation, and the mortality is 60–90 per cent, making it a leading cause of maternal death.

Pulmonary hypertension is now classified into (1) pulmonary arterial hypertension (idiopathic or associated with collagen vascular disease; (2) pulmonary hypertension associated with left-sided heart disease; (3) pulmonary hypertension associated with lung diseases and/or hypoxaemia, e.g., COPD and sleep-disordered breathing; (4) chronic thromboembolic pulmonary hypertension; and (5) pulmonary hypertension with miscellaneous and unclear causes, such as sarcoidosis. There may be ankle oedema and other signs of right-sided heart failure, such as a raised jugular venous pressure, right ventricular heave, and a loud P2, but the onset and progression are insidious, and the diagnosis is frequently missed early in the course of the disease.

Pleural

Pleural effusion secondary to pneumonia or TB, for example, may cause breathlessness, particularly if moderate or large in size (Fig. 2). Rare causes of pleural effusion in pregnancy include lymphangioleiomyomatosis (chylothorax), choriocarcinoma, breast carcinoma and other malignancies, and ruptured diaphragm during labour. Chest examination reveals dullness to percussion and absent or reduced breath sounds over the effusion. Small effusions may be asymptomatic. It is debatable whether labour itself predisposes to the development of pleural effusions. Studies of chest X-rays postpartum

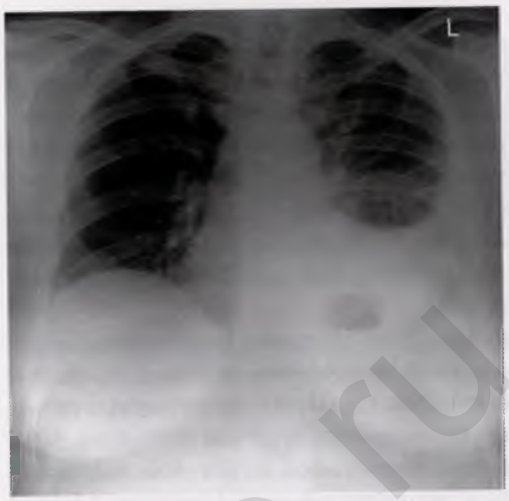

Figure 2 Pleural effusion, left side.

revealed an increased number of effusions, but when ultrasonography was used no increased incidence was observed.

Empyema and *pneumothorax* are discussed elsewhere with reference to non-cardiac causes of chest pain (see Chest pain in pregnancy: non-cardiac causes).

Chest wall

Obesity (body mass index >30) frequently leads to breathlessness and reduced exercise tolerance. Examination may otherwise be normal. *Kyphoscoliosis, ankylosing spondylitis*, and *neuromuscular disorders* may cause respiratory failure because of abnormal lung mechanics or diaphragmatic paralysis. Any patient with one of these conditions complaining of breathlessness should have arterial blood gases checked for evidence of hypoxia and hypercapnia.

Splinting of the diaphragm may occur in ovarian hyperstimulation syndrome (OHSS) and also with gross polyhydramnios. Appropriate management will depend on the severity of OHSS and the stage of the pregnancy; see Amniotic fluid abnormalities.

Metabolic

Anaemia is common in pregnancy, but will usually lead to reduced exercise tolerance and tiredness rather than breathlessness as such. The conjunctivae and nail beds should be examined and a note made of general pallor; however, these signs are unreliable and the blood haemoglobin level should always be checked.

Thyrotoxicosis may occasionally present with breathlessness. Typical features include weight loss, sweating, diarrhoea, irritability, tremor, tachycardia, and eye signs. There may be a goitre on examination of the neck. Diagnosis is confirmed by thyroid function testing.

Acute and *chronic renal failure, metabolic acidosis,* and *systemic sepsis* can cause breathlessness, but the diagnosis should be apparent from the clinical picture.

Usually the diagnosis of breathlessness in pregnancy can be made from the history and physical examination, but a chest X-ray is essential to exclude the more important conditions listed above. Many chronic diseases affect fertility and consequently occur uncommonly de novo in pregnancy. A focused history should thus be obtained.

History

History of presenting complaint

This should include:

- onset of symptoms in relation to timing of the pregnancy;
- duration, chronicity, nature and severity of breathlessness;
- exercise tolerance, especially in relation to activities of daily living, e.g. climbing stairs;
- presence or absence of cough, sputum or haemoptysis;
- relief with inhalers;
- palpitations;
- chest pain;
- weight loss, fevers, anorexia, malaise;
- leg pain;
- nasal and sinus problems;
- sore throat, arthralgia and myalgia.

Past medical history

This should include:

- asthma, hay fever, eczema;
- TB, previous BCG (bacille Calmette–Guérin), cystic fibrosis, bronchiectasis, other lung disease;
- sarcoidosis, kyphoscoliosis, neuromuscular disease, heart disease, recurrent urinary tract infections;
- malignancy (e.g. breast cancer), immunosuppression (e.g. HIV positive);
- psychiatric illness;
- previous history of PE or thrombophilia.

Drug history

- Amiodarone, nitrofurantion, NSAIDs, and inhalers.

Psychological history

- Symptoms of anxiety or depression.

Family history

- Clotting disorders, asthma, atopy, TB, lung cancer, and sarcoidosis.

Social history

- Ability to continue leading normal life, especially going to work, climbing stairs, doing housework, carrying, shopping.
- Living in or travel to area of high TB prevalence, and contact with TB.
- Exposure to allergens, e.g. pets, moulds, hay.
- Occupation, e.g. farmer, factory worker, teacher, and carer.

Physical examination

- *Body mass index* (BMI).
- *General appearance*: confusion, sweating, tremor, pyrexia, cyanosis, pallor, obesity, clubbing, lymphadenopathy, BCG scar, goitre, exophthalmos, lid lag. These may reflect the severity of the disease or point to potential aetiologies.
- *Cardiovascular*: arrhythmia, low or high blood pressure, raised jugular venous pressure (JVP), parasternal heave, gallop rhythm, murmur, loud P2, pericardial rub, leg oedema.
- *Respiratory*: rate, effort, accessory muscle usage, kyphoscoliosis, tracheal shift, dullness to percussion, wheeze, bronchial breathing, reduced or absent breath sounds, crackles.
- *Breast*: lumps, although mammography, if indicated, may be better than examination.
- *Neurological*: muscle wasting, fasciculation, upper or lower limb weakness, sensory loss, cerebellar signs.
- *Skin*: evidence of tuberous sclerosis, sarcoid or systemic lupus erythematosus (SLE).

Investigations

Radiology

Concern is often raised by the patient, partner, or other medical or non-medical staff regarding the risk of ionising radiation to the growing fetus. The potential adverse effects of radiation can be divided into pregnancy loss (miscarriage, stillbirth), malformation, growth or developmental retardation, and carcinogenesis. During the first 14 weeks after conception, radiation-induced malformation, growth restriction, and carcinogenesis do not occur, as the embryo either survives undamaged or is resorbed. Doses of ionising radiation for various radiological investigations are shown in Table 2. It is debatable which units of radiation to use, but the conversion from one to the other is straightforward: 1 rad = 0.01 gray (Gy) = 0.01 sievert (Sv).

Table 2 Radiation dose from various radiological modalities

Radiological modality	Estimated fetal radiation dose (rads)
Chest X-ray	0.00007
Perfusion scan	0.175
Ventilation/perfusion (V/Q) scan	0.215
CTPA	<0.100
HRCT thorax	0.100
Conventional CT thorax	0.265

CT, computerised tomography; CTPA, computerised tomographic pulmonary angiogram; HRCT, high-resolution computerised tomography.

There is no evidence of any increased risk of pregnancy loss, malformation, or growth delay in doses up to 5 rads. This is the equivalent of 71,000 chest X-rays, 50 CTPAs, or 30 V/Q scans, figures worth bearing in mind when considering and discussing the need for these investigations with the pregnant patient. It is possible that doses as low as 1 to 2 rads may increase the risk of childhood cancer such as leukaemia by up to twice the baseline incidence, though this is controversial. The American College of Radiology state that radiological procedures should be performed only in pregnancy if the result is necessary for the care of the patient. When considering any potential adverse effects to the fetus, the risks of not performing important radiological investigations must be taken into account and conveyed to the patient. It can be seen that, for most of the common tests, exposure to radiation is minimal. The tests themselves are essential for arriving at a clear diagnosis that enables a proper management plan to be instituted.

In the first instance, a chest X-ray is crucial to diagnosing or excluding important respiratory conditions such as pneumonia, pleural effusion, pneumothorax, tuberculosis, and sarcoidosis (Figs 1 and 2). Without this simple investigation, it is impossible to manage the patient correctly or make any sensible assumptions about the cause of breathlessness. Similarly, V/Q scanning is essential to the diagnosis of PE. CTPA is useful in the diagnosis of PE when V/Q scanning shows only an intermediate probability of PE and the clinical suspicion is intermediate or high. HRCT is used in the diagnosis of bronchiectasis and interstitial lung disease, but could be avoided until the postpartum period if the result is unlikely to change the immediate clinical management of the condition.

Although the radiation dose from thoracic CT scanning may be acceptable to the fetus, of greater consideration might be the potential excess risk of breast cancer to the pregnant woman herself. A dose of 1 rad may increase the lifetime risk of breast cancer by as much as 14 per cent in exposed women younger than 35 years old. CTPA delivers 2 to 3.5 rads to each breast.

Lung function

The most important lung function tests – the forced expiratory volume (amount blown out) in one second (FEV1), and the FEV1/FVC ratio (FVC, forced vital capacity, is the total volume of air the subject is able to blow out in one manoeuvre) are unchanged in pregnancy. Normal spirometry (FEV1, FVC, and FEV1/FVC ratio) performed with a simple hand-held spirometer (Fig. 3) should rule out any obstructive lung disease (asthma, cystic fibrosis, bronchiectasis, COPD) of sufficient severity to cause breathlessness, although it may also be normal in well-controlled asthma. Spirometry indicative of obstructive lung disease is typified by a low FEV1/FVC ratio (<70 per cent), low FEV1 (<80 per cent), and a characteristic 'scooped out' flow–volume curve, caused by obstruction to the small airways (Fig. 4).

Spirometry should be performed and interpreted only by trained personnel, and one should be wary of misleading computer printout diagnoses! Attention should also be paid to the inspiratory flow–volume

Figure 3 Hand-held spirometer.

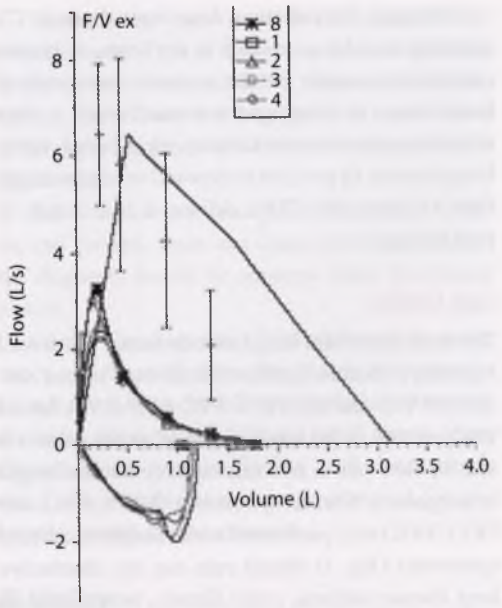

Figure 4 Spirometry (flow/volume [F/V] loop) showing results of several attempts, indicating good reliability (ex = expected).

loop, which may be significantly narrowed in cases of vocal cord dysfunction. Peak flow recordings are essential for the diagnosis of asthma and most useful if measured over a period of at least 2 weeks.

More extensive lung function tests, such as diffusion capacity (transfer factor) and static lung volumes, which are useful in diagnosing and monitoring interstitial lung disease, need to be performed in a respiratory laboratory. Walking oximetry involves asking a patient to walk for 6 minutes with a handheld oximeter attached to the finger. It is a useful test in the diagnosis of unexplained breathlessness for two reasons: (1) it demonstrates how far a patient can walk in that time and with how many stops; and (2) it shows whether there is any oxygen desaturation during the test. In this way, an objective measure can be determined of how far the patient can walk, and whether or not there is any significant respiratory disorder.

Blood tests

In the investigation of the pregnant patient with excessive breathlessness, blood should be taken for haemoglobin, white cell count, urea and electrolytes, D-dimers, and thyroid function tests. Negative D-dimers effectively exclude a diagnosis of PE and should obviate the need for V/Q scanning, but D-dimers increase progressively until term and are, therefore, of most use in early pregnancy. Positive D-dimers are relatively non-specific and may be raised with infections, for example.

Arterial blood gases should be taken in any patient needing further investigation or suspected of having a PE or pneumonia in particular, as significant hypoxia (low PaO_2) usually occurs in these conditions. When interpreting the results, consideration should be given to the fact that pO_2 increases and pCO_2 decreases slightly in normal pregnancy with a tendency towards mild alkalosis.

When to refer the breathless pregnant patient to a respiratory specialist

The following is a list of suggested criteria for referral to a respiratory specialist, when considering the breathless pregnant patient:

- unduly troublesome breathlessness;
- worsening breathlessness;
- acute breathlessness;
- when a CT of the thorax is indicated;
- when detailed lung function testing, such as diffusion capacity, static lung volumes or walking oximetry, is needed;
- uncertainty about performing or interpreting spirometry;
- abnormal chest X-ray or lung function result;
- uncertainty regarding diagnosis.

Summary

Breathlessness in pregnancy is usually physiological in nature, but can generally be distinguished from more serious causes by taking a careful history, performing a physical examination and a chest X-ray. Simple lung function testing should be performed where necessary, and is essential for diagnosing or excluding important respiratory conditions.

Further reading

Guidelines for the diagnosis and management of asthma, COPD, pulmonary embolism, TB, pneumonia, interstitial lung disease, pleural disease and pneumothorax. www.brit-thoracic.org.uk

Mallick S, Petkova D. Investigating suspected pulmonary embolism during pregnancy. *Respir Med* 2006; **100**: 1682–87.

UpToDate. Wolters Kluwer Health. www.uptodate.com

CERVICAL CYTOLOGY, ABNORMAL

Linda Leitch-Devlin and Karina Reynolds

The cervical smear is an important test that screens for premalignant disease of the cervix. This disease is caused by persistent infection with high-risk human papilloma virus (HPV) types. Cervical cells are collected from the cervical transformation zone. Prior to puberty, the squamocolumnar junction is located within the endocervical canal. As a result of the hormonal changes at puberty, there is eversion of the columnar epithelium towards the vagina. At the same time, there is a change in the vaginal pH, which becomes more acidic (pH 4–5). This stimulates 'metaplasia', whereby the columnar epithelium changes to squamous epithelium. This area, essentially where columnar cells have transformed to squamous cells, is called the transformation zone. It is in this area that most premalignant changes occur; therefore, it is essential that the squamocolumnar junction be sampled when taking a smear (Fig. 1). Squamocolumnar junction visibility is classified in the following way: completely visible, partially visible, not visible, as transformation zone types 1, 2, and 3.

In 2003 NICE recommended that liquid-based cytology (LBC) should be the method used for processing cells within the National Health Service Cervical Screening Programme (NHSCSP). There are two technologies in use in the NHSCSP, namely ThinPrep® and SurePath®. Sample takers need to be familiar with their local technology in order to prepare the sample appropriately. NHSCSP guidelines recommend starting screening at the age of 25 years and undertaking smears every 3 years until the age of 50, and then every 5 years until the age of 65. This reflects the rarity of cervical cancer below the age of 25 years.

Dyskaryosis is a cytological term essentially meaning 'abnormal' (dys) 'nuclei' (karyosis). On microscopy there is a change in the nuclear cytoplasmic ratio with an increase in the size of the nucleus compared with the cytoplasm. Increased mitoses and lobulation may also be seen (Figs 2 and 3).

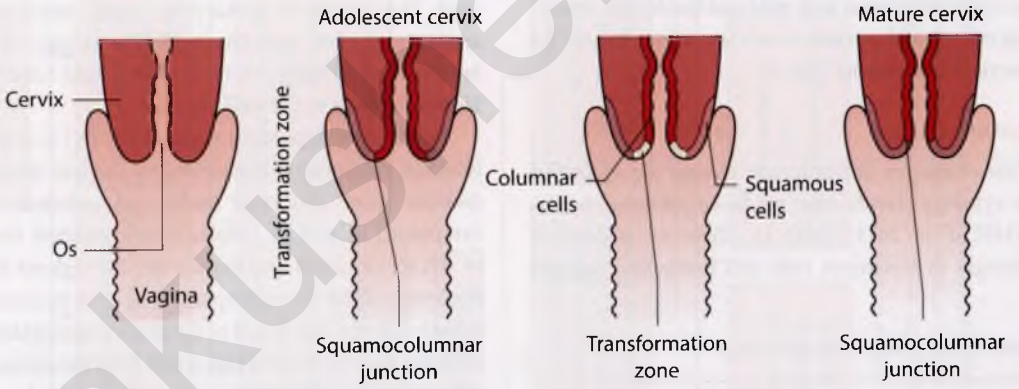

Figure 1 Development of transformation zone of the cervix.

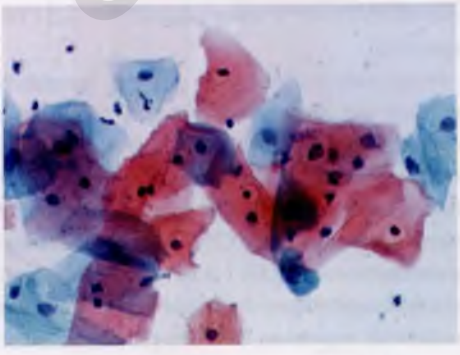

Figure 2 Normal cervical cytology.

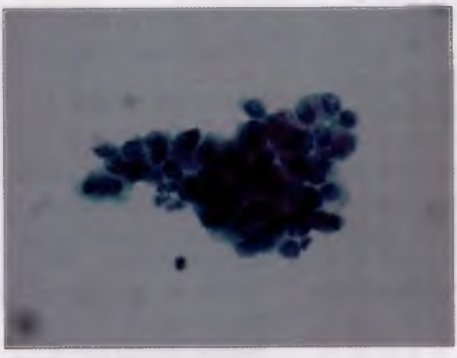

Figure 3 Severe dyskaryosis, change in the nuclear–cytoplasmic ratio.

Colposcopy referral recommendations

Abnormalities in cervical cytology include the following.

Inadequate smear

The smear is considered to be inadequate in several circumstances where definitive diagnosis is not possible. The smear may be poorly prepared at the point of collection (inappropriate sampling device, scanty sampling, or air-dried), may be obscured by blood or inflammatory cells, or may not contain the right type or amount of cells (a slide that contains too few cells or consists entirely of endocervical cells). A repeat sample should not be taken within three months of one reported as inadequate. After three consecutive inadequate results, colposcopic assessment is recommended. The rate of inadequate smears has been dramatically reduced with the implementation of LBC.

HPV implementation

In 2011 the Operating Framework for the NHS in England recommended the adoption of HPV testing as triage for women with mild and borderline screening reports and as a test of cure for women treated for cervical abnormality (Fig. 4).

Borderline smear

Two categories of borderline change are identified in cytology classification guidance published by the NHSCSP in 2013 (Table 1). These are borderline changes in squamous cells and borderline changes in endocervical cells. In both categories the aim is to identify cells where dyskaryosis cannot be definitively excluded.

Table 1 Classification of cervical cytology

Previous terminology (BSCC 1986)	New terminology
Borderline change	Borderline change in squamous cells Borderline change in endocervical cells
Mild dyskaryosis Borderline change with koilocytosis	Low-grade dyskaryosis
Moderate dyskaryosis	High-grade dyskaryosis (moderate)
Severe dyskaryosis	High-grade dyskaryosis (severe)
Severe dyskaryosis ?Invasive	High-grade dyskaryosis/?invasive squamous carcinoma
?Glandular neoplasia	?Glandular neoplasia of endocervical type ?Glandular neoplasia (non-cervical)

Premalignant disease

Women with cervical dyskaryosis are asymptomatic, as premalignant disease of the cervix is a subclinical condition. Symptoms and signs are suggestive of invasive disease or coexisting conditions. Those symptoms requiring investigation include vaginal discharge and intermenstrual, postcoital, and postmenopausal bleeding. The need to appropriately manage symptomatic women under the age of 25 has been recognised by Department of Health (DOH) guidance 2010 (Fig. 5).

According to current NHSCSP guidelines, women with borderline changes or low-grade dyskaryosis and who are found to be positive for high-risk HPV subtype should be seen and assessed in colposcopy, but not necessarily treated. Women who do not have high-risk HPV sub-types present remain on routine recall.

Women with high-grade dyskaryosis, either moderate or severe smears, should be referred for colposcopy. The degree of dyskaryosis (mild, moderate, and severe) often correlates with the changes that are found at histology (CIN 1, CIN 2, and CIN 3). However, this is not always the case.

Cervical intraepithelial neoplasia (CIN) is a histological diagnosis characterised by nuclear abnormalities (large abnormal nuclei and reduced cell cytoplasm) as well as cellular disorganisation (loss of cell stratification and maturation throughout the thickness of the cervical epithelium) and increased mitotic activity. The extent of the above features identifies the degree of CIN (Figs 6 and 7). If the mitoses and immature cells are present only in the lower one-third of the epithelium, the lesion is reported as CIN 1, whereas involvement of the middle and upper thirds as well is reported as CIN 2 and CIN 3, respectively.

Prospective studies show that the spontaneous regression rate of biopsy-proven CIN 1 ranges from 60 per cent to 85 per cent, with regression typically occurring within a 2-year follow-up period. This information has led to the recommendation that patients diagnosed with CIN 1 do not necessarily require treatment. If CIN 1 is not treated, cytological and colposcopic follow-up should be performed until spontaneous regression has occurred or treatment is required. If the lesions progress during follow-up or

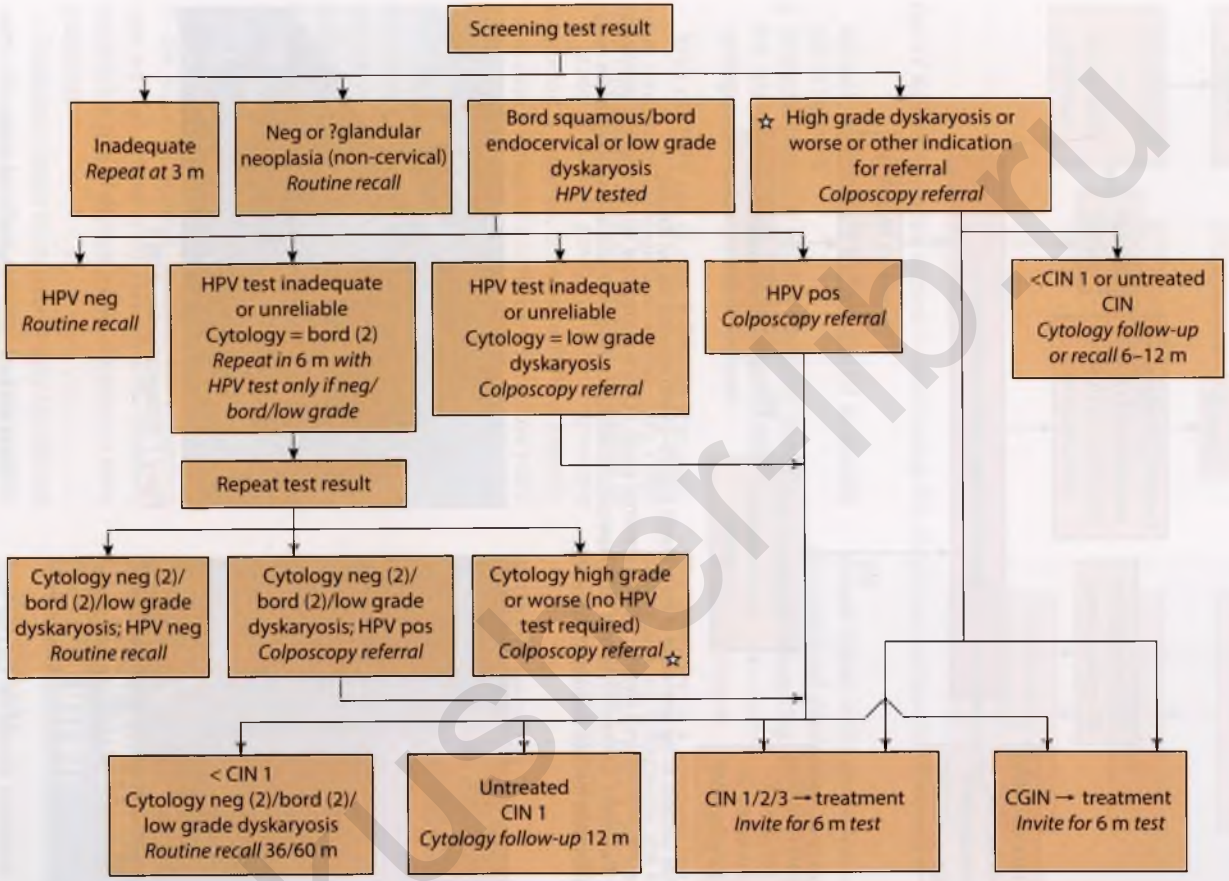

Figure 4 Cervical screening protocol algorithm for HPV triage and test of cure protocol.

Bord, borderline; CGIN, cervical glandular intraepithelial neoplasia; CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; neg, negative; pos, positive; (2) used to denote both categories of negative result (negative and ?glandular neoplasia [non-cervical]) or both categories of borderline result (borderline change in squamous cells and borderline change in endocervical cells); ☆: colposcopy referral without HPV test. Data from http://www.cancerscreening.nhs.uk/cervical/hpv-triage-test-flowchart-201407.pdf, with permission. (For management of untreated CIN 1, test of cure following treatment for CIN 1/2/3, and test of cure following treatment for CGIN, see pages 2–4 of webpage.)

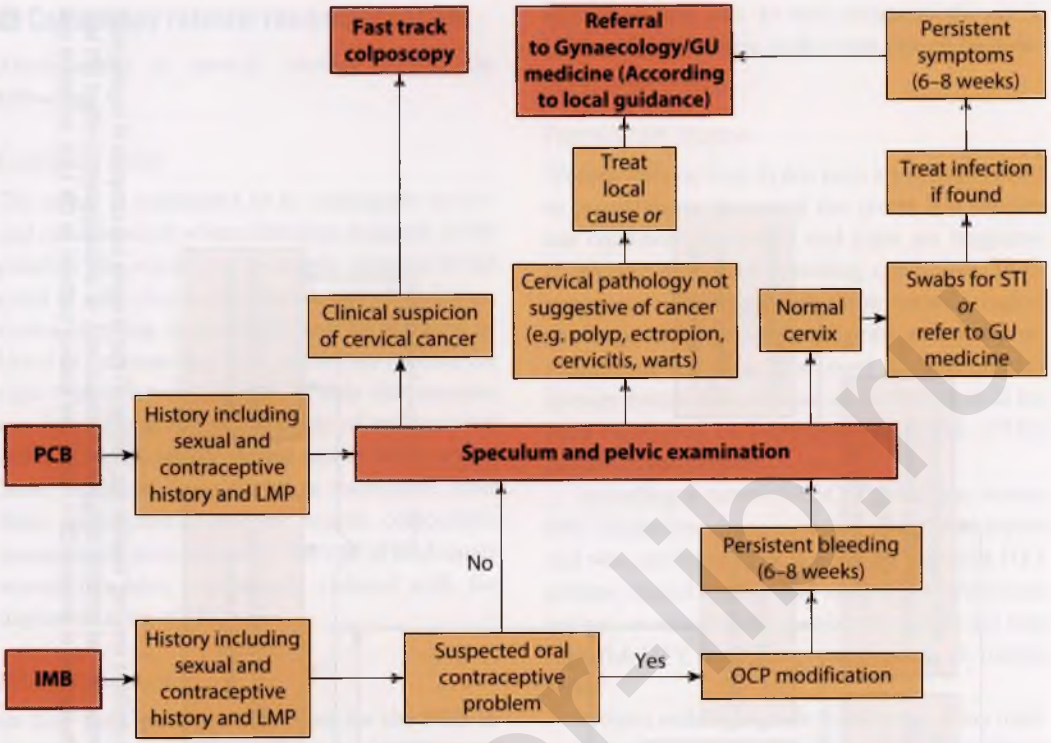

Figure 5 'Clinical Practice Guidance for the Assessment of Young Women aged 20–24 with Abnormal Vaginal Bleeding'.

PCB, postcoital bleeding; IMB, intermenstrual bleeding; LMP, last menstrual period; OCP, oral contraceptive pill; GU medicine, genitourinary medicine; STI, sexually transmitted infection. (Data from http://www.cancerscreening.nhs.uk/cervical/publications/doh-guidelines-young-women.pdf, with permission under the Open Government licence v2.0).

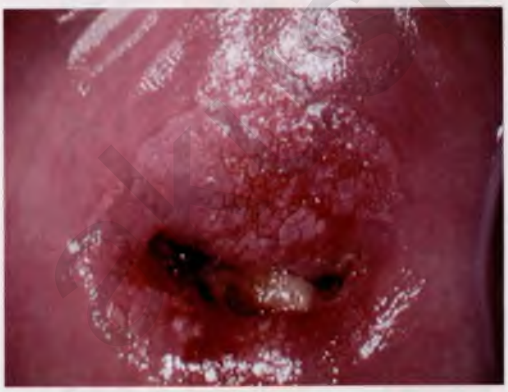

Figure 6 Colposcopic appearance of CIN 3 after the application of acetic acid.

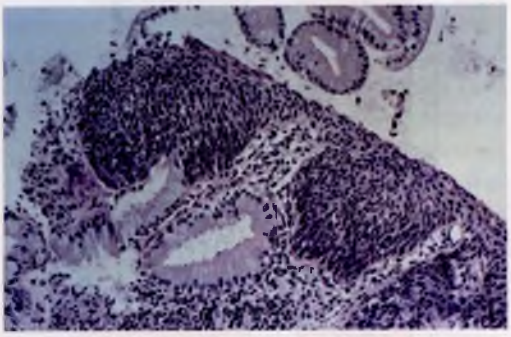

Figure 7 Histological picture of CIN 3.

persist at 2 years, treatment should be carried out. While all grades of CIN have the potential to regress, current guidelines recommend the treatment of CIN 2 and 3.

Colposcopy is a diagnostic tool, the definitive diagnosis being made on histology of the colposcopically directed biopsy.

There are two main types of treatments:

- *Excisional treatments*: generally preferred are knife cone biopsy, laser cone biopsy, large loop excision of the transformation zone (LLETZ or loop). Hysterectomy is occasionally required. With an excisional approach, the transformation zone is completely removed and available for full histological assessment after treatment. In a 'see-and-treat'

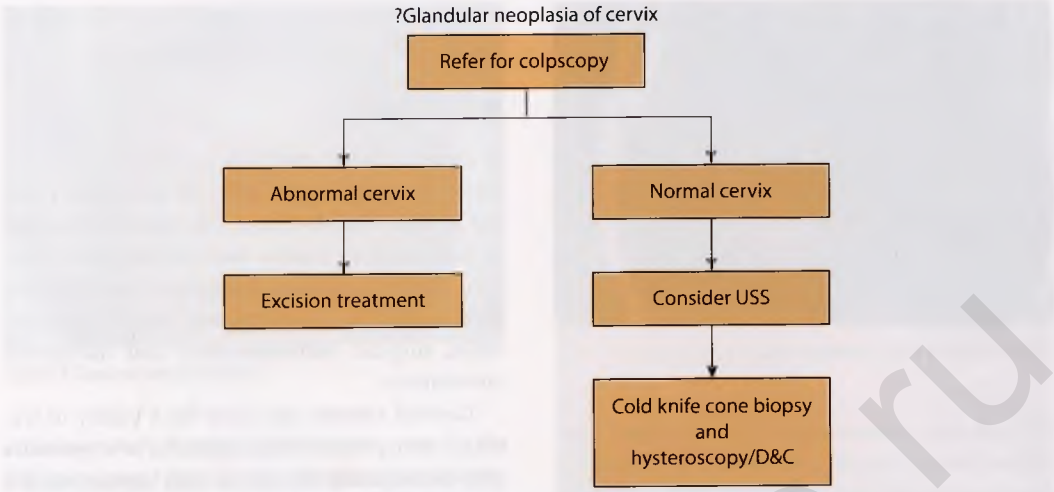

Figure 8 Algorithm for glandular neoplasia on cervical cytology. D&C, dilatation and curettage; USS, ultrasound scan.

approach, the histological diagnosis will not be available prior to treatment.

- *Destructive treatments*: including cryocautery, laser ablation, and electrodiathermy cold coagulation. A histological diagnosis is mandatory prior to treatment.

With the HPV test of cure, follow-up after treatment consists of cytological screening with reflex HPV type testing when the cytology is negative or low grade. If HPV is positive, further colposcopic assessment is required; however, if HPV is negative, the woman will require a further smear in three years.

High-grade cervical glandular intraepithelial neoplasia (CGIN) is a premalignant disease of the cervix but is rarer than CIN. The incidence of glandular neoplasia on cytology is in the order of 0.05 per cent of routine smears. This is a challenging disease, given that cytological screening is unsatisfactory and colposcopic features usually require expert interpretation. The diagnosis is often made by chance while treating CIN, as these conditions often coexist. Fortunately, most cases of CGIN occur within 1 cm of the squamocolumnar junction, but recurrence rates are high (14 per cent), even when the treatment margins are free of disease, as the condition is often multifocal.

Treatment ranges from conservative (in selected cases who wish to retain fertility) to hysterectomy. Conservative options include conisation. On follow-up, it is recommended that regular endocervical cytology in addition to conventional cytology and colposcopy should be performed.

It is important to emphasise that this type of cervical cytological abnormality can be related to disease higher in the genital tract, and this needs to be considered depending on symptoms and colposcopic findings (Fig. 8).

Malignant disease

The smear test is a screening test for premalignant disease and not a diagnostic test for cervical cancer. Cervical cytology from a cervix with an invasive lesion often contains inflammatory cells only.

Useful websites

British Society for Colposcopy and Cervical Pathology: www.bsccp.org.uk

Clinical Practice Guidance for the Assessment of Young Women aged 20–24 with Abnormal Vaginal Bleeding, 2010: http://www.cancerscreening.nhs.uk/cervical/publications/doh-guidelines-young-women.pdf

NHS Cervical Screening Programme (NHSCSP): www.cancerscreening.nhs.uk/cervical/

CERVICAL SWELLING (CERVIX UTERI)

Sotiris Vimplis

The cervix uteri is the lower part of the uterus (womb). This cylindrical-shaped muscular structure is about 3–5 cm in length and partly lies in the upper vagina, extending behind the bladder and in front of the rectum (Fig. 1). It is composed mainly

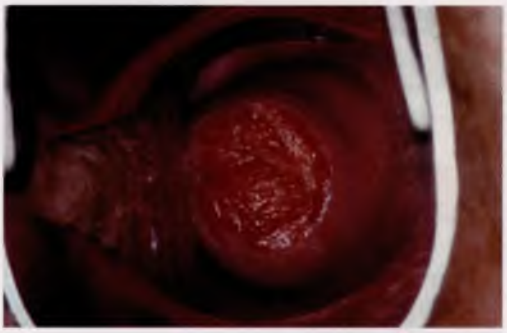

Figure 1 Normal cervix showing a cervical ectropion.

of involuntary muscle superiorly and fibrous connective tissue inferiorly. It is lined by squamous epithelium on the ectocervix, and columnar epithelium on the endocervix. The position of the squamocolumnar junction varies depending on the age of the woman. Likewise the size of the cervix varies, increasing at puberty, during reproductive age, and throughout pregnancy, and then reducing after menopause.

Cervical swellings can be divided into the following categories.

Physiological (nabothian follicles)

Nabothian cysts represent a common cause of cervical swelling (Fig. 2). These mucinous retention cysts occur very frequently and are the result of spontaneous 'healing' of cervical eversion by squamous metaplasia, which covers over and obstructs endocervical glands. They are translucent or opaque, white or yellow lesions ranging from 2 mm to 10 mm in size.

They are usually asymptomatic and need no treatment. They may very occasionally be problematic if they grow very large, in which case they may be treated with cautery or cryotherapy.

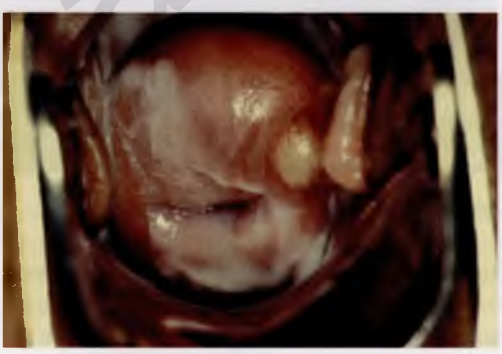

Figure 2 Nabothian follicle on the cervix.

Reactive

In non-infectious cervicitis, a swollen, erythematous, and friable cervix with an associated purulent endocervical discharge may develop. This may be secondary to insults, such as chemical irritation, copper-containing intrauterine contraceptive devices (IUCDs), inappropriate tampon use, pessaries, surgical instrumentation, and therapeutic intervention.

Cervical stenosis can occur for a variety of reasons, causing either a haematometra or a pyometra and, consequently, the cervix may appear swollen and oedematous. In older women, cervical stenosis may be due to atrophy, but in younger women, cervical scarring may result from trauma (lacerations during labour or at the time of abortion) or surgery (cone biopsy, cryotherapy, cervical cauterisation, or radiation therapy for cervical cancer).

Note that the diagnosis of haematometra or pyometra in an older woman should always suggest the possibility of an associated malignancy. The diagnosis may be inferred from the patient's history and biopsy if necessary.

Infective (bacterial, viral, and fungal)

Both acute and chronic cervical infections (acute and chronic cervicitis) can result in some degree of cervical swelling. The organisms most commonly responsible for active inflammation in the cervix include *Candida albicans*, *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and the herpes simplex virus. An acute inflamed cervix is swollen and red, often with a mucopurulent plug exuding from the external os; with herpes it can also become necrotic. Diagnosis is confirmed by taking appropriate swabs from the vagina and endocervical canal.

Cervical warts (Fig. 3) are an uncommon finding and are usually due to human papilloma virus (HPV) types 6 and 11. They may reflect exposure to the oncogenic types of HPV (16 and 18) and should be biopsied, as there may be coexisting cervical intraepithelial neoplasia at their base.

Specific forms of chronic cervicitis that may result in some degree of cervical swelling include tuberculous cervicitis and cervical involvement in

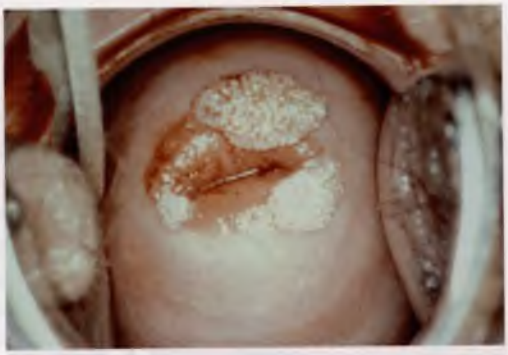

Figure 3 Cervical wart/condyloma.

schistosomiasis. Cervical tuberculosis, rare in the UK, may spread from an upper genital tract disease, which in turn originates from pulmonary tuberculosis. The clinical presentation is either a predominantly hypertrophic or ulcerative lesion, which may be mistaken for carcinoma. The cervix may also be involved with similar features, mainly when tuberculosis presents with a non-caseating granulomatous lesion, in syphilis, granuloma inguinale, and lymphogranuloma venereum.

Diagnosis in these cases may be made on biopsy and a high index of suspicion. The differential diagnosis may be made only by means of Ziehl–Neelsen-stained sections, culture, or animal inoculation of cervical tissue.

Haemorrhagic

Cervical endometriosis may be apparent as blue-red or blue-black lesions 1–3 mm in diameter, which may have been implanted during childbirth or surgery. Occasionally, it can cause postcoital bleeding, and it may present as a cyst or mass either in isolation or as part of the picture of endometriosis (see Pelvic pain and Menstrual periods, heavy and/or irregular). Diagnosis will be made by biopsy.

Neoplastic

Benign

Endocervical polyps (Fig. 4) represent a common swelling on the uterine cervix. They are most often focal and observed in multigravida during the fourth to sixth decades of life. Their size can range from a few millimetres to some centimetres; rarely, a cervical polyp can become so large that it protrudes beyond the introitus and is mistaken for a carcinoma. A polyp

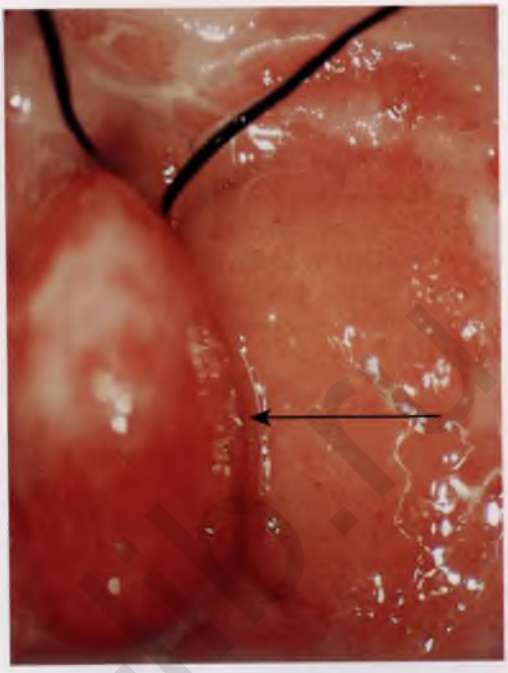

Figure 4 Cervical polyp (arrow) with IUCD strings visible.

is defined essentially as a lump on the end of a stalk without any commitment as to the nature of the lump. In reality several different cervical lesions can mimic a cervical polyp and can be classified only histologically, as the macroscopic appearances may be similar.

The various types include the following:

- *Mesodermal stromal polyp*, also known as pseudosarcoma botryoides, is a benign, exophytic mass almost only observed in the vagina and cervix of pregnant patients. It can be confused with the malignant sarcoma botryoides.
- *Decidual pseudopolyp*: during gestation, decidual change can occur on the ectocervix, with the finding of a raised plaque or pseudopolyp and, as a consequence, can be mistaken for invasive carcinoma. It can occur in the endocervix, resulting in the formation of a polypoid protrusion from the ectocervical external os.
- *Cervical leiomyoma (fibroid)*: cervical myomas are usually single and can cause enlargement and distortion of the cervix, with stretching and narrowing of the canal. The differential diagnosis includes a leiomyoma arising in the fibromuscular tissue of the cervix, and a pedunculated leiomyoma which arises submucosally in the corpus of the uterus and has elongated sufficiently to protrude through the cervical os.
- *Papillary adenofibroma*: a benign cervical neoplasm typically observed in perimenopausal and postmenopausal women, so named because of its resemblance to adenofibroma of the ovary.

- *Adenomyoma.*
- *Fibroadenoma.*
- *Granulation tissue* is very friable and usually occurs following some form of surgery.

All these lesions may present with discharge, contact bleeding (postcoital and intermenstrual), or pressure symptoms, depending on size. However, the vast majority are asymptomatic and are usually incidental findings at the time of routine cervical cytology. The final diagnosis is histological after removal.

Malignant

Primary

Worldwide, cervical carcinoma is the second most common female malignancy, with 500,000 new cases and 274,000 deaths each year. It is the third most common cause of female mortality. The major burden of the disease is now experienced in the developing world, where 83 per cent of cases occur. In the UK, as a result of the introduction of the National Health Service Cervical Screening Programme, the incidence of primary invasive cancer of the cervix has decreased, such that a general practitioner will see one case of cervical cancer every 7–9 years. It occurs at least ten times less commonly than breast cancer in the UK.

The majority of cervical cancers (70 per cent) are squamous in type, 15 per cent adenosquamous, and 15 per cent adenocarcinomas. There is now overwhelming evidence that HPVs are the main cause of both preinvasive and invasive squamous cell carcinoma of the cervix in nearly 100 per cent of the cases. These are mainly the oncological types (HPVs 16, 18, 31, 33, 35). Cervical cancers are usually exophytic cauliflower-type growths or typical epitheliomatous ulcers with accompanying necrosis and haemorrhage (Figs 5 and 6). Small or early lesions may be clinically indistinguishable from cervicitis or ectopy. As the carcinoma grows, it may virtually replace the cervix, resulting in a bulky, irregular, friable growth, and may become distorted if the adjacent vaginal fornices become involved. These features are responsible for the common presenting symptoms of intermenstrual and postcoital bleeding, as well as increased vaginal discharge. Pain is a late feature of this disease. In the event of an endophytic-type squamous cell carcinoma or an adenocarcinoma, the tumour growth tends to occur within the endocervical canal, frequently invading deeply into

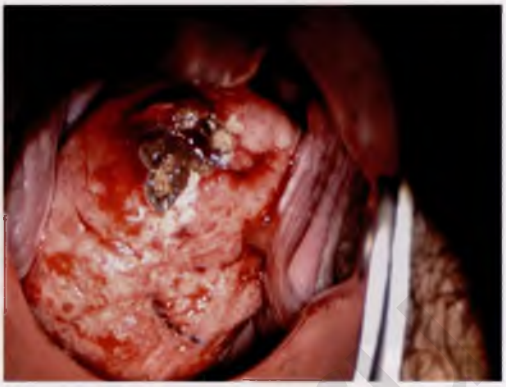

Figure 5 Colposcopic appearance of a cervical cancer.

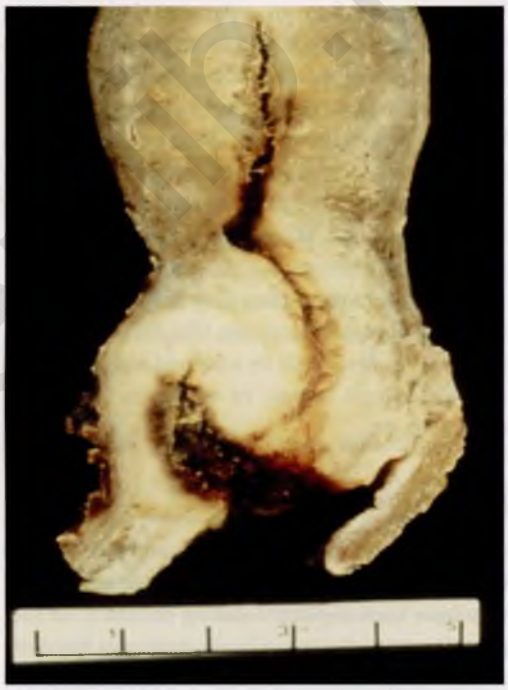

Figure 6 Sagittal view of a uterus with a cancer on the cervix.

the cervical stroma to produce an enlarged, hard, barrel-shaped cervix. In many of these patients, the macroscopic cervical appearances can be normal. Diagnosis requires a biopsy for histopathological review. Apart from stages Ia1 and Ia2 (where histological diagnosis is usually made from a cone or loop cervical biopsy), staging of cervical cancer is clinical, with examination under anaesthetic, cystoscopy, a rectovaginal examination and possible sigmoidoscopy, intravenous urography, and a chest X-ray. Magnetic resonance imaging (MRI) is used pre-operatively for determining tumour size, degree

of stromal penetration, parametrial extension, and lymph node status.

Other rarer malignant tumours that can cause a cervical swelling include lymphoma and leukaemia of the cervix, which are neoplasms of the haematopoietic system whose manifestation in the cervix is usually a reflection of widespread disease. Most patients present with a cervical mass, but they may also complain of vaginal bleeding and discharge. The cervix is typically diffusely enlarged and barrel-shaped. Less commonly the tumour may appear as a polypoid endocervical mass protruding through the cervical os. Sometimes a lymphoma-like lesion (pseudolymphoma), which is a marked inflammatory extensive lesion of the cervix, can be confused with lymphoproliferative diseases and can be clearly identified only by histology. Various types of sarcoma (adenosarcoma, embryonal rhabdomyosarcoma, carcinosarcoma, and leiomyosarcoma) are very rarely encountered as causes of cervical swelling.

Another rare neoplasm of the uterine cervix with a poor prognosis is malignant melanoma. It may initially be misdiagnosed (mainly in the achromic forms) and then discovered at an advanced stage when immunohistochemistry is useful – a definitive diagnosis can be made only through immunohistochemical methods and the exclusion of other primary sites of melanoma.

Secondary

Secondary tumours do occur in the cervix but are usually from other parts of the genital tract. It is uncommon to find an isolated secondary from another anatomical site in the body.

CHEST PAIN IN PREGNANCY: CARDIAC CAUSES

Abhishek Joshi and Sandy Gupta

Chest pain is the commonest presenting complaint in accident and emergency, but fortunately it is not common in pregnancy. The differential diagnosis for chest pain in pregnant women is the same as in non-pregnant women and includes cardiovascular, pulmonary, gastrointestinal, neuromusculoskeletal, and psychogenic aetiologies (Box 1). Cardiopulmonary causes, although less common, carry high mortality in pregnancy and therefore need to be excluded as a priority in patients presenting with chest pain. This section will primarily focus on the life-threatening causes of chest pain in pregnancy.

Box 1 Differential diagnosis of chest pain in pregnancy

Cardiac causes

Ischaemic

- Acute coronary syndrome
- Coronary atherosclerosis
  - coronary spasm
  - coronary dissection
  - coronary thrombosis
- Coronary arteritis

Non-ischaemic

- Aortic dissection
- Pericarditis
- Mitral valve prolapse

Non-cardiac causes

Pulmonary

- Pulmonary embolism/infarction
- Pneumothorax
- Pneumonia with pleural involvement

Gastrointestinal

- Oesophageal spasm
- Oesophageal reflux
- Oesophageal rupture
- Peptic ulcer disease

Neuromusculoskeletal

- Thoracic outlet syndrome
- Lesions of cervical/thoracic spine
- Costochondritis/Tietze's syndrome
- Herpes zoster
- Chest wall pain
- Pleurisy

Psychogenic

- Anxiety
- Depression
- Cardiac psychosis

Coronary heart disease (CHD)

Acute myocardial infarction (MI), the commonest form of acute coronary syndrome in pregnancy, is rare in pregnant women, occurring in 3–6 per 100,000 pregnancies.[1,2] The incidence of MI in

pregnancy may be increasing, reflecting the trend towards older maternal age. Traditional cardiovascular risk factors (smoking, hypertension, diabetes, hypercholesterolaemia, family history) pertain, but are joined by pre-eclampsia, postpartum haemorrhage, thrombophilia, and postpartum infection.[2,3] The mortality from MI in pregnancy is 5–10 per cent, and the risk of death is greatest if the infarct occurs late in pregnancy or in women under 35 years old, or if delivery is within 2 weeks of the infarction.

Cardiac troponin I is unaffected by normal pregnancy, labour, and delivery; therefore, it is the investigation of choice in the diagnosis of acute coronary syndrome, even in the presence of pre-eclampsia.[4] Medical management is indicated in stable patients with non-ST segment elevation infarcts.[5] Thrombolysis is contraindicated for 10 days post-caesarean section and in late pregnancy in case of premature labour, in view of the heightened risk of haemorrhage, and should be reserved for unstable patients with no access to primary percutaneous angioplasty.[6] The higher frequency of coronary artery dissection means that primary angiography and angioplasty is the preferred management for unstable patients. No safety data exists for drug-eluting stents, so bare metal stents are recommended, which also reduces the exposure to clopidogrel.

Women with established CHD should be assessed and treated before conception. Coronary spasm, in-situ coronary thrombosis, and coronary dissection occur more frequently than atherosclerotic CHD.

Coronary arteritis and in-situ thrombosis

Previous Kawasaki disease leading to coronary arteritis with aneurysm formation and thrombosis may present with angina or infarction in pregnancy, and may need coronary artery bypass surgery. Coronary arteritis may be associated with ongoing autoimmune vascular disease and present with infarction in pregnancy or the puerperium. Percutaneous coronary angiography may be essential for recognising the mechanism and anatomy of the infarct in order to tailor appropriate management. Coronary arteritis commonly occurs in the peripartum period and should be distinguished from postpartum cardiomyopathy in the presence of heart failure.

Non-ischaemic causes

Mitral valve prolapse (MVP)

This is the most common congenital heart lesion, and the diagnosis is frequently made in young women of childbearing age. It carries a low risk in pregnancy and rarely requires intervention. Mitral valve prolapse usually presents with atypical chest pain and mid-systolic murmur associated with a mid-systolic click. The management of this disorder during pregnancy has not been well studied. Women with an otherwise normal heart tolerate pregnancy well and develop no further cardiac complications. Furthermore, the incidence of antepartum and intrapartum complications or signs of fetal distress is no greater than in pregnant women without known cardiac disorder. Antibiotic prophylaxis and regular surveillance with echocardiogram in patients with moderate to severe mitral regurgitation is imperative.

Acute aortic dissection

Thoracic aortic dissection is a sudden event in which a tear in the intimal wall of the aorta allows blood to escape from the true lumen of the vessel, rapidly separating the inner layer from the outer layer of the tunica media (Fig. 1). Patients with Marfan's syndrome have elevated risk of dissection secondary to an abnormal number of microfibres in the tissue of the aorta, which may lead to progressive

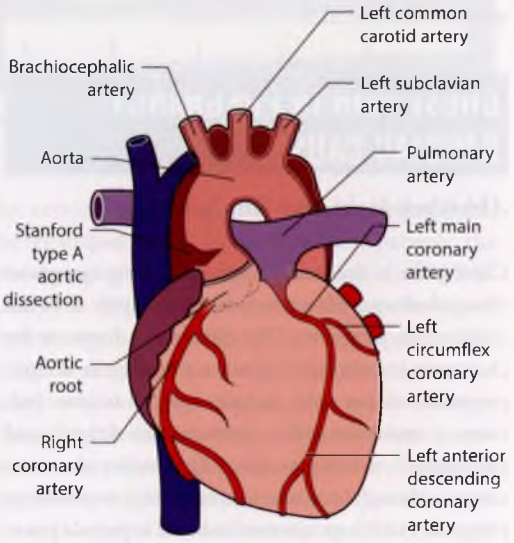

Figure 1 Dissection of ascending aorta.

weakness of the tunica media, and cardiovascular changes in pregnancy magnify this risk.[1] The parietal pericardium is attached to the ascending aorta just proximal to the origin of the innominate artery. Rupture of any part of the ascending aorta leads to extravasation into the pericardial sac. Rapid death results from the subsequent haemopericardium. Dissections of the transverse arch of the aorta are more complex because the brachiocephalic, left common carotid, and left subclavian arteries may be compromised.[7]

Aortic dissection is rare in pregnancy and may be initially overlooked because its manifestations are similar to those for early labour (see Table 1). Pregnant women often experience epigastric discomfort that they may interpret as burning in the chest. Although it is not a symptom of early labour, burning in the chest can be an early symptom of aortic dissection. Blood pressures that differ from one arm to the other or radial pulses that differ in intensity from one arm to the other and the new onset of a diastolic murmur are characteristics that may be used to distinguish this from early labour.

Acute aortic dissection may be apparent on a chest radiograph as a widened mediastinum, particularly in the upper part of the mediastinum and toward the left side of the thorax. Cardiomegaly and pericardial effusions are also common radiographic findings in patients with ascending aortic dissection. An echocardiogram should be obtained primarily to evaluate left ventricular function, aortic valve competence, and size of the aortic root. However, neither a chest radiograph nor an echocardiogram is sufficient for a definitive diagnosis of aortic dissection to be made. Computed tomography (CT), if available, is the emergency diagnostic procedure of choice for aortic dissection.

Table 1 Aortic dissection versus early labour

Symptoms and signs	Aortic dissection	Early labour
Nausea	Present	Present
Anxiety	Present	Present
Epigastric discomfort	Present	Present
Restlessness	Present	Present
Excessive sweating	Present	Present
Arm discrepancy in blood pressure	Present	Absent
Radio-radial delay	Present	Absent
New-onset diastolic murmur	Present	Absent
Burning sensation in the chest	Present	Absent

After definitive diagnosis, repair with a composite graft is the procedure of choice. Preservation of the aortic valve or its replacement with a homograft avoids the need for long-term anticoagulants. Normothermic bypass, progesterone per vaginam, and continuous fetal heart monitoring reduce the risk to the fetus.

Acute dissection originating beyond the left subclavian artery and not involving the proximal aorta should be managed medically. This does not usually need surgery and can be followed by serial magnetic resonance imaging scans. Progressive dilatation to 5 cm or more, recurrent pain, or signs consistent with fresh dissection, such as the development of organ or limb ischemia, are all indications for repair. The baby, if viable, should be delivered by caesarean section before going on to bypass. The anaesthetic management of caesarean section followed by repair of aortic dissection should minimise fetal exposure to depressant drugs while ensuring a well-controlled haemodynamic environment for the mother. Pregnant women with Marfan's syndrome should be considered high risk. A successful outcome hinges on rapid diagnosis and prompt referral to a specialist centre.

Pulmonary embolism (PE)

Pulmonary embolism is the most common cause of direct maternal death in the UK and carries a mortality of 3.5 per cent.[8,9] Pregnancy and the puerperium carry an increased risk of venous thromboembolism, complicating up to 0.2 per cent of all pregnancies.[10] Diagnosis of venous thromboembolism is complicated by the symptoms of dyspnoea and lower extremity oedema overlapping with the common complaints of pregnant patients, and there are no validated diagnostic algorithms or pre-test probabilities.

Risk stratification for all women at risk of pulmonary embolus is essential. Most patients who die of PE have previously identifiable risk factors, and treatment with anticoagulation (usually prophylactic doses of low-molecular-weight heparin [LMWH]) should be offered to all patients at high risk.[1]

Physicians should maintain an appropriately high index of suspicion and request prompt diagnostic imaging in an appropriate sequence (Fig. 2). D-dimer levels rise through pregnancy, but a negative value is

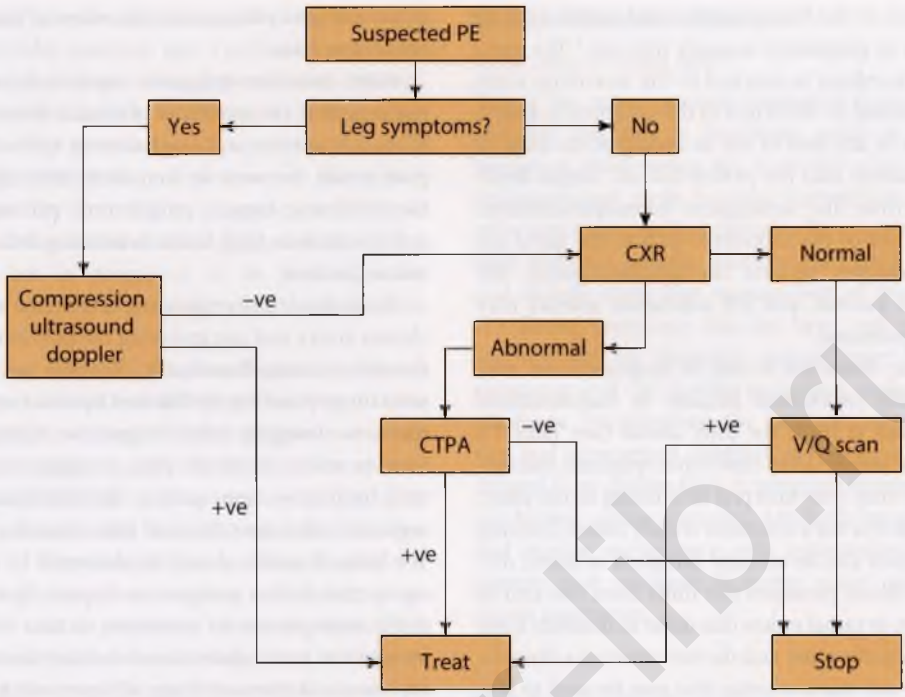

Figure 2 Algorithm for diagnosis and management of pulmonary embolism in pregnancy. CTPA, computerised tomographic pulmonary angiogram; CXR, chest X-ray; PE, pulmonary embolism; V/Q, ventilation/perfusion.

reassuring. In patients with suspected PE, positive D-dimer, and compression Doppler imaging confirming DVT, anticoagulation should be undertaken without radiological confirmation of the pulmonary embolus. In those with negative compression Doppler imaging, CT pulmonary angiography may reduce fetal exposure to radiation, compared to V/Q scans.

In patients with confirmed PE, treatment is with doses of LMWH. Measurement of anti-Xa levels is of unclear benefit, but is reasonable to ensure adequate therapy. Patients often require increasing doses of LMWH to achieve the same anti-Xa level as pregnancy progresses. Unfractionated heparin is used in severe renal insufficiency or in cases where anticoagulation may need to be stopped quickly or reversed.[11]

In acute, life-threatening PE with haemodynamic compromise, thrombolysis is indicated. There is an 8 per cent chance of haemorrhage and 6 per cent chance of fetal loss. There is currently very little data on mechanical thrombectomy.[9]

After delivery, patients should be recommenced on bridging LMWH (6 hours after vaginal birth and 12 hours after caesarean section) and treated with oral vitamin K antagonists until achieving a therapeutic range. Treatment should continue for at least 3 months (6 months if the PE occurred late in pregnancy). Vitamin K antagonists do not enter the breast milk and are safe for breast-feeding babies.

Conclusion

Most women with heart disease have successful pregnancies, but nowadays most cardiologists and obstetricians see only small numbers. Women with known or suspected heart disease, unexplained chest pain, or other symptoms of pregnancy and women who are planning a pregnancy should be referred to a specialist centre. A multidisciplinary approach with experienced cardiologists working as a team with obstetricians, anaesthetists, clinical geneticists, and neonatologists constitutes the optimal care for pregnant women with known, suspected, or new-onset heart disease.

Pulmonary embolism remains a major source of mortality during pregnancy, and investigation and

treatment should be vigilant and prompt. Prevention of PE in high-risk patients should be a priority.

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CHEST PAIN IN PREGNANCY: NON-CARDIAC CAUSES

Simon Quantrill

Introduction

This section should be read in conjunction with the one on cardiac causes of chest pain. It may be difficult to distinguish between the two, especially as cardiac chest pain frequently presents 'atypically'. Non-cardiac causes of chest pain are summarised in Table 1. There are few data on the relative frequency with which these conditions cause chest pain in pregnancy, except for pulmonary embolus (PE), which remains a major cause of maternal mortality. None of the listed conditions are more likely to occur during pregnancy (except for PE) and so the approach to diagnosis should be the same irrespective of the woman being pregnant.

Table 1 Non-cardiac causes of chest pain in pregnancy

More likely	Less likely
Unexplained, 'non-specific'	
Chest wall	
Intercostal myalgia/neuralgia	Tietze's syndrome
Muscular strain	Intercostal myositis
Costochondritis	Osteoarthritis of cervical or thoracic spine; thoracic disc lesion
Trauma ± rib fracture	Vertebral or sternal fracture ± osteoporosis or osteomalacia
Mastalgia	Chest wall abscess (e.g. staphylococcal, TB)
Shingles	Cocaine abuse
Pleura	
Pneumonia	
Infection not visible on chest X-ray (e.g. viral pleuritis, including 'Bornholm disease')	
Pleural effusion due to pneumonia or tuberculosis (TB)	Pleural effusion due to rheumatoid disease, lymphangioleiomyomatosis, malignancy (e.g. choriocarcinoma, breast cancer)
Pneumothorax	Empyema
Pulmonary embolus	Haemothorax
Sickle chest syndrome	Connective tissue disease (e.g. systemic lupus erythematosus)
Mediastinum	
Oesophageal reflux	
Oesophageal spasm	Mediastinitis (e.g. spontaneous or due to oesophageal rupture)
	Pneumomediastinum
	Aortic aneurysm
	Mediastinal tumour (e.g. lymphoma)
Extrathoracic	
Peptic ulceration	Kidney: pyelonephritis, stones
	Gallbladder disease (e.g. acute cholecystitis)
	Liver disease (e.g. hepatitis)
	Acute and chronic pancreatitis

Causes of non-cardiac chest pain

'Non-specific' is a label that is very often used when no other diagnosis can be made. It can also be associated with a history of underlying anxiety or depression.

It is essential to understand the anatomy and physiology of the thorax, especially its innervation, in order to diagnose the cause of chest pain. Thus, diseases that affect only the lung parenchyma, such as interstitial lung disorders, will not give rise to chest pain, as the lungs themselves have no pain fibres in their afferent nerve supply. For chest pain from an intrathoracic cause, there must be parietal pleural involvement. Pneumonia causes chest pain if the infection extends to the pleura: often there will be an associated pleural effusion, although this may be small and difficult to spot. Pain is caused by inflammation of the parietal pleura and not by the fluid itself; accumulation of such pleural fluid will usually give rise to breathlessness (see Breathlessness in pregnancy: respiratory causes) but not pain.

Chest wall

Diagnoses such as '*intercostal myalgia*', '*muscular strain*', and '*costochondritis*' are invariably made on clinical grounds alone after excluding other more serious conditions. There are no laboratory or radiological tests that will confirm these conditions, and the diagnosis must therefore be based on history and examination together with a normal chest X-ray in particular. There are no data to indicate the frequency of these diagnoses in pregnancy. Costochondritis is very common in the general population and results in pain and tenderness, mainly over the upper anterior chest wall. Tietze's syndrome is an uncommon form of costochondritis characterised by chest pain due to inflammatory swelling of the costochondral junctions.

Shingles, the rash caused by the Varicella-zoster virus, which reactivates in the dorsal ganglia after prior chickenpox infection, may result in severe chest wall pain. This may persist after the initial rash has subsided, when it is called post-herpetic neuralgia, and may occur in approximately 20 per cent of cases for unknown reasons, although psychosocial factors may be important. Usually the rash of shingles is obvious, being dermatomal, but pain may precede the development of the rash as well as persist afterwards.

Pleura

Viral pleuritis is a common disorder, but diagnosis is usually based on exclusion of other causes together with a history of coryza or influenza-like symptoms, such as fever, sore throat, generalised arthralgia/ myalgia, malaise, and cough. Examination may reveal a high temperature and occasionally a pleural rub, usually best heard in the lower lateral zone of the thorax. 'Bornholm disease' refers to viral pleuritis with sudden onset of pleuritic chest pain and high temperature, caused usually by Coxsackie B virus. The pain is often severe with chest wall tenderness on palpation, and there may be associated pericarditis/ myocarditis. Other causative organisms include Coxsackie A and echovirus. Virological diagnosis is based on throat swabs, faecal tests, and paired sera samples taken at least 10 days apart. In routine clinical practice it is hard to identify the causative virus and may take up to 2 weeks to obtain results. By that time the patient is likely to have recovered. The diagnosis is therefore usually a clinical one.

Pneumonia is characterised by symptoms of breathlessness, productive cough with sputum, and fever. The chest X-ray will show areas of consolidation. Symptoms may vary considerably, but the chest X-ray is by definition abnormal (see Fig. 1 in Breathlessness in pregnancy: respiratory causes). Findings on physical examination commonly include a high temperature and crackles on auscultation. Bronchial breathing occurs when the consolidation is dense and more extensive.

Pulmonary embolus can cause lateral chest pain due to pulmonary infarction at the edge of the lung (often resulting in a wedge-shaped area of necrosis), which then spreads to the pleura, resulting in pain. Central chest pain due to pulmonary embolus may have the same aetiology, but can also be caused by angina following a large embolus, which puts strain on the right ventricle. The most common symptom of pulmonary embolus is breathlessness, with haemoptysis occurring in only about 9 per cent of cases. Clinical examination will reveal signs concomitant with the size of the embolus, but which usually include an increased respiratory rate and tachycardia, cyanosis, hypotension, and loud second heart sound (P2) occurring with major emboli. There may be a swollen leg with the typical appearance of a deep vein thrombosis (DVT), left-sided in 85 per cent of cases. Diagnosis is made radiologically by ventilation/ perfusion (V/Q) scanning, and PE or DVT can be excluded if D-dimers are negative (see Bleeding disorders in pregnancy, including thrombocytopenia).

The *acute chest syndrome* of sickle cell disease may cause severe chest pain, which is typically lateral, but often not pleuritic in nature. Its incidence in pregnancy is unknown. These patients will be known to have sickle cell disease and are often admitted with a crisis whose predominant features will include pain, especially in the limbs. An underlying cause for the chest pain includes pulmonary embolism – due to thrombus, fat, or bone marrow – and infection, but is found in only 38 per cent of patients. Respiratory infection is commonly due to *Chlamydia pneumoniae, Mycoplasma pneumoniae*, and respiratory syncytial virus, but many other organisms may be responsible. These are usually identified from blood samples sent for serology, although the results may be available too late to alter management. Acute respiratory failure may occur in 13 per cent of cases. Fat embolism can be diagnosed by sputum containing fat macrophages or samples obtained from bronchoscopy, although this may only be possible in patients who are intubated.

Tuberculous pleuritis may cause chest pain when tuberculosis (TB) affects the pleura, causing a pleural effusion (Fig. 2 in Breathlessness in pregnancy: respiratory causes). Typical symptoms also include fever, weight loss, and night sweats, which are usually drenching and nocturnal. Weight loss may be difficult to determine in pregnancy, but failure to gain weight appropriately as gestation progresses may be significant. Breathlessness will depend on the size of the effusion. When TB is restricted to the pleural cavity, it is considered closed and non-transmissible. However, when cough, sputum or haemoptysis are present, then the diagnosis of open transmissible TB is likely, as it will signify concomitant pulmonary involvement. Physical examination will reveal dullness to percussion and reduced or absent breath sounds over the effusion. The diagnosis of pleural TB is usually made by pleural biopsy, as simple aspiration of the effusion will uncommonly be smear

positive: the statistics are smear positive pleural fluid (<5 per cent), culture positive pleural fluid (63 per cent), and pleural biopsy histology (74 per cent). A combination of these tests including culture of the biopsy specimen itself will give the highest possible yield for diagnosis. The smear allows acid-fast bacilli to be seen on direct microscopy of fluid.

Pneumothorax usually presents with the sudden onset of pleuritic chest pain and breathlessness. The pain often subsides quite rapidly, as it is probably due to the sudden shearing off from the chest wall of the parietal pleura. Although primary spontaneous pneumothorax can occur in anyone, it is 9–22 times more common in smokers and usually occurs in those with a tall, thin body habitus. The incidence of primary spontaneous pneumothorax is 1.2 in 100,000 in females, although it is seven times more common in men than women; therefore, its incidence in pregnancy is likely to be low.

There is no reason to suppose that pneumothorax should be any more common in pregnancy with the exception of during labour, when repeated strenuous Valsalva manoeuvres could theoretically increase the risk of subpleural bleb (a small bulla-like structure) rupture, which is the main cause of spontaneous pneumothorax. The clinical diagnosis may be difficult, as physical examination reveals a hyperresonant percussion note and significantly reduced breath sounds on the affected side only when the pneumothorax is of a sufficiently large size. Tracheal deviation in practice is often difficult to determine and only occurs with very large 'tension' pneumothoraces. Chest X-ray is essential to the diagnosis and should be reviewed by a skilled practitioner, as small pneumothoraces are easily missed.

Pneumomediastinum has also been described in pregnancy and may present with chest pain and breathlessness. This condition is even less common than pneumothorax, although the two may coexist owing to a similar underlying cause. Pneumomediastinum may be due to oesophageal rupture and has been reported in association with hyperemesis gravidarum. Subcutaneous surgical emphysema that causes a 'crunching' sensation under the fingertips may be found on palpation of the upper thorax and neck, and a crunching sound may be heard on auscultation of the chest.

Empyema may present with pleuritic or nonspecific chest pain and occurs most frequently as a complication of pneumonia, developing from a simple parapneumonic effusion. It is more likely to occur when there is underlying immunosuppression. Although pneumonia is well described in pregnancy, there are no series or even case reports focused specifically on thoracic empyema in pregnancy. Typically the history is of several weeks' general malaise, with tiredness, fevers, chest pain, and breathlessness, sometimes with a preceding chest infection or documented pneumonia. Weight loss may occur, but again in pregnancy it may be difficult to determine. Physical examination reveals similar findings to a pleural effusion with a dull percussion note and reduced or absent breath sounds over the affected area. An empyema can be loculated, in which case the signs are less typical. Chest X-ray may show an identical picture to that of a pleural effusion, but also demonstrate a pleural collection not typical of a straightforward effusion, owing to loculation. Ultrasound of the chest is a useful tool for demonstrating loculated fluid, estimating the amount of fluid present and guiding drainage. Simple needle aspiration is essential for diagnosis and may reveal pus, but the fluid does not need to be frankly purulent to be classified as empyema and an analysis of fluid pH may be necessary: a pH of <7.2 is usually taken as an indication that complete drainage is needed.

Connective tissue disease, such as *rheumatoid arthritis* (RA), *systemic lupus erythematosus* (SLE), and Sjögren's disease, may cause pleural effusions accompanied by chest pain; however, the presentation is often with breathlessness and no pain. The connective tissue disorder will usually be pre-existing and therefore easily identified as a possible or likely cause of the effusion. Occasionally, one of these conditions may present for the first time with pleuritis, and this could occur in pregnancy, especially as they are generally more common in young women. A history of arthralgia, rashes, and dry eyes may be volunteered. The pleural fluid aspirate and a blood sample should be analysed for the relevant autoantibodies (rheumatoid factor, antinuclear factor, Ro and La antibodies) following a diagnostic tap.

Thoracic malignancy occurs rarely in pregnancy, and if involving the pleura would tend to cause breathlessness more often than chest pain. Pleural effusion may occur but is due to involvement of the visceral pleura, which is not innervated, and/or blockage of lymphatics. Breast cancer frequently spreads to bone and pleura and is the most common malignancy of young women. Bronchial carcinoma usually occurs in later life at an age beyond that of most pregnancies and has rarely been reported.

Chest pain due to any thoracic malignancy will be most likely caused by rib metastases, in which case it will be persistent and often severe, interrupting sleep.

Mediastinum

Oesophageal reflux is extremely common in pregnancy and can result in chest pain, usually manifesting as 'heartburn', a burning sensation in the centre of the chest worse after meals. Up to two-thirds of pregnant women may have reflux, caused by relaxation of the gastro-oesophageal sphincter owing to high progesterone levels. Smoking and alcohol are aggravating factors. However, the expression of heartburn may be different in individual women who may complain of chest pain indistinguishable from other causes. Usually the diagnosis can be made on clinical grounds alone (see Heartburn in pregnancy).

Extrathoracic

Peptic ulcer disease is less common in pregnant women, but the resultant upper abdominal pain may manifest as lower chest pain instead. Endoscopy may be necessary if symptoms fail to clear with drug treatment or complications such as gastrointestinal bleeding are apparent (see Epigastric pain in pregnancy).

Other abdominal diseases, such as *cholecystitis, gallstones, kidney stones, pyelonephritis,* and *acute pancreatitis*, for example, may occasionally present with lower chest pain, which leads to diagnostic difficulty. One of these disorders might be suspected if there are other typical features in the history, such as pain occurring shortly after eating meals (especially with a high fat content) for gallstones; fever and/or rigors with cholecystitis and pyelonephritis; frequency, dysuria and haematuria with pyelonephritis and sometimes kidney stones; spasmodic pain with gallstones and kidney stones; or the presence of possible triggers for acute pancreatitis such as alcohol or known gallstones.

The following provides an approach to the history and examination in the pregnant patient with chest pain (refer also to Chest pain in pregnancy: cardiac causes).

History – key features to be elucidated

History of the presenting complaint

- Duration, onset, severity, nature and radiation of chest pain.
- Relation of pain to meals.
- Aggravating or relieving factors.
- Breathlessness.
- Cough, sputum, haemoptysis.
- Fever, weight loss.
- Arthralgia, myalgia, sore throat.
- Trauma, e.g. fall.
- Leg pain.

Psychological

- Symptoms of anxiety or depression.

Past medical history

- TB or contact history.
- Previous history of thrombosis or embolism, e.g. DVT in previous pregnancy.
- Sickle cell disease.
- Underlying immunosuppression, e.g. human immunodeficiency virus (HIV) disease.
- Connective tissue disease, e.g. SLE, RA, Sjögren's syndrome.
- Asthma.
- Chickenpox.
- Shingles.

Medication

- Prednisolone.
- Previous use of oral contraceptive pill.

Family history

- Clotting disorders.
- TB.

Social history

- Smoking, ethnicity, travel history, contact with TB.

Physical examination – key findings to look for

- *General examination*: fever, sweating, cyanosis, lymphadenopathy, jaundice, anaemia, inflamed throat, evidence of connective tissue disease.
- *Cardiovascular system*: tachycardia, hypotension, raised jugular venous pressure (JVP), parasternal heave, loud second heart sound (P2), gallop rhythm, pericardial rub.
- *Respiratory system*: increased respiratory rate, chest wall tenderness, chest wall masses, tracheal deviation, dullness to percussion, crackles, bronchial breathing, reduced or absent breath sounds on auscultation.
- *Breast*: lumps.
- *Abdomen*: right upper quadrant, epigastric or loin tenderness; enlarged liver.

Investigations

Chest radiography delivers negligible radiation and is crucial to diagnosing or excluding important conditions such as pneumonia and pleural effusion. Similarly, pulmonary embolism cannot be reliably diagnosed without a V/Q scan or CTPA. The consequences of misdiagnosis are potentially far

worse than the negligible risk of harm to the fetus from these tests. Ultrasonography is usually the first investigation of choice for possible abdominal pathology.

Summary

Non-cardiac causes of chest pain are broadly the same in pregnancy as in the non-pregnant state. The most common causes will be non-specific, and often no definite aetiology will be found. More serious causes should be apparent from the history, examination, and simple investigations.

Further reading

UpToDate (Wolters Kluwer Health) www.uptodate.com

www.brit-thoracic.org.uk: Guidelines for the diagnosis and management of pneumonia, TB, pulmonary embolism, pleural disease, pneumothorax.

COLLAPSE IN PREGNANCY

Greg Davis

Most pregnant women are young and healthy, so apart from fainting, collapse is a rare event in pregnancy. It usually indicates a life-threatening emergency, with cardiac arrest estimated to occur once in 30,000 pregnancies. Typically in pregnancy the woman becomes agitated, possibly short of breath, and then confused before losing consciousness and collapsing. The diagnosis may not be clear initially and takes second place to resuscitation. The two may need to occur simultaneously. Immediate assessment will determine whether the woman is conscious and breathing and whether there is any blood loss. Resuscitation should follow the standard Advanced Life Support protocols, and the diagnosis may only become clear as resuscitation proceeds. A flow chart for the diagnosis of the woman collapsing in pregnancy is shown in Fig. 1. The causes are shown in Box 1.

Syncope

Blood pressure normally falls in the second trimester of pregnancy as a result of reduced peripheral vascular resistance. Venous pooling occurs in the lower limbs, and greater muscle activity is more necessary than in the non-pregnant state to ensure adequate venous return. Any factor that exacerbates the physiological changes makes fainting more likely. Standing still for prolonged periods, standing up quickly, and lying supine in late pregnancy are more likely to cause fainting than in the non-pregnant woman. Hot weather increases peripheral vasodilatation and may contribute to the process.

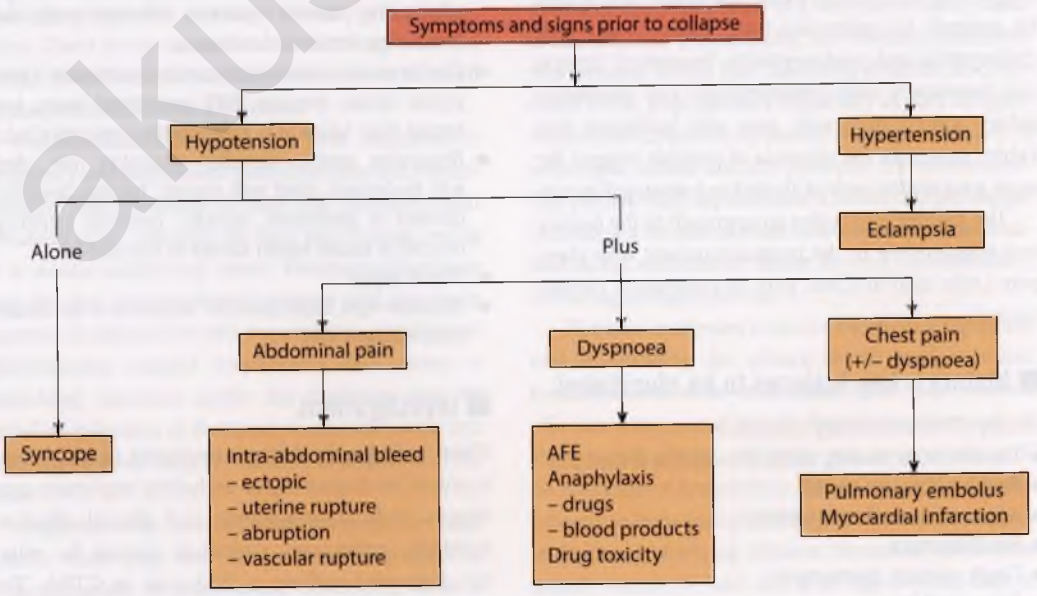

Figure 1 Diagnostic flow chart for the collapsed pregnant woman. AFE, amniotic fluid embolism.

Box 1 Causes of collapse in pregnancy

- Syncope
- Haemorrhage due to:
  - Blood loss – ruptured ectopic pregnancy, placental abruption, uterine rupture, ruptured aneurysm
  - Coagulopathy – sepsis, abruption, amniotic fluid embolism
- Embolism – pulmonary, amniotic fluid, air, fat
- Eclampsia
- Bacterial sepsis
- Myocardial infarction
- Anaphylaxis
- Drug toxicity
- Transfusion reaction

The diagnosis is usually suggested by the situation in which it has occurred, e.g., standing in a hot, crowded, stuffy train after a long day's work. Loss of consciousness is not sudden and is preceded by a feeling of light-headedness or dizziness, cold sweating, and nausea. Observers will note pallor, sweating, and a rapid, weak pulse. If the woman does not sit or lie down, these signs and symptoms will be rapidly followed by complete loss of consciousness and collapse. There may be injury from falling and, less commonly, seizures from cerebral anoxia if the woman is kept in an upright or semi-recumbent position. Consciousness usually returns quickly when the woman is placed in the recovery position.

Haemorrhage

Haemorrhage due to any cause may lead to collapse in pregnancy. Pregnant women have a significant increase in blood volume and may lose 35 per cent of their blood volume without showing signs of hypovolaemia. When they decompensate, it may be more rapid than in non-pregnant women, and the degree of blood loss may be concealed. Fetal distress may be the first sign of hypovolaemia, as maternal blood flow is diverted from the abdominal and pelvic organs to maintain blood pressure and cerebral perfusion.

Blood loss

Ectopic pregnancy usually presents between 6 and 10 weeks of pregnancy, and 50 per cent of women presenting to hospitals will have been previously seen by a doctor who did not make the diagnosis. One in 80–90 pregnancies are ectopic, though rates vary geographically, and this increases to one in 20 if the woman has conceived with assistance. Other risk factors for ectopic pregnancy are previous ectopic pregnancy, tubal damage including previous sterilisation and infection, and a history of fertility problems.

Any woman of reproductive age admitted to hospital with shock and a loss of consciousness should be assumed to a) be pregnant, and b) have a ruptured ectopic pregnancy until proven otherwise. The woman will have signs of shock with tachycardia, rapid respirations, pallor, cold skin, and hypotension. Her abdomen is likely to be distended, and, depending on the level of consciousness, very tender with signs of peritonism – guarding and rebound. The latter are not invariable, however, and distension and tenderness may be difficult to assess if the woman is unconscious. A large intra-abdominal bleed causing shock is usually a straightforward diagnosis, and immediate surgery is required. In women of this age group without a history of trauma, ruptured ectopic pregnancy is the most likely diagnosis and is confirmed by a positive pregnancy test of bloods taken during resuscitation. Blood should be taken for full blood count, cross match, and quantitative human chorionic gonadotrophin (HCG). If the woman's condition is stabilised sufficiently prior to surgery to allow further investigation, ultrasound scanning will reveal an empty uterus and the presence of intra-abdominal blood.

In the second half of pregnancy, placental abruption is the most likely cause of blood loss sufficient to cause collapse, with a combination of concealed and overt bleeding. Hypovolaemia does not, of itself, usually cause collapse; however, the extravasation of blood into the myometrium can lead to a severe coagulopathy, disseminated intravascular coagulation with diffuse bleeding, and consequent haemorrhagic shock. The uterus is usually tender and firm and the fundus may be higher than expected, while the fetal heart rate is either abnormal or absent. While resuscitation is taking place, bloods should be taken for full blood count, group and cross match, Kleihauer and coagulation tests. The woman must be closely observed once she is haemodynamically stable, as a coagulopathy may not be evident at first and develop subsequently.

Spontaneous uterine rupture is rare during pregnancy but more likely if the woman has a history of myomectomy or classical caesarean section. 'Catastrophic' uterine rupture usually presents in the third trimester with the sudden onset of generalised

abdominal pain and shock, which may proceed rapidly to collapse and death. A history of uterine surgery and the degree of abdominal pain suggest uterine rupture or a major intra-abdominal bleed. Resuscitation and immediate surgery are required to save the mother's life. The fetus is usually dead unless the rupture occurs in hospital and delivery is accomplished very quickly.

Abdominal trauma in pregnancy, whether due to automobile accidents, falls, or domestic violence, may lead to abruption, uterine rupture, or significant intra-abdominal bleeding resulting in collapse. Other causes of intra-abdominal bleeding are rare in pregnancy, but the rupture of congenital or pregnancy-related vascular aneurysms, e.g. splenic or adrenal arteries, is thought to be more common in pregnancy, presumably due to increased blood flow and changes in vessel walls.

Coagulopathy

Serious blood loss causing collapse is often exacerbated by coagulopathy in pregnancy. The coagulopathy may be a result of the disease process, e.g. severe pre-eclampsia, after massive blood loss. Coagulation factors should be measured in severe pre-eclampsia but are unlikely to be abnormal if the platelet count is normal. Coagulopathy can be expected if collapse has occurred from abruption, amniotic fluid embolism, or massive haemorrhage of any cause.

Embolism

Pulmonary

Venous thromboembolism occurs in 1 in 1,000–2,000 pregnancies and is a leading cause of maternal death in developed countries. While a lower limb deep venous thrombosis (DVT) is the likely precursor for pulmonary embolism, it is often undiagnosed and the initial presentation may be sudden cardiopulmonary arrest. Risk factors for DVT are prolonged bed rest, maternal age >35 years, parity of three or greater, a personal or family history of DVT, varicose veins, smoking, and known hypercoagulable states such as antiphospholipid syndrome. If the DVT is untreated, 20 per cent of women will develop pulmonary embolism (PE). In pregnant women 15 per cent of PEs are fatal, with two thirds dying within 30 minutes of the embolic event. Confirming the diagnosis of pulmonary embolism takes second place to resuscitation.

Pulmonary embolism is suspected when there is sudden cardiac and/or pulmonary compromise in the absence of other precipitating factors such as blood loss. Collapse may be preceded by chest pain and shortness of breath. Distinguishing between amniotic fluid embolism and pulmonary embolism may be difficult, as the initial presentation will be similar, and adequate resuscitation will be the first priority. When stable, the woman should have a chest X-ray to exclude intrathoracic pathology such as pneumothorax, and a low dose ventilation/perfusion (V/Q) scan to confirm the diagnosis of pulmonary embolism. The V/Q scan is very likely to be diagnostic because of the profound disturbance of maternal physiology in this situation.

Amniotic fluid

Amniotic fluid embolism (AFE) is a rare phenomenon occurring in once in 8,000–80,000 pregnancies, and its incidence increases with maternal age. It usually occurs during labour after rupture of the membranes; however, it has been reported after amniocentesis and first trimester curettage. Classically it is thought to be associated with hypertonic uterine activity and abruption, but these factors are not invariable. The pathophysiology is not clear, but there is respiratory and cardiovascular collapse, which may be profound and fatal within 30–60 minutes, and the mortality rate in the UK is estimated at 20 per cent. If the woman survives longer, a coagulopathy invariably develops rapidly and contributes to the haemorrhagic shock. There are similarities in the presentation to anaphylactic shock, and AFE has been termed the anaphylactoid syndrome of pregnancy.

The presentation is similar to pulmonary embolism, with shortness of breath and rapid collapse. Chest pain is not a feature of AFE; however, if the woman is unconscious there may be no history to aid diagnosis. Provided the woman survives the initial collapse following embolism, the developing coagulopathy distinguishes it from venous thromboembolism. The diagnosis is clinical and the purpose of investigations is to guide treatment. Blood should be taken for a full blood count, coagulation studies, and cross match. If AFE has occurred, these bloods will need repeating frequently to assess the need for blood product replacement. The detection of fetal squames in central venous blood confirms the diagnosis but does not usually assist management.

Intracranial bleeding

Although rare in pregnancy, intracranial bleeding of any cause may lead to loss of consciousness and collapse. This may occur as a result of trauma or spontaneously as seen in a subarachnoid haemorrhage. If traumatic in origin, the case will usually be obvious and should be suspected in any pregnant woman presenting with a significant head injury. Although there may be a preceding history of headache (see Headache in pregnancy), spontaneous acute intracranial bleeding due to subarachnoid haemorrhage or rupture of a saccular aneurysm or arteriovenous malformation (AVM; see Fig. 2) may present with a sudden loss of consciousness and collapse. In most cases, the blood pressure will be normal or elevated, and signs of raised intracranial pressure will be detected with papilloedema and cranial nerve abnormalities. The abrupt history, the clinical signs, and the absence of bleeding all indicate an intracranial cause that will normally need immediate neurosurgical review and probable intervention, though the outlook for many of these cases is poor.

Eclampsia

Eclampsia occurs in 1 in 2,000 pregnancies in the UK, and about one third of eclamptic fits occur antenatally. The diagnosis is often obvious in women with a history of preceding severe pre-eclampsia. These women may present with symptoms and signs of imminent eclampsia: severe headache, persistent visual disturbances, epigastric pain, and hyperreflexia. In these circumstances the seizures are likely to be caused by a hypertensive encephalopathy. However, in 20 per cent of cases the fit is the initial presentation with a normal or only mildly elevated blood pressure. In these women, cerebral vasoconstriction leading to ischaemia and cerebral oedema due to cell death is the most likely cause of the fitting (Fig. 3).

The fit may be witnessed where the woman usually complains of feeling 'unwell', collapses, and loses consciousness. The fit is typically generalised tonic–clonic and short lived. Supportive care should be undertaken during the fit, and magnesium sulphate infusion commenced to prevent recurrence.

If the fit is not witnessed, the diagnosis may be more difficult. A history of pre-eclampsia is suggestive. If conscious, the woman will be confused and her vital signs may be normal. However, her blood pressure will be normal or elevated, in contrast to

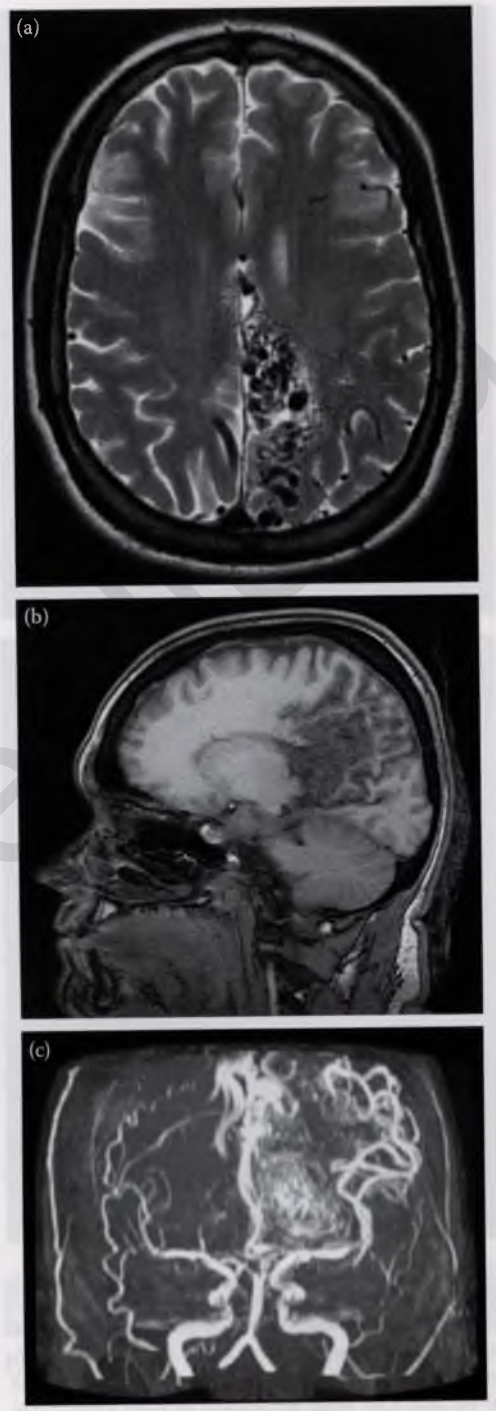

Figure 2 Magnetic resonance imaging (MRI) scans showing a large arteriovenous malformation (AVM) in a pregnant woman who was found collapsed at home. She subsequently had a number of witnessed generalised tonic–clonic seizures. Mother and baby did well and mother had no further seizures after delivery. (a) Axial T2-weighted MRI showing AVM (cluster of dark blood vessels). (b) Sagittal T1-weighted MRI showing AVM (area of low signal posteriorly). (c) Intracranial MR angiogram showing aberrant vasculature.

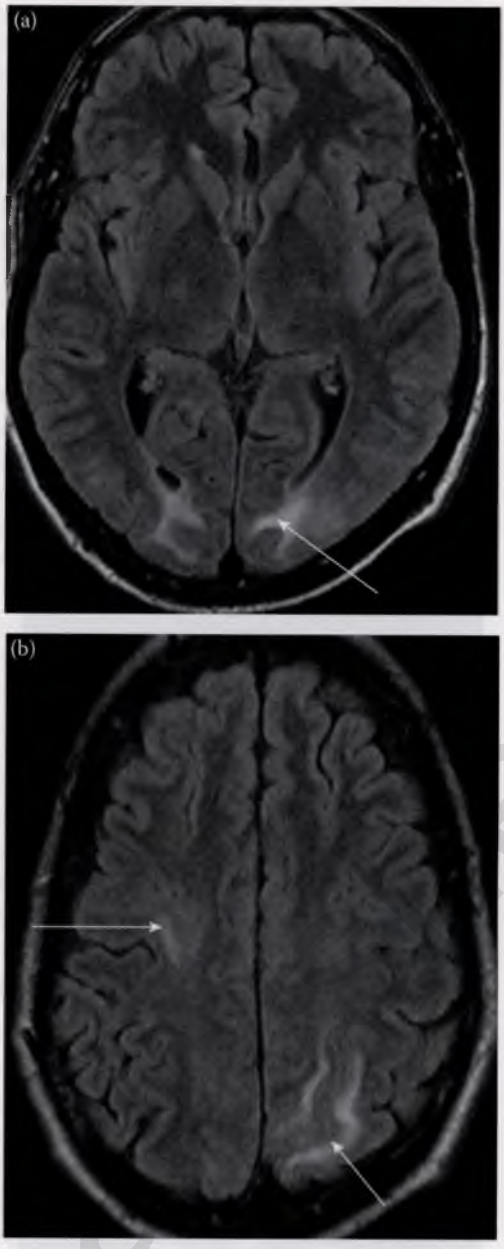

Figure 3 This 34-year-old woman presented with severe pre-eclampsia at 34 weeks' gestation and was found collapsed in a hospital bathroom. She appeared to be postictal, and it was assumed she had suffered an eclamptic seizure. Owing to the uncertainty, a magnetic resonance imaging scan was performed. (a) This axial FLAIR image demonstrates increased signal (arrow), owing to cerebral oedema of the subcortical white matter in the occipital lobes. The increased signal would be even more marked if the changes were a result of infarction. (b) The sporadic nature of the changes seen with pre-eclamptic encephalopathy is shown in this FLAIR image further cephalad, which again shows changes in the left posterior parietal lobe (small arrow), but less marked signal increase in the right posterior frontal white matter (large arrow). FLAIR, fluid-attenuated inversion recovery.

most other causes of maternal collapse. As a result of the fit there may be external trauma or damage to the mouth or tongue.

Bacterial sepsis

Sepsis is defined as infection with systemic effects. Most commonly in pregnancy it is associated with urinary tract infection (UTI) or chorioamnionitis with group A streptococcus or *E. coli*. Failure to recognise the symptoms and signs of sepsis or respond appropriately may lead to septic shock, which can be rapidly fatal. In the context of a maternal infection such as UTI or chorioamnionitis, typically the septic woman will have fever or hypothermia, associated with tachycardia and tachypnoea. As the condition worsens she will become shocked with poor tissue perfusion, hypoxia, hypotension, and oliguria. She will become progressively more confused and eventually lose consciousness. Coagulopathy often develops, contributing to the hypovolaemia. By the time collapse occurs the woman is severely ill and death may occur.

The diagnosis is made by noting the preceding history of infection and the diverse signs, as well as having an increased awareness of the protean nature and danger of sepsis in pregnant women. Blood should be taken for a full blood count, culture, biochemistry, liver function tests, and coagulation studies before treatment. However, treatment with broad-spectrum antibiotics and multi-system support as necessary should be instituted as quickly as possible without awaiting the results of the blood tests.

Myocardial infarction

Although most pregnant women are young and healthy, increasingly, older and less medically fit women are having babies. Women with ischaemic heart disease are at risk of myocardial infarction, although it remains a very rare cause of cardiac arrest in pregnancy. The diagnosis should be suspected when significant chest pain precedes the collapse. There may be a history of cardiac disease, but the diagnosis must be made as resuscitation continues. The woman should have an electrocardiogram (ECG) and cardiac enzymes when she is stable.

Anaphylaxis

Anaphylaxis is a severe, rapid onset allergic reaction which may result in death. It is a multi-system disorder which usually involves shortness of breath,

anxiety, flushing, or itching and may progress to collapse due to hypoxia (upper airway oedema, bronchospasm) and/or shock (vasodilatation, fluid shift, myocardial depression). In pregnant women it is most often seen after the administration of penicillin for group B streptococcus prophylaxis in labour or after the use of a non-steroidal anti-inflammatory drug.

The diagnosis is usually clear because of the link between the woman taking the drug and the reaction occurring. However, the skin changes are often transient and may be missed. If so, the marked airway obstruction in the absence of a history of airway disease makes other causes unlikely. There are no investigations which are helpful in making the diagnosis, and the diagnosis is confirmed by the response to appropriate treatment with adrenaline and intravenous fluids.

Drug toxicity

Although not strictly a 'toxic' effect, the commonest cause of collapse in pregnant women is probably temporary respiratory paralysis as a result of an epidural block ascending too high and paralysing the woman's diaphragm and accessory respiratory muscles. This can happen after a 'top-up', but is more likely after the initial dose. There is usually very effective analgesia and initial motor paralysis. Progressively the woman complains of feeling short of breath or finding it difficult to breathe and becomes more anxious and dyspnoeic before proceeding rapidly to respiratory arrest. The close correlation between the administration of local anaesthetic and the progressive respiratory distress in the absence of circulatory disturbance confirms the diagnosis.

A more truly toxic effect occurs with intravascular injection of a local anaesthetic agent, again typically with the insertion or topping up of an epidural block. Pregnant women appear to be more susceptible because of increased vascularity in the vessels around the epidural space and the increased pressures in the subarachnoid and epidural spaces that occur with contractions. Generally, the longer-acting agents, e.g. bupivacaine, are more toxic than shorter-acting agents such as lignocaine. Signs and symptoms usually occur within minutes of the injection of local anaesthetic. Women may complain of a funny taste, and become confused and short of breath. Respiratory paralysis follows, and cardiac arrest may occur as a result of anoxia and/or myocardial depression. Seizures may also occur as a result of anoxia. It may be difficult to distinguish between a high block and intravascular injection because both occur after injection of local anaesthetic. The latter usually has the characteristic metallic taste and more rapid onset. The treatment is the same, namely cardiorespiratory support until the effect wears off, so a lack of certainty in the final diagnosis is not critical.

Transfusion reaction

Transfusion reactions are common and do not usually cause collapse. However, they are an allergic response to foreign biological material, and anaphylaxis can develop. Symptoms usually occur soon after the transfusion begins, and the cause is therefore obvious.

Conclusion

Collapse in pregnancy is rare. It can be frightening and often unfamiliar to the clinicians present, i.e. midwifery and obstetric staff. The diagnosis of the underlying cause of the collapse may not be immediately obvious. As has been emphasised in this section, resuscitation must begin even if the diagnosis is unclear. The differential diagnosis is not extensive, but in this clinical situation rational thought often deserts us. Prompt introduction of appropriate resuscitation may make the difference between the woman living or dying and give the time necessary to make the correct diagnosis.

Further reading

RCOG Green-top Guideline 56: Maternal collapse in pregnancy and the puerperium. January 2011.

RCOG Green-top Guideline 64a: Bacterial sepsis in pregnancy. April 2012.

COLLAPSE IN THE PUERPERIUM

Greg Davis

Most of the causes of collapse in the puerperium are also seen in pregnancy and this chapter should be read together with the previous section, Collapse in pregnancy. However, collapse in the puerperium is more common, principally due to postpartum haemorrhage. This will therefore be the focus of this section, with a short discussion of the other causes

detailed in the preceding section relevant to the puerperium. Once again it is important to emphasise that resuscitation must be proceeding hand in hand with diagnosis.

A flow chart for the diagnosis of the woman collapsing in the puerperium is shown in Fig. 1. For the purpose of this discussion, 'immediate collapse' refers to within the first 24 hours after delivery and usually within the first few hours, 'delayed' is after 24 hours and within 6 weeks of delivery. The causes of collapse are listed in Box 1 and will be covered in this sequence in this chapter.

Haemorrhage

In contrast to antepartum haemorrhage, the bleeding associated with postpartum haemorrhage (PPH) is usually obvious, although it may initially be obscured by bed linen covering the newly delivered woman. The symptoms and signs of hypovolaemia (shock) may develop rapidly with progressive loss of consciousness as the blood pressure falls. A systematic examination to determine the cause of the bleeding should be undertaken simultaneously with resuscitation and monitoring of the woman's condition (Fig. 2). It should be remembered that in severe haemorrhage there may be multiple factors contributing to the blood loss. For example, blood loss from perineal trauma may add to the bleeding from an atonic uterus, which can be aggravated by a developing coagulopathy due to consumption of clotting factors. Assistance of other staff (e.g., arrest team, anaesthetist, intensivist, and haematologist) may be needed for resuscitation and to contribute to making the diagnosis. Blood samples for full blood count, group and screen, coagulation screen, and renal and liver function tests should be taken right after inserting large bore cannulas.

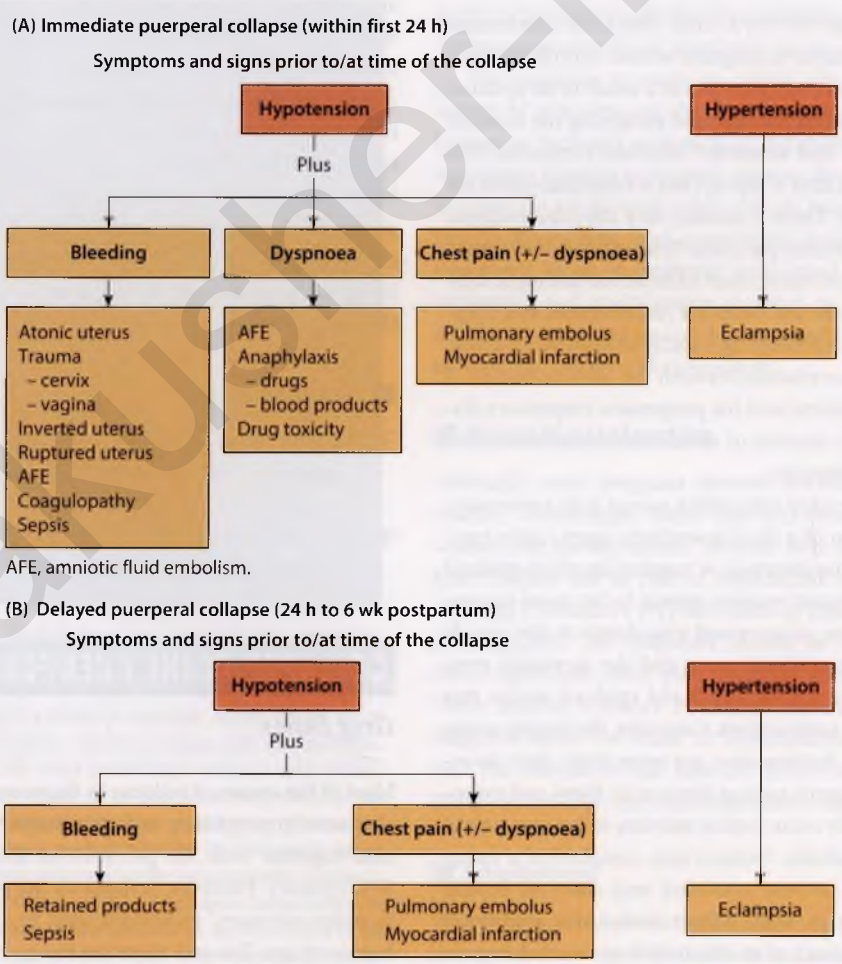

Figure 1 Diagnostic flow chart for the collapsed woman in the puerperium.

Box 1 Causes of collapse in the puerperium

Immediate collapse

(within 24 h of delivery)

- Haemorrhage, due to:
  - Blood loss – atonic uterus, genital tract trauma, uterine rupture
  - Coagulopathy – severe pre-eclampsia, abruption, amniotic fluid embolism, sepsis
- Embolism – pulmonary, amniotic fluid, air, fat
- Eclampsia
- Sepsis
- Myocardial infarction
- Anaphylaxis
- Drug toxicity
- Transfusion reaction

Delayed collapse

(more than 24 h after delivery and less than 6 weeks postpartum)

- Haemorrhage
- Eclampsia
- Infection/sepsis
- Pulmonary embolus
- Myocardial infarction

The causes of postpartum haemorrhage can be classified as the four Ts:

- Tone or lack of it (uterine atony)
- Trauma (vaginal, cervical, uterine)
- Tissue (retained products of conception or blood clot)
- Thrombin or lack of it (coagulopathy)

Blood loss

Atonic uterus

Uterine atony is more likely and should be anticipated if the labour has been prolonged, augmented, or the delivery assisted by forceps or vacuum. Bleeding will continue while the uterus remains atonic, and this must be corrected with oxytocics and abdominal or bimanual massage of the uterus. The contraction of the uterus must be palpated frequently to assess the effects of the measures taken. If the uterus fails to respond, rupture of the uterus, although rare, should be considered.

Genital tract trauma

If the uterine fundus is well contracted when palpated, bleeding must be coming from the lower segment of the uterus, the cervix, or the vagina. Bleeding from the cervix or lower uterine segment should be excluded by using a pack to apply firm pressure to vaginal trauma. Accurate pressure will control bleeding from vaginal trauma. If significant bleeding continues despite the application of pressure, the cervix must be examined for lacerations. In a collapsed woman this should be done under anaesthesia together with exploration of the uterine cavity.

Uterine cause

If vaginal and cervical traumas are excluded by examination, then either retained placenta or products of conception or a poorly retracted lower segment are the likely causes of the bleeding. Gentle exploration of the uterine cavity digitally or using a large, blunt curette will allow the removal of any remaining tissue. Rarely, a uterine rupture may be detected in this manner. Great care must be taken in these circumstances because of the ease with which the uterus can be perforated. If no tissue is detected it is likely that the lower segment is not retracting, and this is usually seen when the placenta has been implanted in the lower segment.

Coagulopathy

In most cases of postpartum haemorrhage sufficient to cause maternal collapse, coagulopathy will contribute to the blood loss. This is most often a consumptive coagulopathy due to depletion of clotting factors with excessive blood loss. Alternatively, it may be associated with sepsis or one of the coagulopathic conditions peculiar to pregnancy (pre-eclampsia, abruption, amniotic fluid embolism, intrauterine fetal death). Repeated blood testing will be necessary to monitor blood and blood product replacement during resuscitation. Input from a haematologist is required to expedite the testing, interpreting the results, and procuring replacement factors. In general, coagulopathy due to consumption is more readily corrected (once bleeding is arrested) than that due to a coagulopathic condition of pregnancy.

Severe pre-eclampsia

Coagulopathy is a feature of severe pre-eclampsia and is usually preceded by a progressive fall in the platelet count. It is not usually of sufficient severity alone to cause collapse, but it may be a contributing factor, as described previously.

Abruption

Although placental abruption is discussed in Collapse in pregnancy as a cause of collapse in pregnancy,

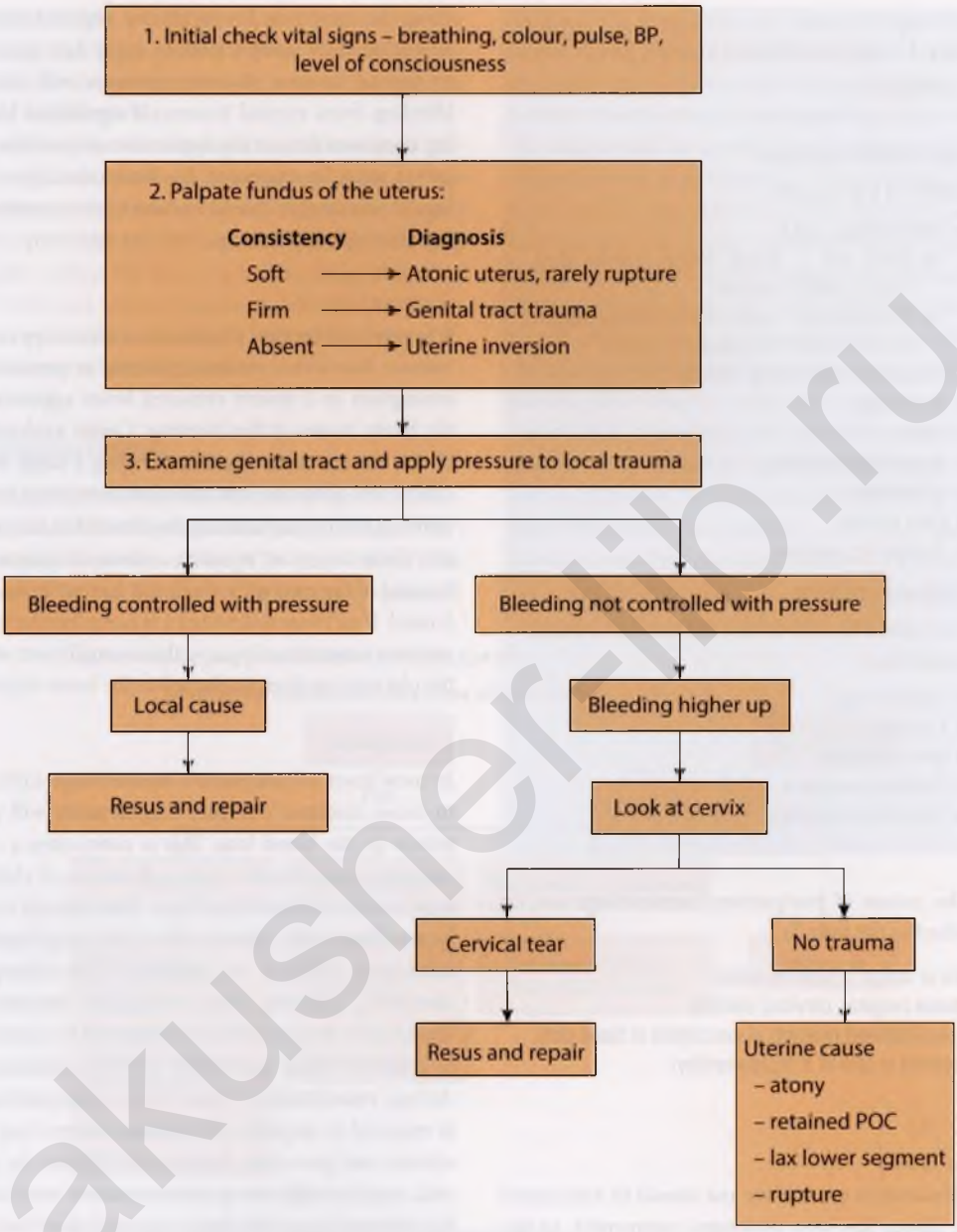

Figure 2 Clinical assessment for causes of postpartum haemorrhage. POC, products of conception; Resus, resuscitation.

collapse after placental abruption is more likely to occur in the puerperium. Often the blood loss may be tamponaded behind the placenta prior to delivery. Significant abruption is usually closely followed by delivery of the baby, either because of rapid labour or urgent caesarean section. However, a severe coagulopathy ensues, and disseminated intravascular coagulation leads to diffuse bleeding and resulting haemorrhagic shock. The diagnosis has usually been made prior to this stage from the history of pain, bleeding, fetal distress, and onset of labour. The uterus is tender, firm, and may be rising.

Amniotic fluid embolism

Amniotic fluid embolism (AFE) is described in more detail in the preceding chapter (Collapse in pregnancy) and below. Rapidly escalating, profound coagulopathy is invariable in AFE.

Sepsis

Maternal sepsis, in particular sepsis due to chorioamnionitis, is also a potent cause of coagulopathy.

Embolism

Pulmonary embolism

Collapse from pulmonary embolism is more likely to occur in the postpartum period than antenatally. Puerperal factors that further increase the risk of pulmonary embolism are dehydration in labour, caesarean section, and immobility following delivery. It should be remembered that the widespread use of prophylaxis against thrombosis for caesarean section has led to a significant fall in maternal deaths from this condition.

There is no difference in the mode of presentation in the puerperium to other times. There may be chest pain and shortness of breath followed by cardiac and/or pulmonary compromise in the absence of precipitating factors such as blood loss. Pulmonary embolism is not usually seen immediately after delivery, being more likely in the first 2–3 days of the puerperium.

Amniotic fluid embolism

Although rare, AFE is most likely to present at the time of, or immediately after, delivery. As with pulmonary embolism there is shortness of breath and rapid collapse, usually without chest pain. The proximity to delivery makes AFE a more likely diagnosis than pulmonary embolism, and this will be confirmed by the rapidly developing coagulation disorder which is a feature of AFE but not pulmonary embolism.

Eclampsia

Eclampsia is more likely to occur postpartum but is rare more than 5 days following birth. The woman will usually be hypertensive, although this may have only developed during labour or even after delivery of the baby. She will usually complain of feeling unwell and may have symptoms of imminent eclampsia (see Collapse in pregnancy). She will often be agitated, and her reflexes will be very brisk with the presence of muscle clonus. If the fit is witnessed, she will be observed to lose consciousness and then have a generalised convulsion. The woman should be kept from harm while magnesium sulphate is prepared to stop the seizure and prevent recurrence. After the seizure, bloods for full blood count, urea, electrolytes, creatinine, and liver function tests should be taken if not undertaken recently. The urine should be checked for the presence of significant proteinuria unless it is already known to be present.

The diagnosis is usually clear because the woman will be hypertensive and there will be evidence of pre-eclampsia with proteinuria and/or haematological abnormalities. If there are no features of pre-eclampsia or the fitting is prolonged or focal in nature, further investigation will be needed. This will usually require a computed tomography (CT) scan and, often, magnetic resonance imaging (MRI) scanning to exclude arteriovenous malformations, space occupying lesions, and other intracranial causes.

If the fit is not witnessed, a history of pre-eclampsia is suggestive and the blood pressure will be normal or elevated. There may be damage to the mouth and tongue or evidence of incontinence.

Myocardial infarction

Collapse in the puerperium due to myocardial infarction is even less common than during pregnancy, as the load on the maternal heart diminishes rapidly after birth. However, it may occur if there are additional demands on an already diseased heart, such as fluid overload during labour or severe hypertension following the administration of ergometrine, and should be suspected when significant chest pain precedes the collapse. There is usually a history of cardiac disease. Electrocardiography (ECG) and cardiac enzymes should be performed when the woman is stable.

Anaphylaxis

Anaphylaxis may occur in the puerperium as in pregnancy. This is frequently as a result of the use of antibiotics for the treatment of infection. Similarly the diagnosis is usually clear because of the close association between the administration of the drug and the reaction occurring.

Drug toxicity

As described in Collapse in pregnancy, collapse due to a high epidural or spinal block, intravenous injection of local anaesthetic, or overdose with magnesium sulphate is equally likely to occur in the immediate postpartum period. Again, the close correlation between administration of the drug and the onset of respiratory distress confirms the diagnosis.

Transfusion reaction

Transfusion reactions are more common in the puerperium as more women receive blood postnatally than antenatally, although it is not a usual cause for collapse. However, should collapse occur, the onset of symptoms soon after the transfusion begins makes the diagnosis clear.

Summary

Collapse in the puerperium is more common than during pregnancy, primarily because of postpartum haemorrhage. In this situation the diagnosis is usually clear and most clinicians involved in maternity care should be skilled in the assessment and management of PPH. However, collapse may be due to other causes and can be equally as frightening as in pregnancy. Once again, resuscitation (Airways, Breathing, Circulation) should begin immediately and the diagnosis made while this is proceeding.

Further reading

RCOG Green-top Guideline 52: Prevention and management of postpartum haemorrhage. April 2011.

CTG ABNORMALITIES

Dhammike Silva and Dilip Visvanathan

Introduction

A cardiotocograph (CTG) is a non-invasive method of recording the fetal heart rate and maternal contractions which became commercially available in the 1960s. A retrospective study done in the late 1970s[1] showed that fetal heart monitoring in labour reduced the incidence of cerebral palsy and perinatal mortality, though this was not confirmed in a subsequent meta-analysis of randomised controlled trials.[2] This meta-analysis has shown no reduction in cerebral palsy, neonatal encephalopathy, or perinatal mortality. Furthermore it has also been shown that using fetal heart monitoring in labour is associated with an increase in obstetric intervention.

The overall incidence of cerebral palsy, neonatal encephalopathy, and perinatal mortality is low. Intrapartum contributions to these conditions are even less frequent. The high false positive rates of an abnormal CTG to predict these conditions therefore explain the increased maternal intervention rates. It is for this reason that attempts are being made for a second line of non-invasive monitoring in the event of an abnormal CTG. Many units today use the STAN (ST wave analysis on fetal electrocardiography) machine for this reason. It is important therefore to confirm fetal compromise with acid–base analysis of a fetal blood sample prior to offering a mother a caesarean section for a non-acute abnormal CTG.

Governing bodies such as NICE and the RCOG have now discouraged the use of CTG in low-risk women. CTG is recommended in only two situations: (1) where there is an increased risk of perinatal death, cerebral palsy, or neonatal encephalopathy, and (2) where oxytocin is being used for induction or augmentation of labour.

Basis of the cardiotocograph

The fetal heart rate monitor recognises and processes fetal heart rate pattern and identifies uterine contractions. Most monitors used in clinical practice include a transducer, which uses ultrasound and the Doppler principle to detect fetal heart movements. These are processed and then displayed on a strip chart. The uterine contractions are detected by the change in maternal abdominal circumference.

The normal CTG

Baseline fetal heart rate (FHR): normal range (110–160 bpm)

This is the mean level of the FHR when it is stable but excludes accelerations and decelerations. Baseline FHR is determined over a time period of 5 or 10 minutes and is expressed in beats per minute (bpm; Fig. 1).

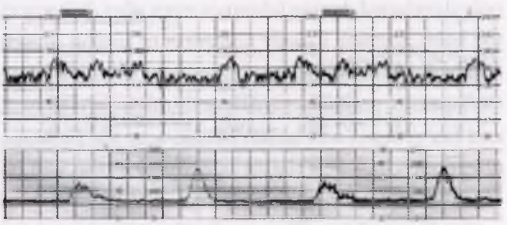

Figure 1 CTG showing a baseline fetal heart rate of 125 bpm, a baseline variability of 7–8 bpm and accelerations. There are no decelerations. The frequency of uterine contractions is 2 per 10 minutes.

Baseline variability: normal range (5–15 bpm)

Baseline variability indicates the integrity of the autonomic nervous system and occurs as a result of beat-to-beat variation in the heart rate. It is measured by estimating the difference in beats per minute between the highest peak and lowest trough of fluctuation in a one-minute segment of the trace between contractions.

Acceleration

An acceleration would be defined as a transient increase in FHR of 15 bpm or more from baseline and lasting 15 seconds or more (Fig. 2). A reactive trace is when there are at least two accelerations in a 20-minute period. It is accepted that the presence of accelerations indicates a vigorous and healthy fetus that will be born with normal blood gases. The significance of no accelerations on an otherwise normal CTG is unclear.

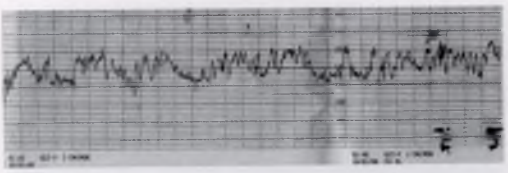

Figure 2 CTG showing accelerations. The presence of accelerations is considered to be a good sign of fetal health and shows that the mechanisms responsible for fetal heart reactivity are intact.

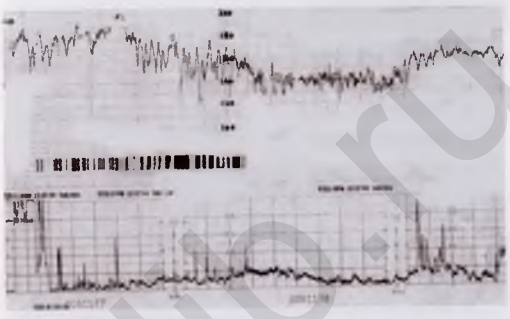

Figure 3 CTG showing a baseline tachycardia secondary to a very active fetus.

Baseline changes in the CTG

Baseline changes in the fetal heart pattern

The baseline FHR is mainly controlled by the autonomic nervous system via the vagus nerve. Stimulation of baroreceptors, which are found mainly in the aortic arch and innervated by the vagus nerve, causes a bradycardia, or slowing, of the FHR. Stimulation of the chemoreceptors found in the aortic and carotid bodies cause a tachycardia, or a quickening, of the heart rate.

Fetal tachycardia

A fetal tachycardia occurs when the baseline FHR is higher than 160 bpm (Fig. 3). It can be moderate (161–180 bpm) or abnormal (>180 bpm).

The sympathetic system matures earlier than the vagus, and hence the baseline FHR tends to fall as gestation advances. One of the compensatory responses to hypoxia is an increase in the baseline FHR. It is important therefore to note changes in the baseline rate as labour progresses. The causes of fetal tachycardia are summarised in Box 1.

Fetal bradycardia

A baseline fetal heart rate of less than 110 bpm is considered a fetal bradycardia (Fig. 4). It may be moderate (100–109 bpm) or abnormal (less than 100 bpm).

It can be physiological in the postterm fetus as a result of continuing development of the vagus. It can

Box 1 Causes of fetal tachycardia

Physiological
- Active fetus
- Fetal prematurity
- Maternal anxiety and stress
- Maternal tachycardia

Pharmacological
- Anticholinergic drugs (atropine)
- Sympathomimetics (ritodrine, terbutaline)

Pathological
- Maternal pyrexia
- Hyperthyroidism
- Fetal hypoxia
- Maternal/fetal anaemia
- Chorioamnionitis
- Fetal tachyarrhythmia

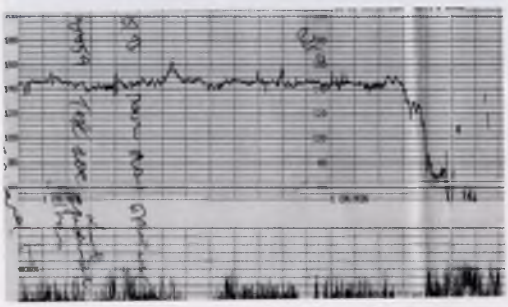

Figure 4 CTG showing a fetal bradycardia secondary to maternal hypotension. Note the epidural top up that was given previously.

Box 2 Causes of fetal bradycardia

Physiological
- Postmaturity
- Cord compression
- Rapid descent
- Vigorous vaginal examination
- Normal variation

Pharmacological
- Epidural and spinal anaesthesia
- Paracervical block
- Benzodiazepines
- Substance abuse (cocaine)

Pathological
- Uterine hyperstimulation
- Maternal seizure
- Maternal hypothermia
- Fetal heart block
- Fetal hypoxia

also occur during head compression. A sustained fetal bradycardia is an obstetric emergency, and such causes as placental abruption, uterine rupture, uterine hyperstimulation, and cord prolapse must be considered. The causes of fetal bradycardia are outlined in Box 2.

Reduced baseline variability

A reduced baseline variability is less than 5 bpm (Fig. 5). It is a non-reassuring baseline if it lasts for more than 40 but less than 90 minutes. If the reduced baseline variability lasts for more than 90 minutes, it is abnormal (see Table 2).

The presence of normal baseline variability requires an intact cerebral cortex, midbrain, vagus nerve, and a cardiac conduction system. A normal baseline variability indicates that the fetus does not suffer from cerebral asphyxia. A gradual reduction of the baseline variability in the presence of other patterns of fetal hypoxia indicates that the fetal compensatory mechanism to maintain cerebral oxygenation is being lost. The causes of reduced baseline variability are summarised in Box 3.

Sinusoidal patter

A regular oscillation of the baseline long-term variability that resembles a sine wave is called a sinusoidal pattern (Fig. 6). This smooth, undulating pattern, lasting at least 10 minutes, has a relatively fixed

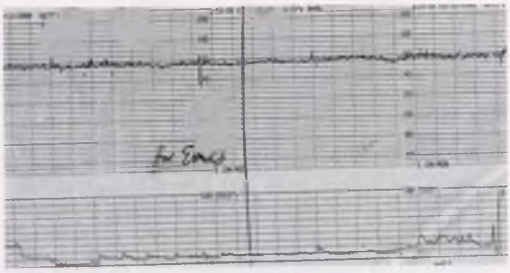

Figure 5 CTG demonstrating a baseline variability of less than 5 beats/minute.

Box 3 Causes of reduced fetal baseline variability

Physiological
- Quiet sleep state

Pharmacological
- Narcotics, e.g. morphine, diazepam
- Magnesium sulphate
- Vagal blockade – atropine or scopolamine
- Substance abuse e.g. heroin

Pathological
- Fetal cerebral hypoxia
- Fetal heart block
- Congenital neurological abnormality
- Other, e.g. in-utero infection, asphyxial event
- Fetal anaemia

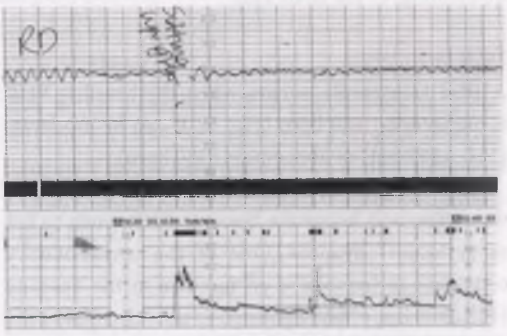

Figure 6 CTG showing sinusoidal pattern. The baby was born by caesarean section and had severe anaemia.

period of 3–5 cycles per minute and an amplitude of 5–15 bpm above and below the baseline. Another distinguishing feature is that baseline variability is absent. The pattern was first described in infants with severe rhesus alloimmunisation and fetal anaemia. It is considered an abnormal finding and associated with a poor fetal outcome.

Periodic changes in the fetal heart pattern

Decelerations

Transient episodes of slowing of the FHR below the baseline level measuring 15 bpm or more and lasting 15 seconds or more. Uterine activity needs to be monitored accurately in order to classify the different decelerations, as management would depend on the type of the deceleration.

Early decelerations Uniform, repetitive, periodic slowing of FHR with onset early in the contraction and a return to baseline at the end of the contraction (Fig. 7). These are usually persistent and occur with each contraction. The causes of early decelerations are physiological – head compression resulting in increased vagal tone – not pathological.

Late decelerations Uniform, repetitive, periodic slowing of FHR with an onset in the mid to end part of the contraction and a nadir more than 20 seconds after the peak of the contraction and ending after the contraction (Fig. 8). In the presence of a non-accelerative trace with baseline variability <5 bpm, the definition would include decelerations <15 bpm. Late decelerations are thought to be caused by a decreased blood flow (associated with a uterine contraction) beyond the capacity of the fetus to extract oxygen. Causes for late decelerations are given in Box 4.

Variable decelerations

Typical variable decelerations These are intermittent periodic variable slowings of FHR with rapid onset and recovery (Fig. 9). Time relationships with contraction cycle are variable and can occur in isolation. Sometimes they resemble other types of deceleration patterns in timing and shape. The causes of variable decelerations are umbilical cord compression, generally in the first

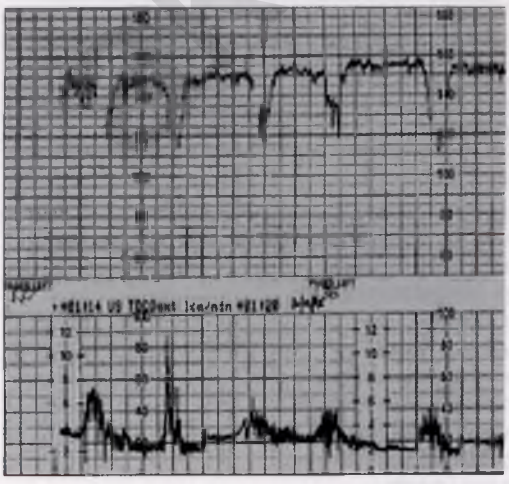

Figure 7 CTG demonstrating early decelerations.

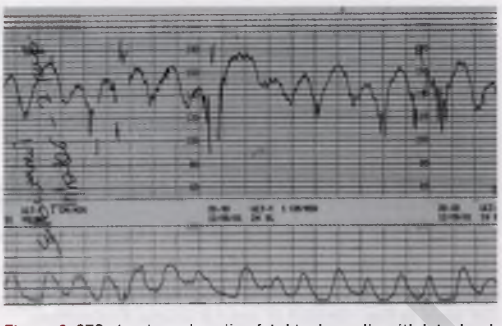

Figure 8 CTG showing a baseline fetal tachycardia with late decelerations secondary to uterine hyperstimulation from intravaginal prostaglandin gel.

Box 4 Causes of late decelerations due to reduction in placental perfusion provoked by uterine contractions

Pre-existing placental dysfunction

- Pre-eclampsia
- IUGR
- Diabetes
- Chronic hypertension
- Postterm pregnancy

Maternal condition

- Diabetic ketoacidosis
- Uterine hyperstimulation
- Maternal hypotension

IUGR, intrauterine growth restriction.

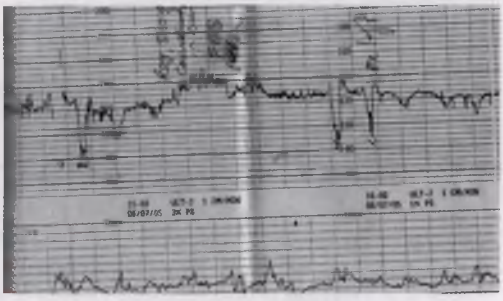

Figure 9 CTG showing variable decelerations. It is important to check the baseline features. Here the baseline rate is 130 beats/minute, with a baseline variability of 10–15 beats/minute and there are accelerations.

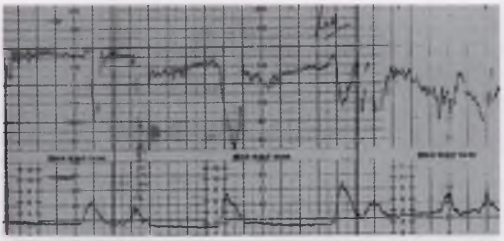

Figure 10 CTG showing shouldering variable decelerations. There is however a baseline tachycardia and a reduced baseline variability. This would be then classified as atypical variable decelerations.

stage of labour, and substantial head compression during the active phase of the second stage of labour. Both of these events cause activation of the vagus nerve with a subsequent reduction in FHR.

Atypical variable deceleration In addition to the features described, variable decelerations are said to be atypical if they have any of the following characteristics (Fig. 10):

- loss of primary or secondary rise in baseline rate (shouldering);
- slow return to baseline FHR after the end of the contraction;
- prolonged secondary rise in baseline rate (exaggerated shouldering);
- biphasic deceleration;
- loss of variability during deceleration;
- continuation of baseline rate at lower level.

These features indicate that the fetus is mounting a compensatory response to hypoxia, which it will develop if persistent over a period of time. It is therefore important to ensure that both types of variable decelerations, especially atypical ones, are recognised and that appropriate action is taken.

Categories of fetal heart trace pattern

It has been recommended by NICE and the RCOG that CTGs should be classified into three groups – normal, suspicious, or pathological – depending on the features that are present. These are outlined in Tables 1 and 2.[3]

Further information about classifying FHR traces includes:

- If repeated accelerations are present with reduced variability, the FHR trace should be regarded as reassuring.
- True early uniform decelerations are rare and benign, and therefore they are not significant.
- Most decelerations in labour are variable.
- If a bradycardia occurs in the baby for more than 3 minutes, urgent medical aid should be sought and preparations should be made to urgently expedite the birth of the baby, classified as a category 1 delivery. This could include moving the woman to theatre if the fetal heart has not recovered by 9 minutes. If the fetal heart recovers within 9 minutes, the decision to deliver should be reconsidered in conjunction with the woman if appropriate.
- A tachycardia in the baby of 160–180 bpm, where accelerations are present and no other adverse features appear, should not be regarded as suspicious. However, an increase in the baseline heart rate, even within the normal range, with other non-reassuring or abnormal features should increase concern about the well being of the fetus.

Table 1 Categories of fetal heart trace patterns

Normal	An FHR trace in which all four features are classified as reassuring
Suspicious	An FHR trance with one feature classified as non-reassuring and the remaining features classified as reassuring
Pathological	An FHR trace with two or more features classified as non-reassuring categories or one or more classified as abnormal

Table 2 Criteria for categories of fetal heart traces

Feature	Baseline (bpm)	Variability	Decelerations	Accelerations
Reassuring	110–160	≥5	None	Present
Non-reassuring	100–109 161–180	<5 for 40–90 minutes	Typical variable decelerations with over 50% of contractions, occurring for over 90 minutes Single prolonged deceleration for up to 3 minutes	The absence of accelerations with otherwise normal trace is of uncertain significance
Abnormal	<100 >180 Sinusoidal pattern ≥10 minutes	<5 for 90 minutes	Either atypical variable decelerations with over 50% of contractions or late decelerations, both for over 30 minutes Single prolonged deceleration for more than 3 minutes	

Fetal blood sampling

If the CTG is pathological but non-acute, it must be decided whether a fetal blood sampling should be undertaken – if possible and appropriate.

If the pH is 7.25 and above (normal) – labour should be allowed to continue and if the abnormality persists a repeat FBS should be performed in 1 hour's time.

If the pH is 7.21–7.24 (borderline) – the repeat FBS should be repeated in 30 minutes. If a third sample is required, a consultant should be involved in further decisions about the labour.

If the pH is 7.20 or less (abnormal) – a category 1 LSCS (delivery within 30 minutes) or vaginal birth if possible expedited with consultant being involved in decision-making.

If FBS is not possible or inappropriate – place mother in the left lateral position, give 500 mL of crystalloid if appropriate and the delivery of the baby should be expedited.

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EPIGASTRIC PAIN IN PREGNANCY

Vincent Cheung, Nishchay Chandra, and Margaret Myszor

History

A full history of the presenting complaint is extremely important, as are any associated symptoms. The history must be interpreted with reference to the gestational age, as aetiologies change throughout pregnancy.

Specific questions that may aid diagnosis include:

- Did the pain start gradually or suddenly?
- Is it dull, aching and constant, or is it sharp and stabbing in nature?
- Is it associated with meals?
- How long after eating does it start?
- Is it well localised and has there been any change?
- Are there any associated features, e.g. nausea and vomiting?
- Are there any obvious relieving or exacerbating factors?

Physical examination

- Clinical findings may be less obvious and more difficult to elicit in pregnancy than in non-pregnant women with the same disorder.
- Peritoneal signs are often absent in pregnancy as a result of lifting and stretching of the anterior abdominal wall. This means that any underlying inflammation is not in direct contact with the peritoneum, thus reducing guarding.
- It may be useful to examine the patient in the lateral decubitus position to help distinguish between uterine and extrauterine pain. This manoeuvre displaces the uterus to one side.
- The intra-abdominal contents change position as the pregnancy progresses. McBurney's point is where the appendix is situated in the first trimester before it moves upwards and laterally towards the gallbladder. The bowel can be displaced to the upper abdomen.
- It may be worthwhile carrying out a vaginal examination if a gynaecological cause is suspected.
- In patients presenting early in pregnancy, it is important to rule out ectopic pregnancy although it should be emphasised that this tends to cause pain in the lower abdomen.

Laboratory investigations

Commonly used laboratory tests have different ranges in pregnancy (see Appendix), and therefore may be of limited use in aiding diagnosis.

Radiological investigations

- Ultrasound scanning is the most commonly used investigation for evaluating a pregnant abdomen. It is safe, and the gallbladder, liver, pancreas, and kidneys can be evaluated easily.
- Ionising radiation that produces exposures <0.5 Gy (= 50 rad) have not been associated with fetal abnormalities or pregnancy loss. However, there is a possible association between prenatal radiation exposure and childhood cancer.[1]
- Ionising radiation (as with computed tomography (CT) scanning) should be used only when absolutely indicated medically and other imaging options have been considered and rejected.
- Magnetic resonance imaging (MRI) is not recommended in the first trimester, and not all MRI contrast agents are approved for use in pregnancy. It has been used in later pregnancy to exclude morbidly adherent placentae. It must be remembered that the duty of care of any attending doctor is primarily to the mother, as the fetus has no legal standing while in utero.

Conditions with increased frequency in pregnancy

The following conditions causing epigastric pain occur more frequently when a woman is pregnant:

- gastro-oesophageal reflux (GORD)/oesophagitis;
- biliary colic;
- acute cholecystitis (due to decreased gallbladder motility and increased cholesterol saturation of bile in pregnancy).

Conditions due to pregnancy

The following conditions can occur as a result of pregnancy:

- rupture of the rectus abdominis muscles;
- ectopic pregnancy (the classical triad of bleeding, lower abdominal pain and amenorrhoea may not be present and symptoms can be non-specific;[2]
- acute fatty liver of pregnancy;
- HELLP (haemolysis, elevated liver enzymes and low platelets);
- spontaneous rupture of the liver (due to HELPP);
- splenic artery aneurysm rupture.

Conditions incidental to pregnancy

Conditions incidental to pregnancy are:

- non-ulcer dyspepsia;
- gastric and duodenal ulceration;
- gastritis and duodenitis;
- irritable bowel syndrome;
- acute and chronic pancreatitis.

Gastro-oesophageal reflux disease

This condition is common in non-pregnant women and almost universal to some degree in pregnancy. Estimates of the proportion of women who experience GORD at some time during pregnancy range from 30 to 80 per cent. It is due to an increased intra-abdominal pressure from a gravid uterus and leads to dysfunction of the lower oesophageal sphincter (Fig. 1). This is also aggravated by increased serum progesterone levels, which cause relaxation of involuntary smooth muscle. There is also delayed clearance of the reflux leading to increased acid exposure times.

Clinical features include:

- heartburn (retrosternal pain related to meals, posture and exercise);
- waterbrash (excess salivation, especially during an episode of pain);
- regurgitation of acid and bile, which can, rarely, give rise to nocturnal sore throat or indeed asthma.

Treatment

General measures include elevation of the head of the bed, small, frequent meals, and avoiding anything that obviously exacerbates the symptoms. Patients should be advised to avoid eating just prior to lying down. Alginates can be very useful for symptomatic relief of mild symptoms. Although there is no conclusive evidence for the safety of H2-receptor antagonists and proton-pump inhibitors in pregnancy, both have been widely used for symptomatic relief of refractory symptoms.

Biliary colic and acute cholecystitis

Asymptomatic gallbladder disease (seen on imaging) occurs in 3–4 per cent of pregnant women. It is

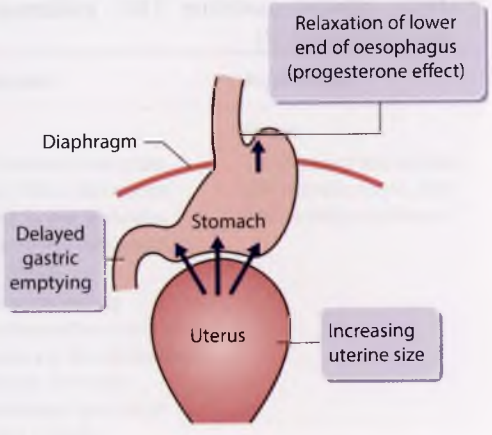

Figure 1 Diagram of factors affecting acid reflux.

estimated that acute cholecystitis occurs in 1 in 1130 to 12,890 pregnancies.

Clinical features

- Pain is usually moderately severe and constant in both acute cholecystitis and biliary colic. It is most commonly felt in the right upper quadrant but can be epigastric radiating to the back.
- Vomiting occurs in 50 per cent of patients.
- Fever is common in cholecystitis.
- Ultrasound scanning is diagnostic and safe.
- Blood tests are of limited value as both leucocytosis and raised alkaline phosphatase levels are observed in healthy pregnancies.
- Transient increases in amylase can occur in 30 percent of those with biliary colic but markedly raised levels suggest pancreatitis. However, amylase may not be elevated in patients with acute on chronic pancreatitis.

Treatment

Conservative treatment with intravenous fluids and analgesia, particularly pethidine, is the initial approach. Broad-spectrum antibiotics should be included if systemic symptoms are prominent. Surgery may be necessary but timing is controversial, with advocates of both surgery postpartum and during pregnancy. Ideally this should be undertaken during the second trimester, which minimises the risks for premature delivery.[3] Laparoscopic cholecystectomy is safe in pregnancy, although caution must be observed owing to potential pressure on the inferior vena cava as well as the increasing size of the uterus.

Acute pancreatitis

This occurs most commonly secondary to gallstones or biliary sludge. It is more prevalent with advanced gestational age, and is associated with a fetal loss of 10–20 per cent. The initial conservative management is similar to that of the non-pregnant patient. Endoscopic retrograde cholangiopancreaticogram and sphincterotomy can be performed safely in patients found to have common bile duct stones as a cause for the pancreatitis.[4] In such cases, the uterus must be protected with a lead shield, and limiting radiation exposure is imperative.

Gastric ulcer

This is a very rare condition in this age group. It presents with epigastric pain after eating, and is often associated with anorexia and weight loss. It is commonly caused by *Helicobacter pylori* and diagnosed endoscopically. First line treatment for *H. pylori* eradication comprises a proton pump inhibitor with amoxicillin plus clarithromycin or metronidazole (triple therapy). Quadruple therapy with PPI, bismuth, clarithromycin, and tetracycline should be avoided, as both bismuth and tetracycline are teratogenic.

Duodenal ulcer

There is a decreasing incidence of this condition in the Western world owing to the declining incidence of *H. pylori*. Almost all cases are caused by this organism or the use of non-steroidal anti-inflammatory agents. The clinical features in this condition include epigastric pain before meals.

Gastritis, duodenitis and non-ulcer dyspepsia

These conditions can present with dyspeptic symptoms of mild to moderate epigastric discomfort and a feeling of fullness after meals. Endoscopy is not usually necessary in a young age group if symptoms are relieved by antacids, H2 blockade, or proton-pump inhibition.

Irritable bowel syndrome

This is a functional disorder comprising recurrent abdominal pain, altered bowel habit, and abdominal distension. Changes in bowel habit occur as a result of the increasing levels of serum progesterone, which acts to relax smooth muscle in the gut wall. Initial management involves optimisation of lifestyle through dietary changes. Those with constipation-predominant IBS should increase water and insoluble fibre intake, and those with diarrhoea-predominant IBS should reduce fat and dairy consumption.

Eosinophilic oesophagitis (EO)

Eosinophilic oesophagitis is a chronic inflammatory condition characterised by a dense infiltrate of eosinophils within the epithelium of the oesophagus. While epigastric pain and reflux symptoms are features, patients typically present with dysphagia and food regurgitation. There is an association with EO and atopic conditions (asthma, eczema, and hay fever). Treatment usually involves swallowing inhaled corticosteroids, and this is considered to be appropriate in pregnancy, provided a careful risk/benefit assessment is performed.[5]

Summary

1 The site of pain in the pregnant woman may be different to that seen in the non-pregnant state.
2 Laboratory investigations may not help because of the change in their normal range found in pregnancy.
3 Radiological investigations are generally contraindicated during pregnancy unless there are extremely good indications for using them. Ultrasound is widely used and is safe in pregnancy.
4 Gastro-oesophageal reflux disease is very common in pregnancy and is consequently the commonest cause of epigastric pain.
5 Other conditions include biliary colic, cholecystitis, pancreatitis, and peptic ulceration, which may need a different management plan in pregnancy.
6 There are rare causes of epigastric pain that occur only in pregnancy. These include HELPP (haemolysis, elevated liver enzymes and low platelets) with spontaneous rupture of the liver, and pre-eclampsia with subcapsular haemorrhage of the liver.

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FEVER, POSTOPERATIVE (GYNAECOLOGICAL)

Probhodana Ranaweera

Introduction

Postoperative fever is a common sign encountered in routine clinical practice.[1] Evaluating and managing a patient with a postoperative fever requires a sound knowledge of pathophysiology and differential diagnosis backed up by clinical experience. Many patients develop fever in the first few days after major surgery, and most of the time this is due to an inflammatory response and resolves spontaneously.[2] However, postoperative fever can be a manifestation of a more serious and sometimes life-threatening complication. Therefore, the differential diagnosis for postoperative fever is broad.

Pathophysiology

Manifestation of fever is due to cytokine release in response to various stimuli.[3] Interleukin (IL)-1, IL-6, tumour necrosis factor (TNF)-alpha, and interferon (IFN)-gamma, which are associated with fever, are produced by a variety of tissues and cells. There is some evidence that IL-6 is the cytokine most closely correlated with postoperative fever.[4] These are released by tissue trauma and do not necessarily signal infection. The magnitude of the trauma is correlated with the degree of the fever response. For example, laparoscopic oophorectomy is associated with less tissue trauma and fewer episodes of postoperative fever than is open oophorectomy.[5]

Importantly bacterial endotoxins and exotoxins can stimulate cytokine release and cause postoperative fever. Bacteria or fragments of bacteria translocated from the colon (e.g., as a consequence of perioperative ileus or hypotension) may be responsible for some episodes of self-limited postoperative fever.[6] Non-steriodal anti-inflammatory agents (NSAIDs) and glucocorticoids suppress cytokine release and thereby reduce the magnitude of the febrile response.

Definition of fever

'Fever is the rise of normal core temperature of an individual that exceeds the normal daily variation

and occurs in connection with an increase in the hypothalamic set point.[7]

The mean oral body temperature is considered to be 36.8°C ± 0.4°C (98.2°F ± 0.7°F). Fever is defined as morning temperature exceeding 37.2°C (98.9°F) or an evening temperature above 37.7°C (99.9°F).[7]

In clinical practice significant postoperative fever is defined as the presence of a temperature higher than 38°C (100.4°F) on two occasions 4 hours apart, excluding the first 24 hours after surgery.[7]

The incidence of postoperative fever as published in the literature varies widely, from 14 to 91 per cent.[8] This may be infectious or non-infectious in origin. Many patients with postoperative fever do not have an underlying infectious cause. A total of 80–90 per cent of patients with fever on the first postoperative day usually have no infection, whereas 80–90 per cent of patients who develop fever on or after the fifth postoperative day commonly have an identifiable infection.[9] Infection is more likely to be present in a patient who develops fever after 2 days of surgery.[10]

Time-related causes of postoperative fever[11]

The time at which the fever begins will suggest its origin. It should be borne in mind that these time-related causes are guidelines and do not serve as absolute rules. There are no rigid demarcations between the time frames described since, on many occasions, there is a temporal overlap in the causes described (see Fig. 1).

Intraoperative causes of postoperative fever are:

- pre-existing sepsis;
- intraoperative septicaemia;
- transfusion reaction;
- heat stroke;
- malignant hyperthermia.

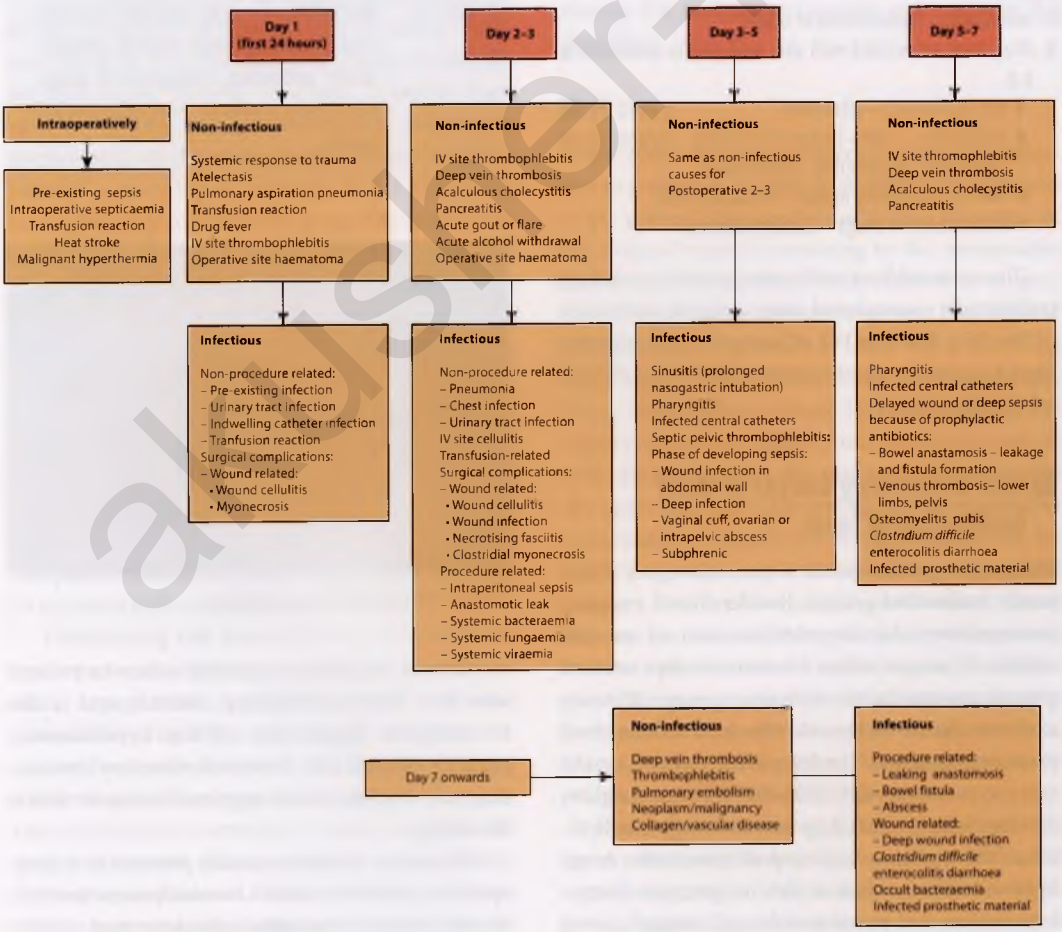

Figure 1 Causes of fever according to time of onset postoperatively.

Miscellaneous causes of postoperative fever

Although not common in the general population, the following should be borne in mind, since a select group of patients may be at risk from these causes:

- sinusitis (prolonged nasogastric intubation);
- pharyngitis;
- infected central catheters;
- ventilator-associated pneumonia;
- nosocomial infections;
- infected haematoma;
- acute gout or flare-up;
- acute alcohol withdrawal;
- hyperthyroidism/thyrotoxicosis/thyroid storm;
- adrenal insufficiency;
- phaeochromocytoma;
- myocardial infarction;
- pulmonary embolism;
- neuroleptic malignant syndrome;
- intracranial pathologies;
- meningitis;
- medications (anaesthesia or other);
- drug fever associated with skin rash and/or eosinophilia, e.g.
  - anti-epileptics – phenytoin;
  - antibiotics – beta-lactam antibiotics, sulphonamide antibiotics, piperacillin, tazobactam;
  - anti-inflammatory agents – indomethacin;
  - intraoperative drugs – succinylcholine.

The causes of fever in the postoperative period are traditionally remembered using a simple mnemonic of five W's. The five W's of causes of postoperative fever according to postoperative day (POD) of fever are shown in Box 1.

Life-threatening causes of early postoperative fever

Malignant hyperthermia is a rare autosomal, dominantly transmitted genetic disorder that is triggered intraoperatively by the administration of succinyl choline. It occurs within 30 minutes after onset of general anaesthesia but may even present 10 hours after anaesthesia. Tachycardia develops, and the blood pressure is unstable. The fever is life threatening and may increase to 41–42°C (105–107°F). Muscle rigidity develops with acidosis, hypoxia, and cardiac arrhythmias. The treatment is to stop all anaesthetic drugs, hyperventilate the patient with oxygen, give dantrolene sodium and procainamide, and initiate cooling and diuresis to prevent precipitation of myoglobin.

Box 1 The five Ws of causes of postoperative fever according to postoperative day (POD)

POD 1–2	*Wind* (respiratory) – atelectasis occurring within 24–48 hours, aspiration pneumonia, ventilator-associated pneumonia
POD 3–5	*Water* – cystitis and urinary tract infection, especially in catheterised patients
POD 4–6	*'W(V)eins'/wings/walking* – deep vein thrombosis, intravenous (IV) site phlebitis in all sites of vascular access IVs
POD 5–7	*Wound* – wound infection (Fig. 2): treatment is drainage, and excision and removal of sutures in some situations; it is essential to diagnose serious problems such as necrotising fasciitis and peritonitis caused by an intestinal leak (internal wound).
POD 7+	*Wonder drugs* – drug reactions (uncommon), including drugs received preoperatively, antibiotics, intraoperative drugs, transfusion products, anti-inflammatory agents

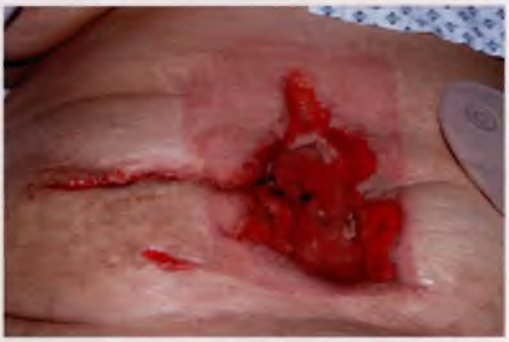

Figure 2 Postoperative wound infection.

Adrenal insufficiency typically occurs in patients who have been on long-term steroids, and is due to iatrogenic suppression of the hypothalamic–pituitary–adrenal axis. Fever and refractory hypotension may develop; steroid supplementation in time is life saving.

Pulmonary embolism usually presents in a postoperative patient as sudden haemodynamic instability and collapse. Fever, although uncommon, may be present.

Alcohol withdrawal frequently presents with fever. Prompt recognition and treatment prevents excessive morbidity and mortality.

Myonecrosis is commonly due to wound infection with *Clostridium* species or group A streptococci. It is a surgical emergency in which the patient presents with shock, tachycardia, fever, and severe septicaemia in the first 24 hours postoperatively. The diagnosis is easily made if the dressing is opened and the wound examined. A copious thin, brownish, and malodorous discharge is present. The skin may be discoloured, and there may be crepitations and bullae formation. The patient is usually in severe pain and restless. If not treated in time, vascular collapse, renal failure, haemoglobinuria, and jaundice develop. Radical debridement of all the involved devitalised tissue and prompt initiation of high doses of penicillin or tetracyclines is mandatory. The rare differential diagnosis is metastatic myonecrosis from adenocarcinoma of the bowel.

Necrotising fasciitis: If the diagnosis and treatment of this condition is delayed, overwhelming sepsis may occur, as it is a rapidly progressing, potentially life-threatening bacterial infection. It results from wound infection with polymicrobes – haemolytic streptococci, staphylococcus, anaerobes, or mixed bacteria – resulting in necrosis of the superficial fascia that characteristically spares the underlying muscle. The toxicity is worse than the associated fever, with hyperthermia or hypothermia, hypotension, tachycardia, and lethargy. Locally the wound has dusky faded skin with subcutaneous oedema, induration, crepitations, hyperaesthesia, and cutaneous bullae formation, and the lesion undermines the skin. Blood tests may show a leucocytosis, haemoconcentration hypocalcaemia, haemolysis, and hyperbilirubinaemia. Hepatic, renal, and pulmonary insufficiency may develop followed by septic shock. The patient should be treated aggressively as would be someone with major burns.

Predisposing risk factors include diabetes mellitus, trauma, alcoholism, an immunocompromised state, hypertension, peripheral vascular disease, intravenous drug abuse, and obesity. A wide excision of the involved wound with debridement and redebridement, if necessary, is performed. Total parenteral nutrition is started via a central line with adequate replacement and correction of calcium, fluids, electrolytes, and calories. Broad-spectrum antibiotics need to be started and changed according to the culture reports once they become available.

Intestinal leak with peritonitis can occur from either an early or delayed leaking anastomotic site or intestinal perforation following intra-abdominal or intrapelvic surgery, where inadvertent enterotomy may have occurred. Early diagnosis depends on a high degree of suspicion with an urgent exploratory laparotomy to repair the leak, perform a peritoneal toilet lavage, start appropriate antibiotics, and resuscitate the patient with fluids, electrolytes, and multivitamins. Ketoacidosis is prevented by ensuring adequate total parenteral nutrition until such time as the patient is permitted oral intake.

Evaluating a patient[12]

It is vital to have a systematic, logical, and holistic approach when evaluating a patient with postoperative fever. A careful history, systematic, and thorough physical examination and targeted investigations are the mainstay for a successful diagnosis. A timely accurate diagnosis will help the physician to manage the patient appropriately and minimise the morbidity.

History

Before addressing the postoperative fever it is important to gather information regarding the background of the patient. This can be easily done by review of the medical records pertaining to the preoperative course and presentation which resulted in surgery. This will give an insight into the patient problem and possible causes, especially if there was pre-existing sepsis (e.g., pelvic abscess, tubo-ovarian masses, pelvic inflammatory disease [PID]). Details of the surgery should be sought from operative notes or even discussing with the surgeon who performed the operation, especially noting any intraoperative complications. Anaesthetic notes are important for identifying any complications during surgery and recovery. Details of the patient's past medical history and any current underlying medical problems may indicate a possible cause. Known drug and food allergies of the patient should be noted, as postoperative fever may be a manifestation of an allergic reaction. Many drugs can cause fever, and it is important to evaluate those prescribed for the patient.

Details of the timing, pattern and degree of fever, other associated symptoms such as chills and rigors, anorexia, arthralgia, and myalgia should be noted. Systemic inquiry of symptoms pertaining to other systems, including respiratory, gastrointestinal,

genitourinary, neurological, and cardiovascular, is important for an early correct diagnosis.

Inquire from the patient and nursing staff about sputum amount, quality, diarrhoea, any areas of skin breakdown, and mobility of the patient. Location of catheters, intravenous lines, drains, and the length of time they have been in situ should be noted.

Examination

The general condition of the patient may provide clues to the cause of fever. This may range from normality to evidence of mild systemic toxicity to a poor general condition with hypotension and systemic vascular collapse.

Noting all the vital signs is relevant. If properly maintained, Modified Early Warning Signs (MEWS) charts provide valuable information regarding the temporal course of the patient's vital signs. The pulse rate is an important sign. It is an ominous sign if the degree of tachycardia is out of proportion to the temperature rise, in which case severe sepsis should be suspected. This is especially true when there is an associated hypotension or oliguria. Tachypnoea usually points to a respiratory problem.

The temperature can be taken orally or rectally, and the site used should be consistent. Oral temperature is 0.5°C less than rectal temperature and 0.5°C higher than the axillary temperature recorded. The pattern and trend of fever should be noted from the MEWS chart.

The surgical incision should always be examined even in the absence of localising symptoms to exclude silent wound dehiscence. Examination of the wound should include inspection of the colour of the peri-incisional skin (whether dusky, erythematous, necrotic, blue or black), any associated induration, oedema, and tenderness. It is also important to look for hyperaesthesia, crepitation, cutaneous bullae, and spreading erythematous streaks. The presence of cellulitis, abscess, necrotising fasciitis, or gas gangrene is usually locally symptomatic. In the early stages of a wound infection, there is increasing tenderness and peri-wound oedema. Later, erythema may develop with elevated skin temperature and fluctuation. There are more local signs with staphylococcal infections than with enteric organisms, when the tenderness is increased but the erythema may be minimal. Other signs of infection, such as tachycardia, malaise, chills, and leucocytosis, may develop.

The depth of any wound breakdown should be assessed to see which structures are affected and whether any necrotic tissue needs to be excised. The nature, colour, and smell of any discharge provide indicators to the nature of the wound infection. The lymph nodes draining the area should also be examined for any evidence of involvement. All intravenous puncture sites with or without indwelling cannulae plus drain sites should be examined for overt skin erythema and tenderness as well as for any underlying swelling, infection, and collection of pus.

The chest should be examined carefully with percussion and auscultation for evidence of collapse, consolidation, and pleural effusion.

The abdomen should be examined for features of peritonitis, localised infection, and subphrenic or pelvic abscess, if any abdominal or pelvic surgery has been performed. Lower abdominal tenderness, rebound tenderness, and tenderness on rectal and vaginal examination with or without the presence of a pelvic mass and vaginal discharge may indicate pelvic cellulitis, infection, or a pelvic abscess.

Tenderness over the kidneys and suprapubic region (bladder) may be present with any urinary tract infection.

Early stages of bone infection may have tenderness only over the affected area. However, with progression there will be swelling, empyema, and ultimately discharge of pus.

If, on examination of the central nervous system, neck stiffness, photophobia and altered consciousness are present, then meningitis and infection of the central nervous system may need to be excluded.

Investigations[13]

Depending on the history and examination, the investigations should be ordered to help in the diagnosis and management of the patient.

The following tests would need to be considered where clinically indicated and appropriate:

- Urinalysis.
- Haematological assessment:
  - complete blood count with total and differential white cell count and peripheral smear;
  - depressed white cell counts are seen in severe sepsis, immunocompromised or malnourished patients; platelet count is elevated as a response to stress but decreases with disseminated intravascular coagulopathy;
  - erythrocyte sedimentation rate/C-reactive protein may be useful markers;

- coagulation screen is important in patients with severe sepsis;
- tests to detect unexpected antibodies are essential in transfusion reactions.

- Serum biochemistry:
  - urea, electrolytes and creatinine;
  - liver function tests;
  - glucose;
  - arterial blood gases – metabolic acidosis is one of the earliest signs of developing septic shock;
  - myocardial enzymes;
  - serum amylase.
- Bacteriological assessment. This should be directed as appropriate and samples taken as indicated in the individual case. Identification of a causative organism and its antibiotic sensitivities should always be attempted prior to starting antibiotics in patients suspected to have an infection as the cause of the fever. The following samples may be required:
  - blood culture;
  - sputum, pleural or peritoneal aspirate;
  - urine;
  - skin and wound swab of discharge or needle aspiration;
  - cerebrospinal fluid (by lumbar puncture);
  - intravascular catheters and drain tip cultures;
  - aspiration of tissue fluid from spreading edge of cellulitis;
  - stool.
- Radiological imaging:
  - chest X-ray;
  - abdominopelvic X-ray – displacement of air-filled organs by a mass is seen in the presence of pelvic abscess;
  - ultrasound and Doppler help detect venous thrombosis, abscesses and haematomas;
  - computerised tomography (CT) and magnetic resonance imaging (MRI) scanning to identify abscesses, haematomas, and other lesions;
  - bone X rays may detect osteomyelitis.
- Electrocardiograms (ECGs) and echocardiography are helpful in myocardial ischaemia, intracardiac thrombosis, and pulmonary embolism.

Management principles[14]

Any unnecessary treatments, including medications and catheters, should be discontinued in patients with postoperative fever. General measures to suppress fever with antipyretics will help to relieve patient discomfort and the physiologic stress and metabolic demands of fever and shivering. This approach is unlikely to mask a significant pathologic condition. Additional treatment depends upon the cause of the fever.

In patients with severe systemic sepsis, fluid resuscitation should be initiated early. Inotropes and vasoactive agents may need to be started to address any myocardial depression associated with systemic infections. In seriously ill patients, respiratory support with oxygen may be required, and they may also need to be transferred to an intensive therapy unit.

The decision to administer antibiotics to a patient with postoperative fever depends upon careful clinical assessment, including an appraisal of the patient's stability. Patients who have undergone major surgery and are receiving intensive care treatment as well as those who are haemodynamically unstable should generally be treated empirically with broad-spectrum antibiotics after appropriate cultures have been obtained. Nosocomial pathogens are often resistant to many antimicrobials; appropriate broad-spectrum regimen should be used depending on site of suspected infection and antimicrobial resistance in the local setting. Liaison with the microbiologist should be established at an early stage. If a source of fever is not apparent and blood cultures show no growth after 48 hours, then discontinuation of antimicrobials should be seriously considered.

If a site of infection is identified and/or cultures are positive, the broad-spectrum regimen should be focused to cover the probable or known causative organism(s). Antimicrobial treatment beyond the empiric period of 48 hours should be reserved for patients in whom an infection has been identified. Carefully selecting antimicrobial treatment can help to avoid adverse medication reactions and to minimise the prevalence of resistant organisms in the hospital.

Surgical intervention may be required in the form of wound debridement, and excision of infected wound or diseased organ to eliminate the source of infection and drainage of pus. Swabs and tissue should be sent for Gram stain, culture, and sensitivity at this point, even if sent earlier, followed by saline-soaked dressings. Correction of lesions causing obstruction of the hollow organs and elimination of spaces in which infection may develop are necessary.

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FEVER, PUERPERAL

Dhammike Silva and Dilip Visvanathan

Definition of puerperal pyrexia

Puerperal pyrexia is commonly defined as a temperature elevation to 38°C on two occasions after the first 24 hours postpartum.[1]

History

Puerperal fever was one of the commonest causes of maternal death before the concept of antisepsis and introduction of antibiotics. The use of unsterile instruments, repeated vaginal examinations in labour, and physicians examining patients without washing their hands were contributing factors. It was only in 1847 that Ignaz Semmelweis, a Hungarian physician working in the Vienna General Hospital, discovered that hand washing could significantly reduce the incidence of puerperal sepsis.

Hospital-acquired infections are increasing and all hospitals have strict antisepsis protocols which involve careful hand-washing and disinfection with alcohol before and after contact with patients. Sepsis has once again become a significant cause of mortality. Analysis of cases has shown that this results from delay in recognition, treatment, and identification of the patient who is seriously unwell. In this section the causes of puerperal fever, the stages of sepsis, and the surviving sepsis care bundle will be discussed (see also Fever, postoperative).

Causes of puerperal fever

The commonest cause of puerperal pyrexia remains infection of the genital tract, which is a common problem in the developing world. However, infections at other sites as a consequence of the delivery or concurrent infection also need to be considered. Non-infective causes include venous thromboembolism, which needs to be excluded as it is now the commonest direct cause of maternal death in the UK. These causes of puerperal pyrexia are summarised in Fig. 1.

Uterine infection

Endometritis is one of the most common serious complications of the puerperium and is a major cause of maternal morbidity. Major risk factors for developing postpartum uterine infection include pre-existing chorioamnionitis and caesarean section

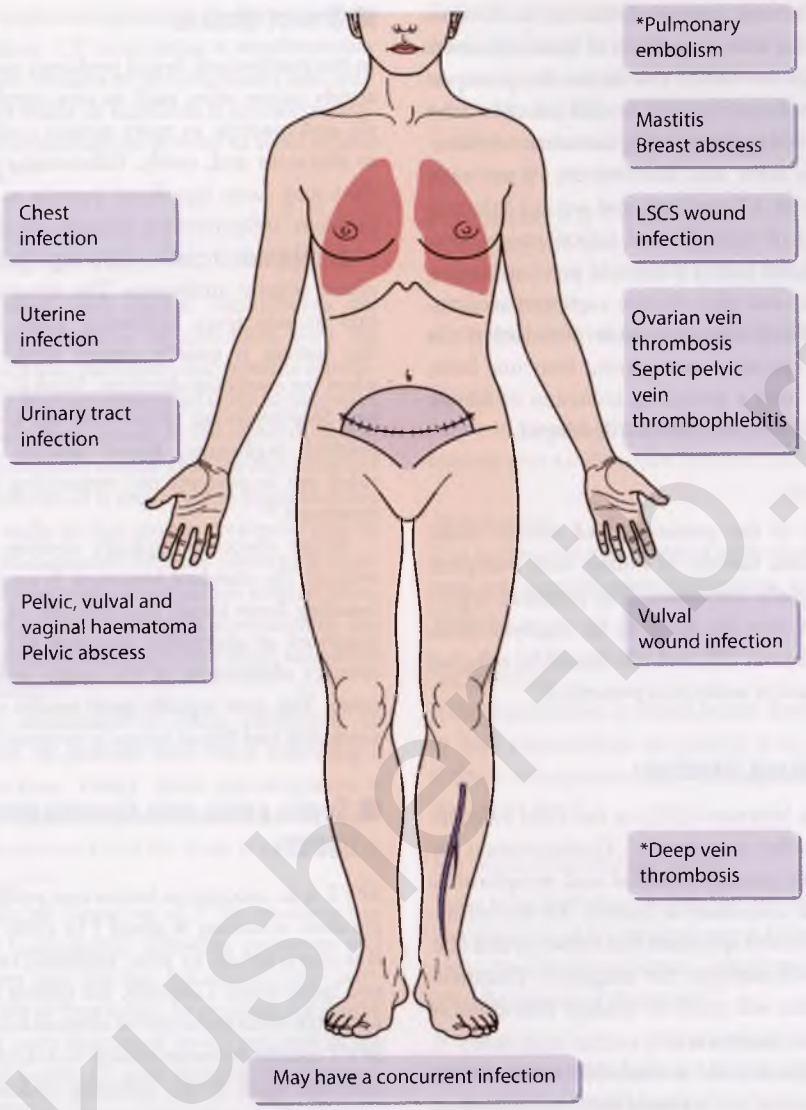

Figure 1 Causes of puerperal pyrexia (* denotes non-infective causes). LSCS, lower segment caesarean section.

(LSCS) as well as a history of prolonged rupture of membranes and repeated vaginal examinations for cervical assessment. It is commonly caused by *E. coli* or group A or B streptococcus.[2–4]

Cardinal symptoms of a uterine infection are the presence of a foul-smelling discharge and a fever of 38°C or more, together with a tender uterus on examination. It is usually due to a combination of organisms and consequently responds to broad-spectrum antibiotics. Early involvement of microbiologists can be invaluable in seriously ill patients and in those who fail to respond to conventional antibiotics. Endometritis in the presence of retained products of conception on ultrasonography warrants timely uterine evacuation. Intravenous antibiotics are continued until the patient has been afebrile for at least 24 hours.[1,5] Most units give prophylactic antibiotic therapy at caesarean section, which reduces the infection risk by approximately 60 per cent. Prophylactic antibiotics are also given to women with prolonged rupture of membranes.

Infection of abdominal wounds and vulval wounds (LSCS and episiotomy)

Lower segment caesarean section (LSCS) wound

Inspection of the abdominal wound for swelling, discharge, and cellulitis is important in the postpartum period. In cases of discharge from the wound,

swabs for bacterial culture should be undertaken followed by the commencement of broad-spectrum antibiotics. In one study,[6] risk factors for postoperative fever, endometritis, and wound infection were analyzed in 761 consecutive caesarean sections. Postoperative fever was observed in 12 per cent, endometritis in 4.7 per cent and wound infection in 3 per cent of cases. Wound infections were less frequent in cases with a history of previous caesarean section(s) and after elective caesarean sections. However, wound infections were increased if the duration of operation was greater than one hour, if there had been a preceding induction of labour, or if puerperal endometritis had developed.

Perineal wound

Examination of the perineum and wound swabs before antibiotic therapy in women with puerperal pyrexia is equally important. The common organisms in both sites are likely to be staphylococcal, streptococcal, or E. coli, and this should be reflected in the spectrum of antibiotics prescribed.

Urinary tract infection

Urinary tract infection (UTI) is the most frequent infection in the puerperium. Contamination by catheterisation, urinary retention and, symptomatic bacteriuria all contribute to cystitis. An uncontaminated, catheterised specimen that shows pyuria and bacteriuria will establish the diagnosis. Treatment with antibiotics will result in prompt resolution of the infection in most cases.[1,7]

Stray-Pedersen et al.[7] studied 6803 women in the postpartum period and screened them for bacteriuria by culture of voided midstream urine (MSU). A significant growth was found in 8.1 per cent. The urine was recollected in this latter group by suprapubic aspiration, and bacteriuria was confirmed in 52 per cent, corresponding to an incidence of bladder bacteriuria of 3.7 per cent. A history of previous urinary tract infection, bacteriuria in pregnancy, operative delivery, epidural anaesthesia, and bladder catheterisation increased the risk of postpartum urinary tract infection. Only 21 per cent of the women complained of dysuria; this symptom occurred significantly more often after operative delivery and in patients with previous urinary tract infection. This lack of urinary symptoms suggests that all women with postpartum pyrexia should have an MSU sent for culture and sensitivity.

Breast disease

In the puerperium, breast problems range from relatively minor ones, such as sore nipples, milk stasis, and mastitis, to more serious conditions, such as abscesses and, rarely, inflammatory neoplasms. They may cause significant pyrexia as a presenting problem. Inflammatory changes are easily treated with frequent breast emptying; infectious processes require antibiotics. The symptoms of mastitis include fever, erythema, pain, and malaise. The patient is usually several weeks postpartum when the condition develops. *Staphylococcus aureus* and *Staphylococcus epidermidis* are the commonly isolated organisms. Breast abscess need to be ruled out in patients not responding to antibiotic treatment.[1,8]

Breast abscesses typically develop in lactating women. The standard treatment is surgical incision, breaking down loculi, and drainage of pus. Benson[9] suggested an alternative approach of curettage and primary obliteration of the cavity under antibiotic cover. This gave equally good results with reduced morbidity (see Breast lumps in pregnancy).

Septic pelvic vein thrombophlebitis (SPVT)

SPVT is an uncommon but serious postpartum complication occurring in about 1 in 2,000 pregnancies. It is characterised by pain, antibiotic resistant fever, and tachycardia. Clinically, the patient appears well with little tenderness and no obvious localising signs. SPVT usually becomes evident 4–8 days postpartum after the signs of the initiating endometritis have resolved. The use of contrast-enhanced computerised tomography (CT) increases the diagnostic certainty. Treatment is by heparin and broad-spectrum antibiotics. If there is no resolution of the fever after 1 week of therapeutic heparin, further investigations to exclude a pelvic abscess or haematoma are required so that surgical drainage may be carried out.[10,11]

Ovarian vein thrombosis

Ovarian vein thrombosis is a rare but potentially serious complication following childbirth. The incidence is about 1 in 6000 deliveries. The majority of patients present during the first week postpartum with fever and right lower quadrant abdominal pain. This condition can mimic an appendicular abscess with leucocytosis on haematological investigation.

Colour Doppler sonography is the favoured diagnostic procedure, CT scan being a supplementary tool. Treatment consists of anticoagulants and antibiotics. A high index of suspicion is crucial to diagnose and treat this condition in order to avoid serious consequences.[12,13]

Vulval, vaginal, and pelvic haematoma

Puerperal, vulval, and vaginal haematomas are uncommon complications of childbirth with the potential for serious morbidity and possible mortality. Prevention through using good surgical technique with attention to haemostasis in the repair of lacerations and episiotomies should limit the occurrence of these complications. It is important to diagnose these haematomas early so that prompt treatment may be carried out. Management includes correcting hypovolaemia and intervention with active surgical management if the haematoma is large or expanding. The use of surgical drains may be a beneficial adjunct to the management.[14,15]

A pelvic ultrasound is often performed in the evaluation of patients with fever following a caesarean section. Under these circumstances a bladder-flap, or a subfascial haematoma is occasionally demonstrated and the fever is attributed to these findings.[16–19]

In a study by Gemer et al.,[20] the incidence of bladder-flap haematomas following caesarean section was 9 per cent but was not significantly associated with febrile morbidity. In contrast, subfascial haematomas were diagnosed in 4.5 per cent of the patients, and nearly all were associated with postoperative fever.

A subfascial haematoma also has the potential for significant spread, and its volume is difficult to estimate. Thus proper recognition of subfascial haematomas and its distinction from superficial haematoma and bladder flap haematoma is important.[21]

Stages of sepsis and the sepsis resuscitation bundle

The stages of sepsis

A consensus panel of the American College of Chest Physicians and the Society of Critical Care Medicine defined each stage of what is thought to be the process by which an inflammatory response can result in multi-organ failure and death.[22]

Systemic inflammatory response syndrome (SIRS)

When the body is challenged with a severe bloodborne infection, it mounts an inflammatory response, referred to as SIRS.

SIRS may be recognised when two or more of the following are present:

- temperature >38°C or <36°C;
- heart rate >90 bpm;
- respiratory rate >20 bpm or arterial carbon dioxide tension <32mm Hg;
- abnormal white cell count >12,000 or <4000/μL.

Sepsis

Sepsis is present when there are two or more SIRS features plus a culture-documented infection.

Severe sepsis

This occurs when in a patient with sepsis and symptoms and signs of organ dysfunction, as described in Table 1.

Septic shock

If the hypotension or raised lactate does not respond to fluid resuscitation, the patient is in septic shock. If this is not corrected, multiple organ failure occurs, leading to death.

The sepsis resuscitation bundle

Tasks to be performed within the first six hours of the identification of severe sepsis are as follows (modified from the Surviving Sepsis Campaign Resuscitation 'Bundle' (group of therapies):[23]

1. Obtain blood cultures prior to antibiotic administration.
2. Administer broad-spectrum antibiotic within one hour of recognition of severe sepsis.
3. Measure serum lactate.

Table 1 Features of organ dysfunction associated with sepsis

Feature	Criteria
Hypotension	Systolic <90 mmHg MAP <65 mmHg >40 mm decrease from normal BP
Lactate levels	>4 mmol/L
Altered mental status	Drowsiness, confusion
Hypoxaemia	Oxygen saturation <93%
Oliguria/renal dysfunction	<0.5 mL/kg/h or raised creatinine/urea
Coagulopathy	INR >1.5

BP, blood pressure; INR, internation normalised ratio; MAP, mean arterial pressure.

4 In the event of hypotension and/or a serum lactate >4 mmol/L deliver an initial minimum 20 ml/kg of crystalloid or an equivalent.
5 Apply vasopressors for hypotension that is not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) >65 mmHg.
6 In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4mmol/l, a central venous line should be inserted in order to:
   a Achieve a central venous pressure (CVP) of ≥8 mmHg
   b Achieve a central venous oxygen saturation ($ScvO_2$) ≥70% or mixed venous oxygen saturation ($ScvO_2$) ≥65%.

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FITS IN PREGNANCY

Peter Muller, revised by Win Win Khine

Definition

There are three terms that seem to be interchangeable: fits, convulsions, and seizures. In a convulsion, the body muscles contract and relax rapidly and repeatedly, resulting in uncontrollable shaking. In a seizure there is abnormal excessive or synchronous neuronal activity in the brain; the outward effect can vary from uncontrollable jerking movements (tonic–clonic) to just a momentary loss of awareness. For the purpose of this section, a fit with tonic–clonic activity with or without loss of consciousness is the major concern as it may affect both mother and fetus adversely.

Causes

The causes of fits in pregnancy can be divided into obstetric and non-obstetric:

- Obstetric
  - eclampsia;
  - postdural puncture.
- Non-obstetric
  - stroke (haemorrhage, arterial and venous thrombosis);
  - hypertensive disease (hypertensive encephalopathy, pheochromocytoma);
  - space-occupying lesions of the central nervous system (brain tumour, abscess);
  - reversible posterior leukoencephalopathy syndrome (RPLS);
  - metabolic disorders (hypoglycaemia, uraemia, inappropriate antidiuretic hormone secretion resulting in water intoxication);
  - infection (meningitis, encephalitis);
  - idiopathic epilepsy;
  - pseudoepilepsy;
  - thrombotic thrombocytopenic purpura, thrombophilia;
  - use of illicit drugs (e.g., methamphetamine, cocaine);
  - drug or alcohol withdrawal.

Eclampsia

Eclampsia is a convulsive condition associated with pre-eclampsia. It is a clinical diagnosis based on evidence of one or more generalised convulsions and/or coma in a pre-eclamptic woman and in the absence of other neurological conditions. Eclamptic seizures are almost always self-limiting, with a usual duration of 60 to 75 seconds (seldom longer than three to four minutes). It can occur anytime from the 2nd trimester to the puerperium (see Collapse in pregnancy).[1,2,3]

Despite advances in detection and management, pre-eclampsia/eclampsia remains a common cause of maternal death.[4,5]

Incidence

The incidence of eclampsia has been relatively stable at 1.6 to 10 cases per 10,000 deliveries in developed countries. In developing countries, however, the incidence varies widely from 6 to 157 per 10,000 deliveries. An eclamptic seizure occurs in 2–3 per cent of severely pre-eclamptic women not receiving anti-seizure prophylaxis. The seizure rate is estimated to be 0–0.6 per cent in women with pre-eclampsia without severe features.[4–7]

Aetiology

The exact cause of seizures in women with eclampsia is not known, though it is thought to be cerebral oedema. The following two hypotheses have been proposed:

- Cerebral overregulation in response to high systemic blood pressure results in vasospasm of cerebral arteries, under perfusion of the brain, localised ischaemia/infarction, and cytotoxic (intracellular) oedema.
- Loss of auto-regulation of cerebral blood flow in response to high systemic pressure (i.e., hypertensive encephalopathy) results in brain hyperperfusion particularly in arterial border zones, and may lead to breakdown of the blood–brain barrier (endothelial damage) allowing extravasation of fluid and blood products into the brain parenchyma (extracellular oedema).

Features of severe pre-eclampsia which may occur before the seizure[1,4,5,8,9]

- Severe headache, persistent frontal or occipital headache, headache that persists and progresses despite analgesic therapy.
- Visual disturbances (e.g. photophobia, diplopia, blurred vision, homonymous hemianopia, loss of vision, scotomata).
- Right upper quadrant or epigastric pain.
- Altered mental status.
- Shortness of breath.
- Systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥110 mmHg on two occasions at least four hours apart while the patient is on bed rest.
- Thrombocytopenia <100,000 platelets/microL.

- Progressive renal insufficiency (serum creatinine >1.1 mg/dL or doubling of serum creatinine concentration in the absence of other renal disease).
- Pulmonary oedema.

Risk factors for pre-eclampsia and eclampsia[4,5,8–10]

- Nulliparity.
- Age >40 years or <18 years.
- Pre-eclampsia in a previous pregnancy.
- Family history of pre-eclampsia.
- Chronic hypertension.
- Chronic renal disease.
- Antiphospholipid antibody syndrome or inherited thrombophilia.
- Vascular or connective tissue disease.
- Diabetes mellitus (pre-gestational and gestational).
- Multiple pregnancy.
- High body mass index.
- Black race.
- Hydrops fetalis.
- Unexplained fetal growth restriction.
- Prolonged inter pregnancy interval.
- Partner-related factors (new partner, limited sperm exposure, e.g., previous use of barrier contraception).
- Hydatidiform mole.

Non-white, nulliparous women from lower socioeconomic backgrounds are the group at highest risk of developing eclampsia. The peak incidence is in the teenage and low-twenties years, but there is also an increased incidence in women over 35 years of age.[5,10]

The association between severity of blood pressure and onset of seizure is unclear.

In general, women with typical eclamptic seizures who do not have focal neurological deficits or coma do not require an electroencephalogram or cerebral imaging studies.

Timing of eclampsia[4,5,8,10]

The frequency of eclampsia in antepartum is 38–55 per cent, in intrapartum 13 to 36 percent, in postpartum <48 hours 5–39 per cent, and in postpartum >48 hours 5–17 per cent.

Eclampsia prior to 20 weeks of gestation is rare and should raise the possibility of an underlying molar pregnancy or antiphospholipid syndrome.

Effect on mother

Maternal complications occur in up to 70 per cent of women with eclampsia and include abruptio placentae, disseminated intravascular coagulopathy, acute renal failure, hepatocellular injury, liver rupture, intracerebral haemorrhage, transient blindness, cardiorespiratory arrest, aspiration pneumonitis, acute pulmonary oedema, and postpartum haemorrhage.[9–11]

Hepatocellular damage, renal dysfunction, coagulopathy, hypertension, and neurological abnormalities typically resolve following delivery. However, brain damage from haemorrhage or ischemia may result in permanent neurological problems and is the most common cause of death in eclamptic women.

HELLP syndrome (haemolysis, elevated liver enzymes, low platelets) develops in approximately 10–20 per cent of women with pre-eclampsia/eclampsia.

Maternal mortality rates of 0–14 per cent have been reported over the past few decades. Maternal mortality and severe morbidity rates are lowest among women receiving regular prenatal care managed by experienced physicians in tertiary centres (maternal mortality 0–1.8 per cent). The highest rates are in developing countries where prenatal, intrapartum, and neonatal care are compromised by limited resources.[4,5]

Effect on fetus[4,5,11,12]

Short fetal bradycardia for a few minutes is a common finding during and immediately after an eclamptic seizure, and emergency caesarean delivery is not always necessary. Stabilising the mother by administering anti-convulsant drugs, oxygen, and antihypertensive drugs can help the fetus recover in utero.

Resolution of maternal seizure activity is associated with a compensatory fetal tachycardia and loss of variability, sometimes associated with transient fetal heart rate decelerations. If the fetal heart rate tracing remains non-reassuring for more than 10 or 15 minutes with no improvement despite maternal and fetal resuscitations, then the possibility of an occult abruption should be considered and emergency delivery may be indicated.

Premature delivery, abruptio placenta, and intrauterine asphyxia are the primary causes of perinatal death in eclamptic pregnancies. Perinatal mortality ranges from 2 to 23 per cent and is closely related to gestational age.

Perinatal morbidity is also closely related to gestational age. In addition, there is a two- to three-fold increased risk of delivery of a small-for-gestational-age infant.

Management[1,9,10]

This involves stabilising the mother followed by delivery of the fetus. This could be induction of labour or caesarean section depending on the clinical findings.

The drug of choice is magnesium sulphate, and clear guidelines have been set out by NICE for the management of this condition, with an expectation that every maternity unit would have a protocol in place to deal with this problem.

The risk of recurrence in a subsequent pregnancy is in the order of 2 per cent.

One problem is that eclampsia cannot always be predicted, and the level of blood pressure elevation does not correlate well with its incidence, though it does with the risk of stroke.

Differential diagnosis for non-eclampsia seizures

Eclamptic seizures are clinically and electroencephalographically indistinguishable from other generalised tonic–clonic seizures.

The following conditions are particularly important in pregnant women who have a seizure in the first half of pregnancy when eclampsia is rare and in those with focal neurological deficits, prolonged coma, or atypical eclampsia.

Stroke (haemorrhage, arterial and venous thrombosis)

Cerebrovascular disease during pregnancy can be categorised into:

- thrombosis/ischaemia (including arterial and venous infarction);
- haemorrhage (including intracerebral and subarachnoid haemorrhage).

Normal physiologic changes associated with pregnancy, combined with pathophysiological processes unique to pregnancy, predispose women to develop a stroke during pregnancy and the puerperium.

Pregnancy is a hypercoagulable state that is due, in part, to the progressive increase in resistance to activated protein C in the second and third trimesters, as well as decreased protein S activity, increased fibrinogen, increased factors II, VII, VIII, X, XII and von Willebrand factor, and increased activity of fibrinolytic inhibitors.

Pregnancy and the postpartum period are associated with a marked increase in the relative risk and a small increase in the absolute risk of ischemic stroke and intracerebral haemorrhage, with the highest risk during the puerperium.

The major causes of stroke are:

- hemorrhagic stroke from aneurysms, arteriovenous malformations, and pre-eclampsia/eclampsia;
- ischemic stroke from cerebral venous sinus thrombosis, pre-eclampsia/eclampsia, and thromboembolism related to valvular heart disease.

The risk of thrombosis is increased in women with antiphospholipid syndrome or an inherited thrombophilia, such as factor V Leiden, the prothrombin gene mutation, or a deficiency of antithrombin III, protein C, or protein S.

There are also several rare causes of stroke that are seen exclusively in pregnancy and the puerperium, such as trophoblastic and amniotic fluid embolism.[13]

Diagnosis

An imaging study of the brain is an essential component of the evaluation, regardless of cause. Non-contrast head computed tomography (CT) is typically the first diagnostic study in patients with suspected stroke. The main advantages of CT are widespread access and speed of acquisition. However, magnetic resonance (MRI) is safer during pregnancy. In addition, MRI may be more sensitive than CT for the detection of small infarcts, and MRI with diffusion-weighted sequences is superior to CT for the diagnosis of early infarction.[14]

Hypertensive disease (hypertensive encephalopathy, phaeochromocytoma)

Hypertensive vasculopathy is the most common aetiology of spontaneous intracerebral haemorrhage.[15]

Space-occupying lesions of the central nervous system (brain tumour, abscess)

Features suggestive of a brain tumour in a patient complaining of headaches include nausea and vomiting (present in about 40 per cent of cases), a change in prior headache pattern, and an abnormal neurological examination. In addition, many patients with a brain tumour report worsening of headache after a change in body position, such as bending over, or with manoeuvres that raise intrathoracic pressure, such as coughing, sneezing, and the Valsalva manoeuvre. These activities lead to a period of raised intracranial pressure (ICP), which uncommonly can cause a loss of consciousness.

Seizures are among the most common symptoms of gliomas and cerebral metastases. The incidence of seizures is higher with primary tumours than with metastatic lesions. Seizures can be either generalised or focal. In patients who have focal seizures, the clinical presentation is dependent upon the tumour location. It must be emphasised that brain tumours in pregnancy are extremely uncommon.[16]

Reversible posterior leukoencephalopathy syndrome (RPLS)

The symptoms of this condition consist of headaches, seizures, confusion, and visual disturbances with characteristic neuroimaging findings. Typical findings are symmetrical white matter oedema in the posterior cerebral hemispheres, particularly the parieto-occipital regions, but variations do occur. It is a common clinical syndrome resulting from a number of different causes that are grouped together because of similar findings on neuroimaging. Hypertension is usually, but not invariably, present. Some experts suggest that RPLS is an indicator of eclampsia, even when features of pre-eclampsia (hypertension, proteinuria) are not present. In a series of 47 patients diagnosed with eclampsia, 46 had RPLS on neuroimaging; the only patient without RPLS was subsequently found to have an underlying seizure disorder.[14,17]

The pathogenesis of RPLS is unclear, but it appears to be related to disordered cerebral autoregulation and endothelial dysfunction.

Metabolic disorders (hypoglycaemia, uraemia, inappropriate anti-diuretic hormone secretion resulting in water intoxication)[18]

Hyponatraemia

Acute hyponatraemia causes cerebral oedema. Symptoms include:

- nausea and malaise, which are the earliest findings;
- headache, lethargy, seizures, coma, and respiratory arrest can occur if the serum sodium concentration falls below 115 to 120 mEq/L;
- acute hyponatraemic encephalopathy may be reversible, but permanent neurological damage or death can occur.

Hypernatraemia

Hypernatraemia is a mirror image of hyponatraemia. A rise in the serum sodium concentration and osmolality causes water movement out of the brain. The rapid decrease in brain volume can cause rupture of the cerebral veins, leading to focal intracerebral and subarachnoid haemorrhages and possibly irreversible neurological damage. The clinical manifestations of acute hypernatraemia begin with lethargy, weakness, and irritability, progress to twitching, seizures, and eventually coma.

Hypoglycaemia

The symptoms of hypoglycaemia in patients with and without diabetes are non-specific but may include tremor, palpitations, and anxiety/arousal, sweating, hunger paresthesia, cognitive impairment, behavioural changes, psychomotor abnormalities, and seizure, and can lead to coma.

CNS infections (encephalitis, meningitis)

Viral infections of the central nervous system (CNS) can result in the clinical syndromes of encephalitis and aseptic meningitis. A wide variety of other viruses can infect the CNS, including mumps, measles, varicella-zoster virus (VZV), rubella, influenza, and herpes simplex virus type 1.

Viral encephalitis can be either primary or post-infectious encephalitis. Primary infection is characterised by viral invasion of the CNS. Neuronal involvement can be identified on histology, which may also show inclusion bodies on light microscopy or viral particles on electron microscopy. The virus can often be cultured from brain tissue. In contrast, in post-infectious encephalitis, a virus cannot be detected or recovered and the neurones are spared. Post-infectious encephalitis is an immune-mediated disease. Seizures are common with encephalitis, and focal neurological abnormalities can occur, including hemiparesis, cranial nerve palsies, and abnormal tendon reflexes. Patients may appear confused, agitated, or obtunded.[19,20]

The clinical presentation of viral meningitis is generally non-specific, with fever, headache, nausea and vomiting, occasionally accompanied by photophobia and a stiff neck. Patients with bacterial meningitis are usually quite ill. The classic triad of acute bacterial meningitis consists of fever, neck stiffness, and a change in mental status, which may include lethargy and confusion. Headache is common and typically described as both severe and generalised.

Thrombotic thrombocytopenic purpura or thrombophilia and haemolytic uraemic syndrome

Thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) are acute syndromes with abnormalities in multiple organ systems that demonstrate microangiopathic haemolytic anaemia and thrombocytopenia.

Neurological manifestations can include coma, confusion, seizure, transient ischemic attack, stroke, reversible posterior leukoencephalopathy syndrome, and headache.

When developing during or after pregnancy, the distinction between TTP-HUS and severe pre-eclampsia or HELLP is important for therapeutic

and prognostic reasons. However, the clinical and histologic features are so similar that establishing the correct diagnosis can often be difficult; furthermore, these disorders may occur concurrently.[19,20]

Idiopathic epilepsy

Usually the patient has a history of epilepsy' however, it may rarely present for the first time during the pregnancy. The frequency of seizures does not increase during pregnancy in the majority of women with epilepsy.[21]

Pseudo-epilepsy

This is not very often seen in pregnancy. The features that distinguish it from epilepsy include:[22]

- prolonged/repeated seizures without cyanosis;
- resistance to passive eye opening;
- downgoing planter reflexes;
- persistence of a positive conjunctival reflexes.

Postdural puncture

This is an uncommon cause of fits and usually presents with headache (see Headache in pregnancy). However, the warning signs include:

- typical postdural headache (relieved by lying down);
- associated neck stiffness, tinnitus and visual symptoms;
- onset usually within 4–7 days after dural puncture.[22]

Use of illicit drugs (e.g., methamphetamine, cocaine) and drug and alcohol withdrawal

History of recreational drug and alcohol abuse can be assessed by a toxicology screen on the urine.[22]

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Useful websites

https://www.nice.org.uk/guidance
http://www.uptodate.com
www.rcog.org.uk/greentop guidelines

GALACTORRHOEA

Ismail Wong

Galactorrhoea is defined as milky discharge from the breast not related to pregnancy and usually 1 year after pregnancy and cessation of breastfeeding. Galactorrhoea is typically bilateral and multiductal, though can be unilateral and spontaneous in nature.[1,2] It can also be yellow, green, or brown. It is important to distinguish galactorrhoea from bloody or serosanguinous nipple discharge, which may point toward more a sinister underlying cause such as breast cancer. Galactorrhoea is commonly caused by hyperprolactinaemia when accompanied by amenorrhoea. Hyperprolactinaemia is a condition caused by elevated serum prolactin levels which could be physiological, pathological, or idiopathic in origin. The incidence of galactorrhoea is variable, and it can occur up to 90 percent of women with hyperprolactinaemia.[3] In women who have regular ovulatory cycles with galactorrhoea, the prolactin level is usually normal but it can also have been raised by macroprolactinaemia, which is the inactive form of prolactin.

Physiological causes of galactorrhoea and hyperprolactinaemia can be caused by excessive nipple or breast stimulation during sex, suckling, or self-manipulation. Other transient causes of hyperprolactinaemia are vigorous exercise and physical or psychosocial stress. Hyperprolactinaemia is commonly caused by certain medications (see Box 2) or by a pituitary tumour such as prolactinoma. Prolactinomas account for 25–30 per cent of functioning pituitary tumours and are the most frequent cause of chronic hyperprolactinaemia. Prolactinomas are classified as microadenomas (<1 cm) and macroadenomas (>1 cm). Other causes include hypothalamic and pituitary stalk lesions, hypothyroidism, chronic renal failure, and neurogenic stimulation from the chest wall. (see Boxes 1 and 2).

A detailed history and clinical examination can provide important clues in the assessment of patients with galactorrhoea. A pregnancy history should be taken to exclude pregnancy-related galactorrhoea. A detailed drug history should also be taken to exclude medication-induced galactorrhoea. The patients should be evaluated for symptoms related to hyperprolactinaemia such as amenorrhoea, oligomenorrhoea, decreased libido, infertility, and symptoms related to hypothalamic-pituitary disease such as headaches, visual disturbances, poor appetite, polydipsia, and polyuria. Cold intolerance, tiredness, and constipation may suggest hypothyroidism-related hyperprolactinaemia. Breast examination will confirm the diagnosis of galactorrhoea. It is important to exclude any nodules and other discharges.

Box 1 Causes of galactorrhoea

Physiological causes
- Pregnancy
- Nipple or breast stimulation
- Chronic emotional stress

Pathological causes
- Pituitary lesions
  - prolactinoma
  - acromegaly
- Hypothalamic lesions
  - craniopharyngioma
  - meningioma
  - germinoma
  - sarcoidosis
  - histiocytosis
- Lesions involving chest wall
  - breast/chest surgery
  - burns
  - herpes zoster
  - trauma
  - spinal cord injury
- Systemic illness
  - hypothyroidism
  - chronic renal failure

Idiopathic
- Normoprolactinaemia galactorrhoea.

Box 2 Some drugs inducing galactorrhoea

- Dopamine depleting agent
  - methyldopa
  - reserpine
- Dopamine receptor blockers
  - risperidone
  - metoclopramide
  - phenothiazines
  - selective serotonin reuptake inhibitors
  - tricyclic antidepressants
  - butyrophenones
- Inhibition of dopamine release
  - codeine
  - morphine
  - heroin
- Histamine receptor blockade
  - cimetidine
- Lactotrophs stimulator
  - verapamil
  - high-dose oral contraceptive pills

Visual field testing should be performed in patients if there have been any visual problems or where a pituitary lesion is suspected.

After breast and nipple pathology has been excluded in patients with galactorrhoea, the serum prolactin level should be measured. With an elevated prolactin level, measurement should be repeated to confirm the raised level. Hyperprolactinaemia is usually defined as fasting serum prolactin levels of above 530 mIU/L (25 ng/mL) in women at least 2 hours after waking up. Serum prolactin levels are higher in the afternoon than in the morning and hence should preferably be measured in the morning, although diurnal and physiological variations occur. Once pregnancy has been excluded, thyroid and renal functions should be measured. If no identified cause of hyperprolactinaemia is found by history, examination, or thyroid and renal function tests, a magnetic resonance imaging test should be performed. High prolactin levels are commonly associated with a prolactin-secreting prolactinoma. Computed tomography (CT) can be performed if magnetic resonance imaging (MRI) is not available, but the resolution is inferior. In cases where no causes of hyperprolactinaemia have been identified and no adenoma can be visualised with MRI, then it is referred to as idiopathic hyperprolactinaemia.

Treatment of galactorrhoea should be directed at the underlying cause. The decision to treat galactorrhoea should be based on the severity of the galactorrhoea, the level of serum prolactin, the patient's desire for fertility, and other symptoms related to hypothalamic and pituitary tumour or stalk effect. Medication-induced galactorrhoea should be replaced with alternative drugs. Hypothyroidism should be treated with thyroxine replacement. Dopamine agonists are the mainstay treatment for most patients with galactorrhoea and hyperprolactinaemia. Dopamine agonists have been shown to be effective in normalising the prolactin level, shrinking the pituitary adenoma, and restoring reproductive hormones and ovulation. Bromocriptine and cabergoline are the commonest dopamine agonists used for treatment. Cabergoline is better tolerated owing to fewer side effects and is more effective than bromocriptine. Cabergoline is given at a dose of 0.25 mg to 2 mg weekly, and bromocriptine at a dose of 2.5 to 15 mg daily. Patients with isolated galactorrhoea and normal prolactin levels do not require treatment if they are not bothered by the galactorrhoea and are not pursuing fertility. Those patients who have symptomatic idiopathic galactorrhoea usually respond to a short course of a low-dose dopamine agonist. In idiopathic hyperprolactinaemia, where no apparent causes are identified, there is accumulating evidence that this involves macroprolactinaemia, which is characterised by large protein complexes (more than 150 kDa) as the dominant forms of the prolactin.[4] Clinically, the women with macroprolactinaemia do not always display hyperprolactinaemia-related symptoms such as galactorrhoea or menstrual disturbances.[5] Identification of macroprolactinaemia is clinically important to avoid unnecessary repeated radiological investigation and treatment. Investigation for macroprolactinaemia should always be done in cases with asymptomatic hyperprolactinaemia women.[6]

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GENITALIA, AMBIGUOUS (INCLUDING CONGENITAL ANOMALIES)

John Ho

It is estimated that genital anomalies occur in 1 in 4500 live births. The birth of a child with ambiguous genitalia is a social emergency. The first encounter of the parents with the health professional in the delivery room may have a lasting impact on parents and their relationship with their infant. The neonate should be referred as 'your baby' or 'your child', and not 'he', 'she', or 'it'. It is best not to attempt a diagnosis or offer gender assignment at the first encounter. It is important to emphasise that the infant with genital anomaly has the potential to become a functional member of society. Genital anomaly is not shameful. It should be explained to the parents that, although the best course of action may not initially be clear, the health care professionals will work with the family to reach a decision that is best suited in the particular circumstances.

There has been significant progress in diagnosis, understanding the pathology, improvement in surgical techniques, understanding the psychosocial issues, and accepting the place of patient advocacy. Terms such as intersex, pseudohermaphroditism, hermaphroditism, and sex reversal are all controversial, and are perceived by parents as potentially stigmatising and confusing. The European Society for Paediatric Endocrinology (ESPE) and its American counterpart, the Lawson Wilkins Pediatric Endocrine Society (LWPES), have jointly published a consensus statement on the management and nomenclature of intersex disorders. The new nomenclature for this condition is disorders of sex development (DSD). DSD is defined by congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical. The proposed changes in nomenclature are outlined in Table 1.

Table 1 Proposed revised nomenclature for intersex conditions

Previous	Proposed
Intersex	Disorders of sex development (DSD)
Male pseudohermaphrodite: undervirilisation or undermasculinisation of an XY male	46, XY DSD
Female pseudohermaphrodite: overvirilisation or masculinisation of an XX female	46, XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46, XX testicular DSD
XY sex reversal	46, XY complete gonadal dysgenesis

It is helpful to examine the child in the presence of the parents to demonstrate the precise abnormalities of genitalia. One should emphasise that the genitalia of both sexes develop from the same fetal structures and either overdevelopment and underdevelopment is possible, and that the abnormal appearance can be rectified and the child will be raised either as a boy or a girl. It is also important not to encourage the parents to name the child or register the birth until the sex of rearing is established.

Normal genital development

Undifferentiated gonadal tissue with potential to develop into either a male or female genital structure is present in the fetus as early as 6 weeks' gestation. The presence or absence of genetic and hormonal influences, which are responsible for the active process of male differentiation, dictate the genital appearance of the neonate. An abnormality along the male pathway that interferes with masculinisation or, in the case of a genetic female, the presence of virilising influences on the female embryo results in an intersex condition.

The sex-determining region in the Y chromosome (*SRY*) gene situated on the short arm of the Y chromosome is responsible for male sex differentiation. The undifferentiated gonad forms a testis under the influence of *SRY*. Testosterone from the testes stimulates maturation of Wolffian structures (vas deferens, epididymis, and seminal vesicles), and anti-Müllerian hormone suppresses the Müllerian structures (fallopian tubes, uterus, and upper vagina). Peripheral conversion of testosterone to dihydrotestosterone in the skin of external genitalia is responsible for the

masculinisation of genital structures. The major part of male differentiation is complete by 12 weeks' gestation. Penile growth and testicular descent progress throughout the pregnancy.

Female sexual differentiation occurs in the absence of *SRY*.

Clinical findings in a neonate with suspected DSD

Apparent male

- Severe hypospadias with separation of scrotal sacs.
- Hypospadias with undescended testis.
- Bilateral impalpable testes with or without micropenis in a term neonate (Fig. 1).

Apparent female

- Foreshortened vulva with single opening.
- Inguinal hernia containing a palpable gonad.
- Clitoral hypertrophy (Fig. 2).

Indeterminate

- Ambiguous genitalia.

Causes of genital abnormality in a neonate

Conceptually, it is simpler to think of the causes in terms of histology of the gonads, which dictates the prognosis with regard to fertility. This is outlined in Table 2.

Clinical evaluation

A detailed obstetric history is vital to determine the possibility of maternal endocrine disturbances or any exposure to drugs or hormonal agents. A positive family history of unexplained neonatal death, abnormal genital development, abnormal pubertal development, or infertility should be determined, as well as a history of consanguinity. This may point to an autosomal recessive disorder.

Physical examination includes examination of the phallus, the extent to which the urogenital sinus has closed, and the position of urethral meatus. Fullness and rugosity of labioscrotal folds should be noted, and an attempt should be made to palpate any gonads in these folds or the inguinal region. This may require considerable patience.

To make a definitive diagnosis based solely on physical findings would be unwise, as the appearance of external genitalia can be extremely variable even in the same clinical condition. The only conclusion that can be made from a palpable gonad is that the diagnosis is not a genetically female infant with congenital adrenal hyperplasia (CAH).

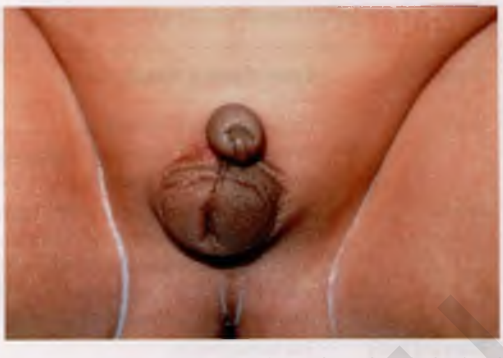

Figure 1 A male infant with micropenis and underdeveloped scrotum.

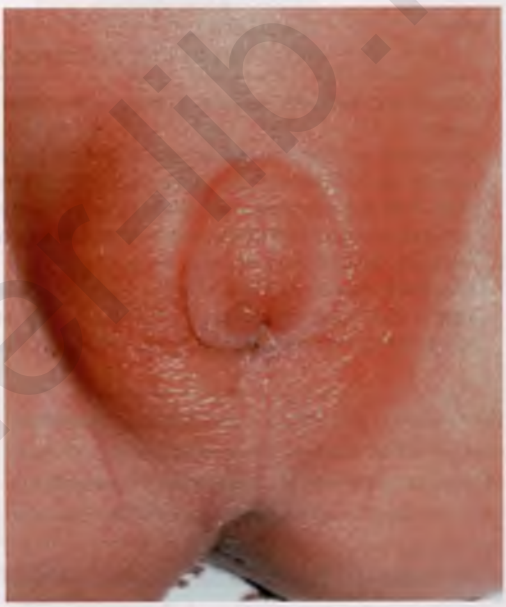

Figure 2 A female infant with clitoromegaly and fullness of the labia. Congenital adrenal hyperplasia is the underlying diagnosis.

Investigations

The commonest cause of genital anomaly in a neonate is CAH. Hence a biochemical screen for this disorder is indicated in all infants with signs of virilisation and non-palpable gonads. 21-Hydroxylase deficiency is the commonest enzyme deficiency (95 per cent) responsible for CAH. An elevated 17-hydroxyprogesterone is suggestive of CAH secondary to 21-hydroxylase deficiency; however, a more extensive biochemical panel is advised for the rarer form of CAH. The infant's electrolytes should be monitored closely, as hyponatraemia

Table 2 Causes of genital anomaly according to gonadal tissue

Gonadal	Cause of genital anomaly tissue
Ovary	Congenital adrenal hyperplasia Maternal source of virilisation (luteoma, exogenous androgens) Placental aromatase deficiency
Testis	Luteinising hormone receptor defect: Leydig cell hypoplasia/aplasia Androgen biosynthesis defect: 17-OH steroid dehydrogenase deficiency, 5α-reductase deficiency, StAR (steroidogenic acute regulatory protein) mutations Defect in androgen action: complete/partial androgen insensitivity syndrome Disorders of anti-Müllerian hormone (AMH) and AMH receptor: persistent Müllerian duct syndrome
Ovary and testis	True hermaphrodite
Dysgenetic gonads	Gonadal dysgenesis (Swyer syndrome)[a] Denys–Drash syndrome[b] Smith Lemli Opitz syndrome[c] Camptomelic dwarfism[d]
Other	Cloacal exstrophy MURCS (Müllerian, renal, cervicothoracic somite abnormalities)

[a] *Gonadal dysgenesis* (Swyer syndrome): a phenotypic female with 46, XY karyotype who does not have any functional gonads to induce puberty.

[b] *Denys–Drash syndrome*: a rare disorder consisting of the triad of (1) congenital nephropathy, (2) Wilms tumour, and (3) genital anomaly resulting from mutation in the Wilms tumour gene (WT1) situated on chromosome 11 (11p 13).

[c] *Smith–Lemli–Opitz syndrome*: a rare disorder caused by defect in cholesterol synthesis; it is autosomal recessive in inheritance. Affected individuals have multiple congenital anomalies: intrauterine growth restriction, dysmorphic facial features, microcephaly, low-set ears, cleft palate, genital anomaly, syndactyly, mental retardation.

[d] *Camptomelic dwarfism* (bent limbs): this has an autosomal dominant inheritance and is caused by mutations in SOX9 (a sex-determining region in the Y chromosome-related gene located at the long arm of chromosome 17). Features include short stature, hydrocephalus, anterior bowing of the femur and tibia, talipes, and poor masculinisation.

(low sodium) and hyperkalaemia (raised potassium) often manifest from 48 hours onwards and demand appropriate intervention (treatment of hypovolaemia and circulatory collapse, provision of sodium and hydrocortisone).

A karyotype (chromosome analysis) is also done as an initial investigation. A fluorescent in situ hybridisation for the Y chromosome can be obtained within 48 hours in most places; however, a detailed karyotype (with G banding) often takes up to 1 week.

An ultrasound scan by an experienced person can identify the presence of ovaries and a uterus relatively quickly, and can be suggestive of a female sex.

Further investigations are needed if the CAH screen is negative and the gonad(s) are palpable. A genitogram (preferably by a paediatric radiologist experienced in children's urological anomalies) is required to identify a vagina, a uterine canal, and fallopian tube(s) or the vasa deferentia. Appropriate biochemical tests will be required to identify any testosterone biosynthetic defect, 5α reductase activity, or androgen sensitivity. These investigations are best undertaken in a tertiary centre which has expertise in dealing with this condition.

A summary of these investigations is shown in Figures 3 and 4 outlines the adrenal steroid hormone synthesis.

Deciding the sex of rearing

This is based on a number of considerations:

- fertility potential;
- capacity for normal sexual function;
- endocrine status;
- potential for malignant change;
- availability of corrective surgical procedures and timing of surgery.

Management, prenatal diagnosis, and treatment

Disorders of sex development (DSD) rarely present prenatally. The investigations and management can be complex. Straightforward cases are usually managed by the paediatric endocrinologists. Complicated cases should be referred to a highly specialised tertiary centre where multidisciplinary input is required from the clinical geneticist, paediatric endocrinologist, paediatric urologist, psychologist, and sometimes a gynaecologist.

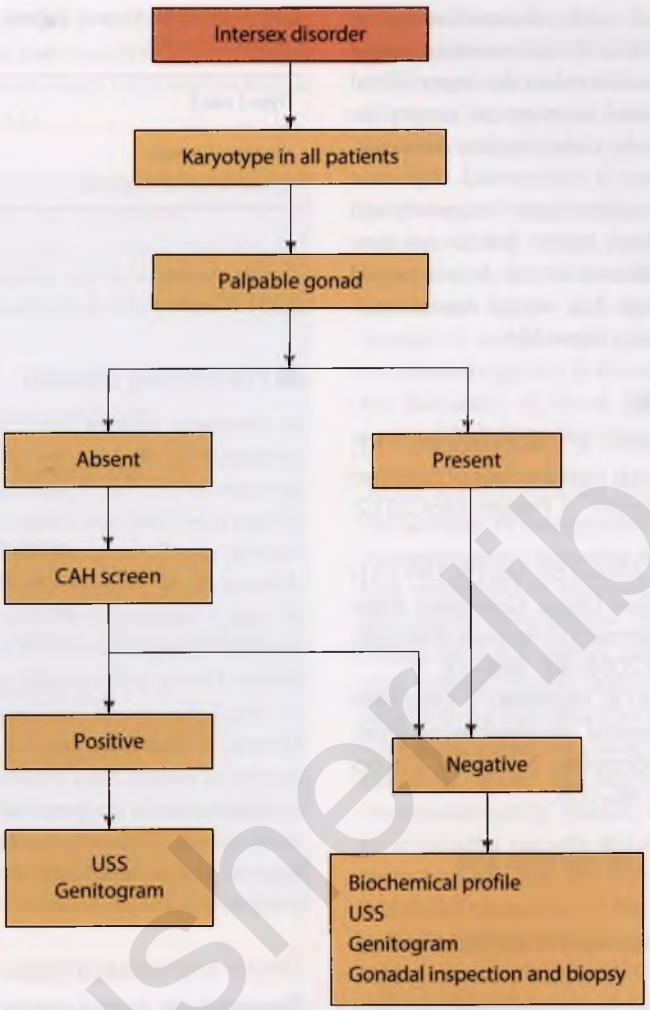

Figure 3 Laboratory and imaging studies in newborns with genital anomaly. CAH, congenital adrenal hyperplasia; USS, ultrasound scan.

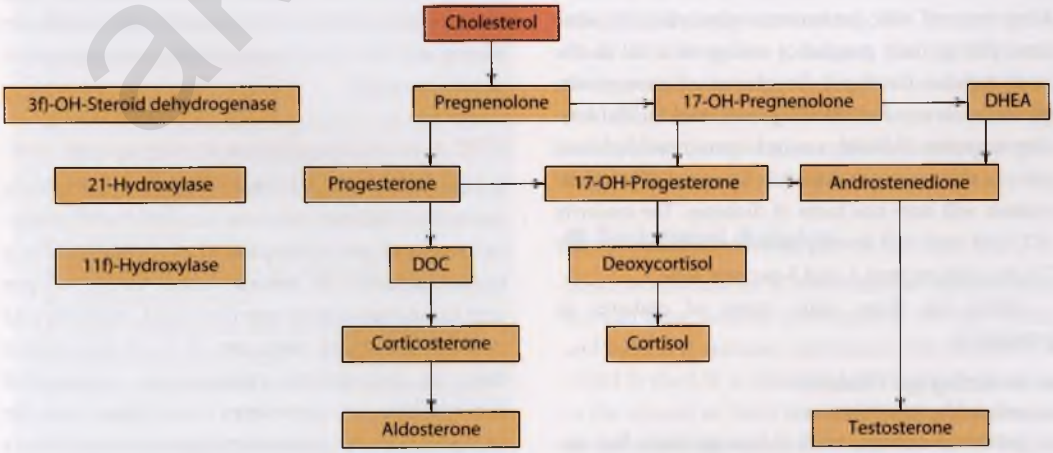

Figure 4 Adrenal steroid hormone synthesis pathway. DHEA, dehydroepiandrosterone sulphate; DOC, deoxycorticosterone.

Prenatal treatment with dexamethasone, as early as 6 or 7 weeks from the last menstrual period (LMP), have been shown to reduce the degree of fetal virilisation and the need for postnatal surgery for female babies affected by 21-hydroxylase deficiency. However, this treatment is controversial. High-dose steroid may have a negative impact on growth and neurodevelopment. Male fetuses that do not have virilisation and unaffected female fetuses would be exposed to the high-dose steroid unnecessarily before prenatal diagnosis is possible.

Further reading

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Useful website (for parents and professionals)

http://www.bsped.org.uk/patients/index.html

GLYCOSURIA OF PREGNANCY

Bashier Dawlatly and Rina Davison

Most women will demonstrate glycosuria at some time during their pregnancy owing to a fall in the renal tubular threshold for glucose. Consequently, glycosuria is not a reliable diagnostic tool for diabetes. Any suspicion of diabetes must be confirmed by blood glucose measurement. About 2–5 percent of pregnant women will have one form of diabetes. The majority (87.5 per cent) will develop gestational diabetes, while 7.5 per cent are type 1, and 5 per cent type 2.

There are three main types of diabetes in pregnancy:

- pre-existing type 1 diabetes;
- pre-existing type 2 diabetes;
- gestational diabetes, which is hyperglycaemia first recognised in pregnancy.

Table 1 Definitions of type of diabetes mellitus from oral glucose tolerance test results

Type 1 and 2	Gestational
Fasting ≥7 mmol/L	Fasting ≤5.6 mmol/L
2-hour value ≥11.1 mmol/L	2 hours ≥7.8 mmol/L

Interpretation of the oral glucose tolerance test (OGTT) leads to the definitions shown in Table 1.

Pre-existing diabetes

In European women, the incidence of diabetic pregnancy is relatively low (about 1 in 300 of all pregnancies) but this depends on the local prevalence of both type 1 and type 2 diabetes in women of childbearing age. There are marked ethnic and national differences, e.g. there is a tenfold greater incidence of type 1 diabetes in women aged 15–40 years in Northern European countries compared to Southern Greece. Owing to the younger age of onset observed in type 2 diabetes in Far Eastern, Middle Eastern, Hispanic American, African, South Asian, and Caribbean women, the prevalence of diabetes may be as high as one in ten pregnancies in some of these communities. Pregnancy in a diabetic mother carries a greater risk to both mother and the offspring than pregnancy in the general obstetric population.

Effect of pregnancy on diabetes

Physiologically, normal pregnancy is associated with an increase in maternal insulin production and insulin resistance. Therefore, maternal insulin dosage requirements increase as pregnancy progresses – up to 2–3 times the pre-pregnancy doses. Maternal renal disease and proliferative retinopathy may accelerate during and after pregnancy, thereby making regular review essential.

Effect of pre-existing diabetes on pregnancy outcome

Recent data confirm that women with poorly controlled diabetes have an increased rate of miscarriage and pre-eclampsia. These women have a higher incidence of preterm labour and a >60 per cent caesarean section rate. Perinatal, stillbirth and neonatal mortality rates are all 5–10-fold higher than in non-diabetic pregnancies. Congenital abnormalities are up to three times higher than the background rate, particularly neural tube defects and congenital heart disease. Over half of singleton

babies have a birth weight over the 90th centile for their gestational age and one-third of term babies are admitted to neonatal units for problems such as hypoglycaemia (Box 1).

Box 1 Obstetric and perinatal complications of pre-existing diabetes

Maternal

- Miscarriage
- Pre-eclampsia
- Increase in caesarean section rate
- Premature labour
- Long-term risk of type 2 diabetes

Fetal

- Congenital abnormalities:
  - HbA1c <8–5% risk
  - HbA1c >10–25% risk
- Macrosomia – prolonged labour, prematurity, birth trauma
- Intrauterine growth restriction
- Neonatal hypoglycaemia (8–60% prevalence)
- Respiratory distress syndrome
- Hypocalcaemia
- Intrauterine death – fasting >5 mmol/L in the last 4–8 weeks' gestation
- Later risk of obesity and diabetes

Management of pre-existing diabetes

The essential basis of treatment is good metabolic control, most importantly beginning before conception (see Box 2).

Box 2 Pre-conception management of pre-existing diabetes

- Patient education regarding benefits of tight diabetic control to improve pregnancy outcome
- Healthy life style and weight loss if BMI is more than 27 kg/m^2
- Contraception advice
- Review of drug therapy for pregnancy
- Ophthalmology review
- Serum creatinine and urine for microalbumin checks
- Optimised diabetic control, i.e. HbA1c <6.1%
- Switch type 2 diabetic patients to metformin and/or insulin
- Start pre-conceptual folic acid 5 mg daily

Pregnant women should be managed in a joint pregnancy/diabetic clinic by obstetricians and physicians with expertise in the care of such women. Dieticians, midwives, and specialist diabetes nurses should also be an essential part of the multidisciplinary team.

First trimester management

Accurate dating of the pregnancy is an obstetric imperative and is best confirmed by ultrasound examination at the time of the nuchal screening between 11 and 14 weeks' gestation. Patients should be reviewed regularly in the antenatal diabetic clinic for discussion of blood glucose self-monitoring results and advice on increasing insulin requirements.

Second and third trimester management

The keystone of management is achieving maternal normoglycaemia. Increasing maternal insulin resistance necessitates an increased insulin dose. The target capillary blood glucose should be 4–5 mmol/L fasting and 4.5–7 mmol/L postprandially. All pregnant diabetic women should be on a strict low-sugar, low-fat, high-fibre diet and a four-times-daily basal bolus regime, i.e., three pre-meal injections of fast-acting insulin and one nocturnal injection of intermediate-acting insulin. Obstetric supervision by a specialist midwife and obstetrician should be more frequent than for uncomplicated pregnancy. A detailed ultrasound of the fetus at 18–20 weeks' gestation with particular assessment of the fetal heart is necessary. Uterine artery Doppler at the same time will help identify women at risk of pre-eclampsia and fetal growth restriction. Serial scans from 28 weeks will allow detection of intrauterine growth restriction and evolving macrosomia (>4 kg) and hydramnios. The risk of late unexplained fetal death may be less when blood glucose control is good. The timing and mode of delivery has to balance the risk of prematurity with its associated complications against the risk of late intrauterine death and macrosomia with its attendant complications. Most obstetricians plan delivery between 38 and 39 weeks.

Gestational diabetes

Gestational diabetes (GDM) may be asymptomatic but can have serious consequences for the mother and baby if it remains undetected. The incidence of GDM in the UK is about 1 in 20. It usually develops in the second or third trimester induced by changes in carbohydrate metabolism and decreased insulin sensitivity. It is 11 times more common in women

Box 3 High-risk groups for gestational diabetes

- Obese women, body mass index >30 at booking
- First-degree relative with diabetes
- A history of polycystic ovarian syndrome
- Gestational diabetes in a previous pregnancy
- Macrosomia in a previous pregnancy
- A previous unexplained stillbirth or neonatal death
- Women who have glycosuria on two or more occasions in the current pregnancy
- Age >40
- Family origin non-Caucasian

of Asian background and three times more common in black women compared to European women. Glycosuria is common during pregnancy and should not be used as an indication for GTT. Women at risk of GDM (Box 3) should be offered GTT between 24 and 28 weeks. However, women with previous GDM should have the GTT earlier, at 16 weeks, and if negative this should be repeated at 28 weeks.

The reason for diagnosing as early as possible is that GDM is associated with increased perinatal morbidity and macrosomia in the same way as pre-existing diabetes.

Management

Diet, education, and frequent blood glucose monitoring at home is essential. At present, basal bolus insulin treatment is advised for all mothers with gestational diabetes whose venous plasma glucose despite diet remains >5.8 mmol/L fasting or 8 mmol/L postprandially. It may be that even lower criteria will be shown to decrease the prevalence of fetal macrosomia. Regular ultrasound assessment for fetal growth is not needed unless the glycaemic control is not satisfactory or metformin and/or insulin need to be prescribed. It the woman needs hypoglycaemic agents, then induction of labour may be considered around 38–39 weeks depending on the quality of that control. If control is good on diet only, then induction of labour can be deferred to 40–41 weeks.

Pre-pregnancy counselling for women at risk of GDM

In women who have a high risk of gestational diabetes, a pre-pregnancy educational programme on nutrition and lifestyle will reduce the number who require active treatment. Previous gestational diabetes is very likely to recur, and often the woman remains diabetic. Women identified as having GDM have a greatly increased risk (up to 50 per cent) of developing type 2 diabetes within 10–15 years, and hence lifestyle modification is essential for both pregnancy and the long-term non-pregnant state.

Management of diabetes during active labour

Insulin infusion regimes for women with established diabetes and women with gestational diabetes who are on insulin are standard. For women with gestational diabetes treated with diet alone, blood glucose levels should be monitored during labour, and intravenous insulin and dextrose infusion should be started only if the blood monitoring stix are persistently above 8.

Management after delivery

Women with established type 1 diabetes

Dextrose and insulin infusions should be continued until the women are eating and drinking normally. Once eating and drinking, they should return to their pre-pregnancy insulin doses immediately after delivery.

Women with established type 2 diabetes

This is the same as for type 1 diabetes but, once eating and drinking, they can usually return to their pre-pregnancy oral medication.

Women with gestational diabetes treated with insulin

The insulin should be stopped immediately after delivery once these women are eating and drinking. It is important to remember that all women who have gestational diabetes require a fasting blood sugar 6–10 weeks after delivery to ensure type 2 diabetes has not developed.

HAEMATEMESIS IN PREGNANCY

Shahana Shahid and Nishchay Chandra

Key points in management

Definitions

- Haematemesis is the vomiting of red or altered 'coffee-ground' blood.
- Melaena is the passage of black, tarry, foul-smelling stools and occurs if blood loss is >50 mL.

Presentation

- Haematemesis with or without melaena.
- There may be associated symptoms of lethargy, dizziness, shortness of breath, abdominal or retrosternal pain.
- There may be signs of hypovolaemic shock.

Management of haematemesis

1. Full blood count, clotting, urea and electrolytes, liver function tests (± cross-match).
2. Large-bore intravenous access.
3. Fluid resuscitation (crystalloid or colloid); blood if severe.
4. Nil by mouth if endoscopy anticipated.
5. Proton-pump inhibitor following endoscopy if indicated.
6. Gastroenterology review.

Common causes in pregnancy

- Mallory–Weiss tear.
- Oesophagitis.
- Gastric or duodenal ulceration or erosions.

Introduction

Haematemesis is defined as the vomiting of blood and indicates bleeding from the upper gastrointestinal tract proximal to the ligament of Treitz, that is, from the oesophagus, stomach, or duodenum. 'Fresh' haematemesis refers to the vomiting of bright red blood and commonly represents a significant, large-volume, active bleed caused either by the erosion of the gastric mucosa and underlying arterial vessel (e.g. as in the case of a peptic ulcer) or by varices. Vomiting of small amounts of altered blood ('coffee-ground' vomit) is common but rarely of significance. Coffee-ground haematemesis occurs in patients with either gradual blood loss or in those who have recently bled, and is to the result of stomach acid converting haemoglobin to haematin. The passage of at least 50 mL of blood into the upper gastrointestinal tract gives rise to melaena – the passage of black, tarry, foul-smelling stools – and occurs a few hours after bleeding has occurred.

The causes of haematemesis to be considered in a pregnant woman are the same as for the general population. However, there are certain diagnoses more likely in pregnancy, e.g., hyperemesis leading to a Mallory–Weiss tear. Similarly, some causes of acute haemorrhage common in the general population, such as non-steroidal anti-inflammatory drugs (NSAIDs) or acute alcohol use, are less frequent in pregnancy, but should always be considered in the differential diagnosis.

As with all cases of upper gastrointestinal bleeding, clinical evaluation is key to determining the severity of the bleeding. Assessment of the woman's haemodynamic status forms the mainstay of the initial management and will determine the need for prompt fluid resuscitation and urgent endoscopy. Calculating a severity score for bleeding can help 'risk stratify' patients for urgency of endoscopy (Table 1).

A thorough history and examination will point to the underlying aetiology of haematemesis in the majority of instances. For example, if recurrent vomiting occurred before the haematemesis, the most likely diagnosis will be a Mallory–Weiss tear. Those with chronic peptic ulceration (a diminishing number due

Table 1 Glasgow-Blatchford Score. Score of 0, consider early discharge; score of 6 is high risk of requiring endoscopic intervention[1]

Parameter	Score
Urea	
≥6.5 <8.0	2
≥8.0 <10.0	3
≥10.0 <25.0	4
≥25	6
Hb (M)	
≥12.0 <13.0	1
≥10.0 <12.0	3
<10.0	6
Hb (F)	
≥10.0 <12.0	1
<10.0	6
Systolic BP	
100–109	1
90–99	2
<90	3
Other	
HR ≥100	1
Malaena	1
Syncope	2
Liver disease	2
Cardiac failure	2

BP, blood pressure; Hb, haemoglobin; HR, heart rate.

Table 2 Five most common causes of upper gastrointestinal bleeding

Peptic ulcer	35–50%
Mallory–Weiss tear	5–15%
Gastroduodenal erosions	8–15%
Oesophagitis	5–15%
Gastro-oesophageal varices	7–10%

to the treatment for *Helicobacter pylori*) will sometimes give a long history of dyspepsia or previous ulceration. A history of alcoholism or physical signs of chronic liver disease, such as spider naevi, may indicate varices, although fertility is often reduced in cirrhosis.

Causes of haematemesis

The common causes of haematemesis within the general population are illustrated in Table 2.[2] Rare causes include angiodysplasia, Dieulafoy's lesion, portal hypertensive gastropathy, thrombocytopenia, disseminated intravascular coagulation/coagulopathy, and Osler–Weber–Rendu syndrome.

Swallowed blood

Bleeding from the nose, mouth, or throat can be swallowed and later vomited, masquerading as blood loss from further down the gastrointestinal (GI) tract. This would usually be of small volume; however, nose bleeds in pregnancy can be heavy. Careful history and examination will again distinguish this from gastrointestinal bleeding and prevent the need for endoscopy.

Gum disease in pregnancy would rarely be severe enough to cause haematemesis.

Oesophagus

Hiatus hernia and reflux oesophagitis

Hiatus hernia is a common finding. The incidence of both hiatus herniae and associated reflux oesophagitis is increased owing to the raised intra-abdominal pressure and the effect of increased progestogens on the smooth muscle of the lower oesophageal sphincter during pregnancy. These will normally cause retrosternal burning and water brash, but irritation of the lower oesophagus by gastric acid can occasionally lead to haematemesis. Treatment in pregnancy centres on lifestyle and dietary modification followed by pharmacological acid suppression if problems continue.

Oesophageal ulcer

Oesophageal ulcer is an infrequent cause of haematemesis and is usually benign in this age group. It may be associated with hiatus herniae and reflux oesophagitis.

Mallory–Weiss tear

A linear tear in the mucosa at the oesophagogastric junction due to forceful vomiting can result in haematemesis. Nausea and vomiting occurs in 70–85 per cent of pregnancies,[3] but will not normally cause further problems beyond the first trimester. Hyperemesis gravidarum, however, can cause intractable vomiting, which usually occurs at 8–12 weeks' gestation and has an incidence of 0.5–2 per cent.[3] There is an increased risk of developing Mallory–Weiss tears owing to the sustained nature of vomiting.

Treatment is to control the vomiting, but occasionally Mallory–Weiss tears will require endoscopic intervention. There is some evidence linking hyperemesis with *H. pylori* infection,[4] so eradication, if found at endoscopy, may be warranted.

Oesophageal varices (Fig. 1)

Varices develop as a result of portal hypertension, most commonly due to cirrhosis. Oesophageal variceal bleeding has been reported in up to 78 per cent of pregnant women with cirrhosis and pre-existing varices. Variceal bleeding is often severe and frequently accompanied by haemodynamic instability, requiring prompt resuscitation and endoscopic therapy (banding or injection sclerotherapy). There may be physical signs of chronic liver disease (jaundice, spider naevi, palmar erythema, ascites), but their absence does not exclude portal hypertension and varices.

The physiological changes that occur during pregnancy may exacerbate the pathophysiological changes that occur in portal hypertension[5] and make variceal haemorrhage more likely. To avoid complications, known cirrhotics should undergo endoscopic screening and eradication of varices either pre-conception or early in the second trimester. Prophylactic treatment with non-selective beta-blockers such as propranolol should be considered to reduce portal pressures and reduce the risk of variceal bleeding. Propranolol is not teratogenic but can have adverse effects on the mother or fetus, including bradycardia and hypoglycaemia.[6]

Stomach

Gastric ulcer

There is no increased risk of gastric ulcers in pregnancy. Symptoms prior to haematemesis include epigastric pain, often soon after eating, and there may be associated anorexia; however, symptoms can be non-specific. There is an association with

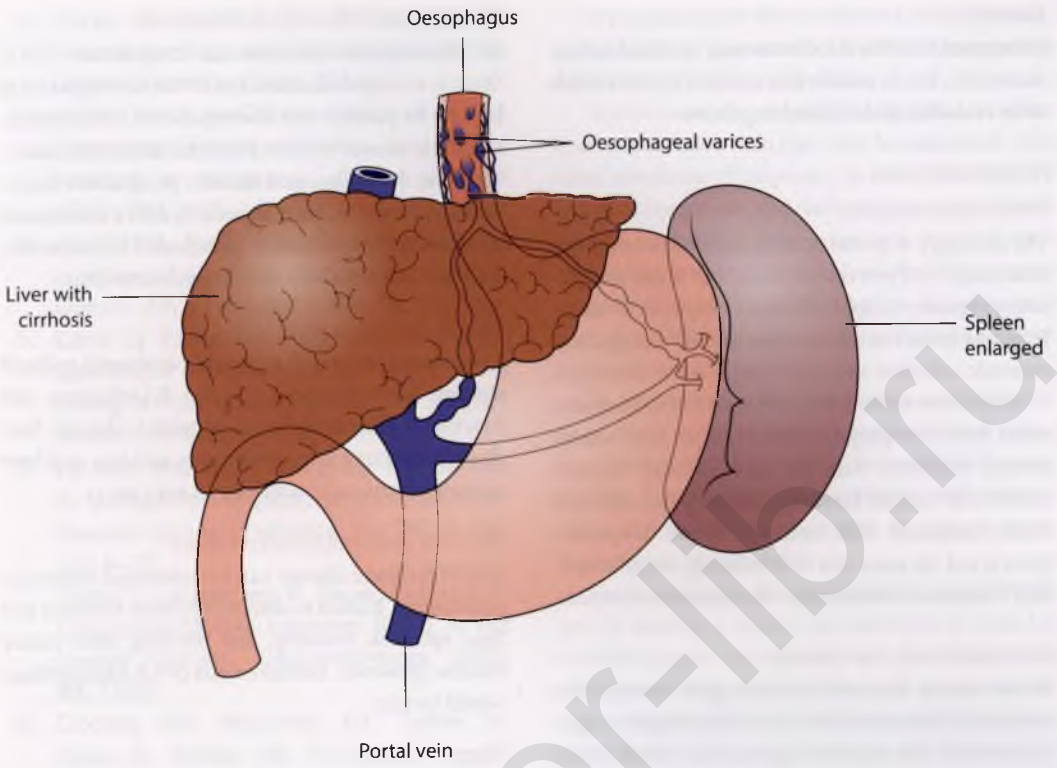

Figure 1 Oesophageal varices.

NSAIDs, and also with *H. pylori* (approximately 60 per cent of benign, non-NSAID-induced gastric ulcers are associated with *H. pylori*).

Acute gastritis

In acute gastritis, bleeding can occur from small erosions or minute ulcers and, as such, is normally of small volume. The patient will often complain of epigastric pain, nausea, and vomiting. NSAIDs are the most common cause of bleeding from erosive gastritis, and their use should be avoided during pregnancy. Other causes include ingestion of alcohol or irritant foods. Ingestion of corrosive liquids, such as strong acids or alkalis, is rare but serious. The woman may have an ulcerated oral mucosa and a background history of psychiatric illness. Acute tropical infections including dengue, yellow fever, blackwater fever, and variola can lead to gastritis.

Rarities

- Angiodysplasia (a connective tissue disorder) – idiopathic, or associated with aortic stenosis or Osler–Weber–Rendu syndrome (autosomal dominant inheritance, characterised by angiodysplastic lesions in mucosal membranes).
- Dieulafoy's lesion – a dilated bleeding blood vessel (usually seen in the upper part of the stomach) that erodes the gastric mucosa with no surrounding ulceration.

Duodenal disorders

There are no particular associations between pregnancy and duodenal disease.

Duodenal ulcer

Duodenal ulcers are often asymptomatic before bleeding occurs from the ulcer eroding a vessel. Classically the pain, if present, is epigastric, radiates to the back, and is relieved by eating. As with gastric ulcers, bleeding can be massive and initial management should be effective resuscitation followed by endoscopy. The majority of duodenal ulcers are associated with *H. pylori* infection (73–95 per cent).[7,8] Duodenal ulcers are seldom associated with malignancy, hence, unlike gastric ulcers, a repeat endoscopy to assess healing is not necessary.

H. pylori infection in the developed world is becoming increasingly uncommon in the childbearing age group. Empirical treatment is therefore not recommended as there is a lack of data regarding proton pump inhibitors (PPI) safety in pregnancy.[6]

Duodenitis

Inflammation of the duodenum may also lead to haematemesis, but is usually less severe. *H. pylori* needs to be excluded as the underlying cause.

Portal hypertension

Portal vein obstruction

The aetiology of portal vein thrombosis is unknown in around 8–15 per cent of cases, but it can complicate pregnancy (especially in eclampsia). In unselected patients, the other causes include malignancy, systemic infection and myeloproliferative disorders.

Portal vein thrombosis can present with haematemesis from oesophageal varices. As the liver retains normal synthetic function and clotting remains unaffected, variceal bleeding may be better tolerated when compared with cirrhotic bleeds. Moreover, there is not the same risk of developing encephalopathy. Treatment is endoscopic band ligation of varices.

Cirrhosis/chronic liver disease

As previously discussed (oesophageal varices), this can lead to haematemesis from oesophageal or gastric varices. The haemorrhage is often made worse by the associated thrombocytopenia or coagulation abnormalities).

Other causes

Disordered haemostasis

Many medical conditions can lead to disordered haemostasis, some of which are associated with pregnancy. Generally, by far the most common cause of deranged clotting encountered is iatrogenic secondary to anticoagulant use.

However, warfarin is teratogenic and heparin in pregnancy is used only in specific clinical scenarios (e.g. for the treatment of pulmonary embolism).

Thrombocytopenia

Low platelets are found in 7–8 per cent of pregnancies,[9] but most of these will be due to gestational thrombocytopenia (mild) and unlikely to cause GI haemorrhage. Even in the HELLP syndrome (haemolysis, elevated liver enzymes, low platelets), the thrombocytopenia is usually moderate and haematemesis would be an unusual presentation or complication.

Severe thrombocytopenia (<50 000 mL) causing GI haemorrhage during pregnancy is rare and will usually be due to a concomitant unrelated illness, e.g. leukaemia. Alternatively, it could occur as part of disseminated intravascular coagulation.

Disseminated intravascular coagulation

In disseminated intravascular coagulation (DIC), there is widespread activation of the clotting cascade leading to platelet and clotting-factor consumption. Obstetric causes include placental abruption, amniotic fluid embolism, and massive postpartum haemorrhage. However, haematemesis is a very uncommon complication in pregnancy-associated DIC, especially as DIC is usually short-lived in such situations.

Chronic liver disease

Liver disease may result in thrombocytopenia, reduced clotting factor synthesis, vitamin K deficiency, and functional abnormalities of platelets. Chronic liver disease is uncommon in pregnancy, as it may well have a significant impact on fertility in any case.

Inherited haematological conditions

Von Willebrand disease can be autosomal dominant or recessive. It leads to defective platelet function and thus epistaxis, bruising, and bleeding after minor trauma. However, haematemesis or GI haemorrhage would be rare.

Drugs

These are covered above (NSAIDs and anti coagulants).

Miscellaneous causes

Scurvy, a rare cause of haematemesis, is due to vitamin C deficiency, and would normally cause bleeding, swollen gums, anaemia, and cutaneous haemorrhages.

Endoscopy in pregnancy

Historically, there was some reluctance to use endoscopy during pregnancy. However, it is now considered to be safe in pregnancy,[3,6] ideally carried out after the first trimester. It can provide a definitive diagnosis and allow effective endoscopic therapy. Factors to consider include maternal position (left lateral tilt to avoid intra-abdominal vessel compression from fetal pressure), risk of aspiration due to suboptimal lower oesophageal sphincter tone, and importance of maintaining haemodynamic stability and respiratory function for fetal well-being.

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HAEMATURIA (BLOOD IN THE URINE)

Tony Hollingworth

This condition is defined as the presence of red blood cells in the urine, and should not be confused with haemoglobinuria, in which the pigment alone is filtered through the kidneys. It can be divided into:

- microscopic haematuria, where blood is found on 'dipstick' testing;
- macroscopic haematuria or frank haematuria, which is an unusual symptom to present to the gynaecologist.

The causes will vary with age and also with the presence of absence of a pregnancy.

In pregnancy, the urine is checked with a 'dipstick' at each visit. It is unusual to find frank haematuria without other obvious symptoms.

In most cases, the cause of the haematuria is infection. Any urinary infection may be associated with some symptoms of frequency, dysuria, and offensive urine, although not invariably so. In non-pregnant women, haematuria may occur as a result of contamination from menstrual blood flow. In younger women, the causes are usually benign, including urinary tract infection, stones and insertion of a catheter for any length of time.

In postmenopausal women, the complaint may be of blood in the urine when in actual fact it is due to postmenopausal bleeding for whatever cause. Bladder carcinoma may also present with haematuria, and this diagnosis should be considered in women over the age of 40.

In gynaecology, the investigations may be limited to sending a midstream specimen of urine for microbiological investigation, an ultrasound scan of the renal tract, and possible cystoscopy. Usually these patients will be referred to an urologist. Many countries have adopted guidelines for the investigation of haematuria, such as the American Urological Association and the European Association of Urologists guidelines. More recently, guidelines from NICE have recommended referral to exclude a possible malignancy.

Box 1 gives a list of causes of haematuria for completeness. The classification can be either anatomical, starting from the kidney and working down the tract, or by type of condition.

Box 1 Causes of haematuria in women

- Physiological
  - menstruation
  - caruncle – eversion of urethral meatus
- Infection
- Pyelonephritis
- Cystitis
- Urethritis
- Tuberculous infection of kidneys and bladder
- Trauma
  - renal injury
  - foreign body in bladder including urinary catheter
  - foreign body in urethra

- Inflammatory/autoimmune
  - glomerulonephritis
  - polyarteritis nodosa
  - chronic interstitial nephritis
  - irradiation changes to renal tract
- Stones
  - renal, ureteric, or vesical
- Tumours – benign and malignant
  - renal
  - ureteric
  - bladder
  - urethral
- General
  - drugs, including anticoagulants
  - bleeding disorders

Useful website

www.nice.org.uk/CG027

HAND PAIN IN PREGNANCY

Sharmistha Williams

The incidence of hand pain increases in pregnancy especially in the third trimester. Although the exact aetiology is unknown, changes in physiology that can explain this increased incidence include intra- and extravascular fluid shifts, hormonal fluctuations, and musculoskeletal changes. This is borne out by the fact that symptoms are worse in women with twins and triplets compared with singleton pregnancies. Women can present with hand pain for the first time or as an exacerbation of an existing symptom. Hand pain tends to recur in subsequent pregnancies, and a past history of this symptom is therefore important. Musculoskeletal causes of hand pain can be due to inflammatory or mechanical disorders of muscles, tendons, nerves, and joints in the hand or be part of a systemic rheumatic disorder. Local causes are summarised in Box 1.

From this list, one of the most common causes is carpal tunnel syndrome (CTS), the rest of the conditions being relatively rare. Only CTS and De Quervain's tenosynovitis are more common during pregnancy. Only carpal tunnel syndrome will be discussed here.

Box 1 Local causes of hand pain in pregnancy

- Carpal tunnel syndrome
- De Quervain's tenosynovitis
- Trauma – fracture/dislocation
- Osteoarthritis
- Repetitive strain injury
- Inflammatory arthritis

Carpal tunnel syndrome in pregnancy

The anatomy of the carpal tunnel and the passage of the flexor tendons and the median nerve in it are shown in Fig. 1. The limited space in the carpal tunnel would explain why the median nerve gets compressed when the hand swells with oedema.

The exact incidence of CTS in pregnancy is not known owing to a paucity of good data. In non-pregnant women the prevalence is estimated to range from 0.7 per cent to 9.2 per cent.[1] Pregnancy related CTS ranges from 31 to 62 per cent, which falls to 7–43 per cent when electro-diagnostic studies are used.[2] The commonest musculoskeletal condition in pregnancy is backache (see Back pain in pregnancy). The next most common condition is CTS. The reason for CTS being so common in pregnancy is multifactorial. Pregnant women are more prone to

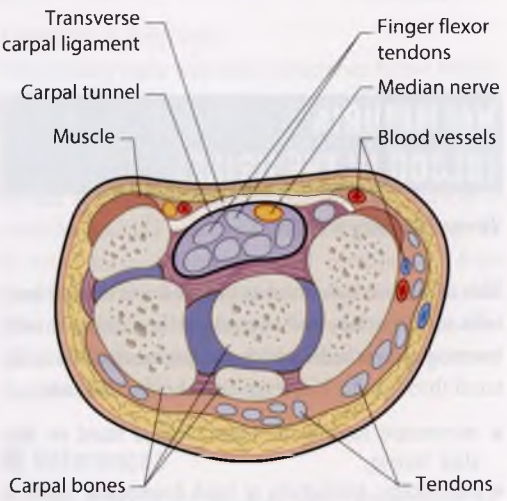

Figure 1 Anatomy of the carpal tunnel (from Botting and Schofield, *Brown's Skin and Minor Surgery 5E*, CRC Press 2014, with permission).

generalised oedema, with up to 80 per cent of women complaining of swelling of the limbs. This is caused by a combination of a reduction in plasma albumin and colloid osmotic pressure, peripheral vasodilatation, increased circulating plasma volume, and an increase in antidiuretic hormone levels. Oedema in the carpal tunnel (which is a restricted space – see Fig. 1) would therefore cause median nerve compression. Women with significant hand oedema, which prevents them from wearing rings, have an increased incidence of CTS. This explains why women with pre-eclampsia have an increased incidence of this condition.

There is a well-known association of altered glucose metabolism and of CTS with insulin resistance and increased fasting blood glucose levels being independent risk factors.[4] Studies have also shown that the peripheral nerves of pregnant women are more sensitive than those of non-pregnant women.[5]

It is important to understand the cutaneous and motor supply of the median nerve in the hand. The median nerve supplies the lateral three and a half fingers and corresponding areas of the palm and the distal end of the dorsum of the same fingers as shown in Figure 2. The median nerve supplies the 1st and 2nd **L**umbricals, **O**pponens pollicis, **A**bductor pollicis brevis, and **F**lexor pollicis brevis muscles (remembered by all medical students with the mnemonic 'LOAF' – the latter three composing the thenar eminence 'OAF').

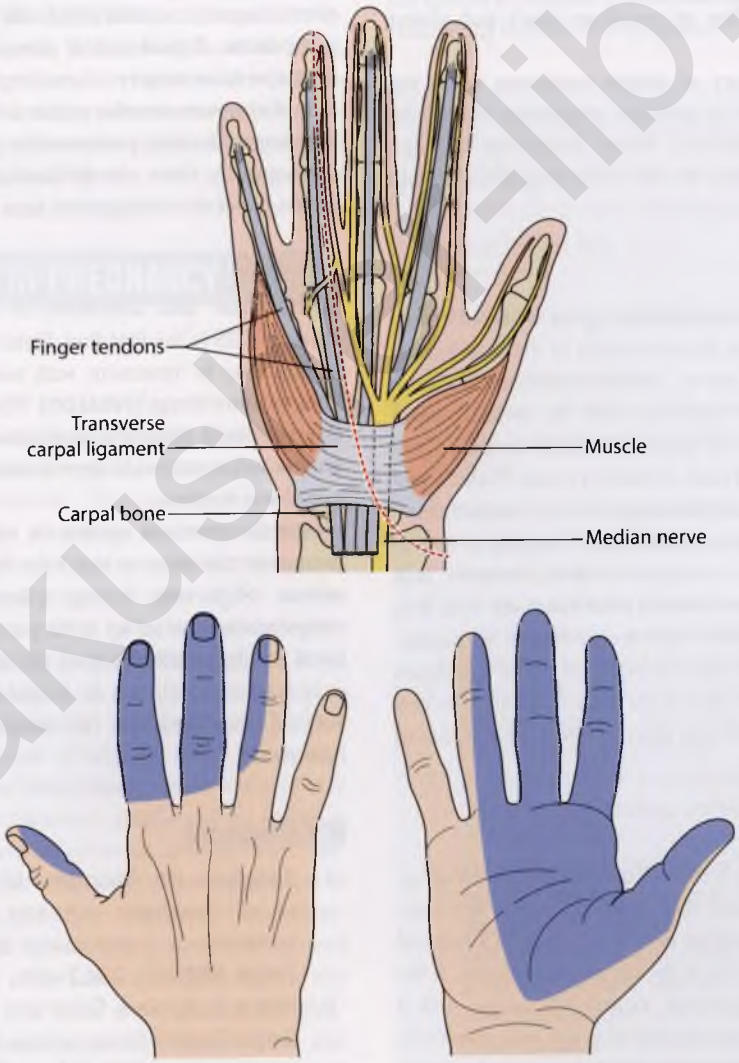

Figure 2 Palmar and dorsal cutaneous distribution of the median nerve (adapted from Botting and Schofield, *Brown's Skin and Minor Surgery 5E*, CRC Press 2014, with permission).

History

Women usually complain of swelling and pain in the hand that is associated with tingling and numbness. More than 50 per cent of pregnant women report worsening symptoms at night.[3] Symptoms are also aggravated with repetitive hand movements. Using the knowledge of the anatomy of the median nerve, careful questioning would reveal that the numbness is in the area over the thenar eminence and the lateral three and a half fingers. Weakness of thumb opposition may manifest as difficulty in buttoning shirts and writing. Symptoms may involve both hands. In some women symptoms may present in the first and second trimester with a rapid and progressive nature. However, presentation is usually in the third trimester and has an insidious onset and slower progression.

A past history of similar symptoms when not pregnant or in a previous pregnancy should be ascertained. Inquiries about gestational diabetes and pre-eclampsia in the index pregnancy should be made.

Examination

Examination includes checking for a loss of sensation and 2-point discrimination in the distribution of the median nerve. Muscle weakness in thumb apposition and abduction may be present. There may be evidence of thenar eminence atrophy. There are many tests (Tinel's, Phalen's, reverse Phalen's, and Durkin's) that aim to compress the median nerve and reproduce the numbness and tingling in its distribution. These compression tests, however, lack sensitivity and are therefore not routinely used. It is important to ensure that the woman is normotensive and a urine dipstick does not show significant proteinuria. Risk factors for gestational diabetes and results of a recent oral glucose tolerance test should be checked.

Investigations

The diagnosis is a clinical one, though electrodiagnostic studies have their uses. As nerves are compressed demyelination occurs, resulting in a reduced conduction velocity at the site of compression. If the compression progresses, axonal loss occurs with a decrease in the recruitment of motor unit potentials. As the muscle gets progressively denervated it shows fibrillations and a further decrease in recruitment of motor unit potentials. (To improve the strength of a muscle contraction, existing motor units are usually successively activated and new motor units are recruited and activated.)

Nerve conduction studies are able to demonstrate a reduction in nerve conduction velocity and decrease in recruitment of motor unit potentials. Electromyography is able to demonstrate the muscle fibrillations and decrease in recruitment of motor unit potentials. The value of these tests is to confirm that the symptoms are from local compression and not from proximal compression at the level of the brachial plexus or median nerve. If severe local median nerve compression is diagnosed, the surgeon can manage postoperative expectations more realistically, which is an additional advantage. The indication for the use of electrodiagnostic studies in the non-pregnant woman is a positive clinical and/or provocative test where decompression surgery is contemplated. As 85 per cent of symptoms resolve within 2–4 weeks of delivery,[5] surgery is rarely performed in pregnant women. Consequently, there are no standardised guidelines for the use of electrodiagnostic tests in pregnancy.[6]

Treatment

Identification and treatment of any underlying cause of CTS is the first line. Flexor tendon inflammation may be treatment with non-steroidal anti-inflammatory drugs (NSAIDS). Optimal control of elevated blood glucose concentrations and a screen for pre-eclampsia with appropriate treatment may improve symptoms.

Specific treatment options for carpal tunnel syndrome are the same as those for the non-pregnant woman. Night-time resting splints provide good symptomatic relief in up to 82 per cent of women.[5] Local corticosteroid injections provide improvement of symptoms, which lasts for longer than 15 months.[7] Surgical decompression in pregnancy is rarely indicated.

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HEADACHE IN PREGNANCY

Greg Davis

In their lifetime, 99 per cent of women will experience headaches and about one third of women will get significant headaches while pregnant, particularly in the second trimester. The majority of headaches (>95 per cent) in pregnancy are benign (primary headaches), but fear of a serious intracranial cause may lead pregnant women to present for review. Of those pregnant women with primary headaches, about two thirds will have migraine and one third tension-type headaches.

The pain of headaches is thought to arise in a widespread network of sensory fibres which surround intracranial blood vessels. These sensory fibres originate in the trigeminal ganglia and are found in the adventitial layer of all major cerebral blood vessels. Headache may result from direct stimulation of these fibres causing pain or secondary to the inflammatory effects of vasoactive neuropeptides released after stimulation of the sensory fibres. In light of this complex interaction, there are a number of potential points for intervention with treatment. It also explains why there are various pharmacological agents with different mechanisms of action that are effective in some headaches and not others.

Reproductive hormones and, in particular, oestrogen, influence this system directly and indirectly by modifying cerebral blood flow and concentrations of neurochemicals. For example, prior to puberty males and females are equally affected by migraine, but there is a 3 to 1 ratio in favour of females after puberty.

Classification

The 2013 International Headache Society Classification divides headaches into primary (e.g. migraine or tension), where headache is the dominant symptom, and secondary, where it is usually part of a systemic condition (e.g. pre-eclampsia, trauma) (Box 1). Although not specific to pregnancy, this classification is useful for considering headaches in pregnancy.

Box 1 The International Classification of Headache Disorders, 3rd edition (beta version), The International Headache Society, 2013

Part one: Primary headaches

1. Migraine
2. Tension-type headache
3. Trigeminal autonomic cephalalgias
4. Other primary headache disorders (cough, exertional)

Part two: Secondary headaches

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial or cervical vascular disorders e.g. subarachnoid haemorrhage, imminent eclampsia, acute ischaemic stroke
7. Headache attributed to nonvascular intracranial disorder (idiopathic intracranial hypertension, post dural puncture, tumours)
8. Headache attributed to a substance or its withdrawal (alcohol, cocaine, caffeine withdrawal, medication overuse)
9. Headache attributed to infection (meningitis)
10. Headache attributed to disorder of homeostasis (hypoglycaemia, hypoxia)
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure (sinusitis, jaw pain, tooth abscess)
12. Headache attributed to psychiatric disorder (depression, anxiety)

Part three: Painful cranial neuropathies, other facial pains and other headaches

13. Painful cranial neuropathies and other facial pains (trigeminal neuralgia, Bell's (facial nerve) palsy
14. Other headache disorders

After excluding headache due to pre-eclampsia, the vast majority of headaches in pregnancy will be either migraine or tension-type headaches, and most women presenting with headache in pregnancy will not need extensive investigation. However, because of the possibility of serious underlying pathology, the clinical significance of the presenting symptoms must be assessed with a careful history and appropriate examination. In general, a sudden onset of pain or change in the pattern of chronic headache makes a serious cause more likely (Box 2). Associated features such as fever, neck stiffness, focal neurological signs, and hypertension are indications for full investigation.

Box 2 Features suggestive of underlying pathology with headache in pregnancy

- Sudden onset or increase in severity
- Change in pattern of chronic headache
- Neurological symptoms or signs
- Change in the level of consciousness, personality or cognition
- Meningism
- History of recent trauma
- Hypertension or endocrine disease

Clinical assessment

As with any pain, when assessing headache, the quality, location, severity, time course, plus exacerbating and relieving factors should be fully explored. The woman should be questioned to elicit any neurological symptoms associated with the headache, such as numbness, tingling, loss of or alteration in sensation or movement, and systemic disturbance such as fever, anorexia, and skin rashes. A complete medication history should be taken to rule out medication overuse in chronic headache and to assess what has been helpful in alleviating the symptoms. Simple analgesics such as paracetamol are not likely to relieve significant headaches caused by underlying pathology.

Examination should begin with blood pressure measurement and a brief general physical examination with particular attention to any system of interest, e.g., throat and sinuses if an upper respiratory tract infection is suspected. A more detailed examination will not usually be necessary in pregnancy. However, if there are focal neurological symptoms, a neurological screening examination should be performed comparing the affected with the non-affected side. The family or companions should be questioned on any changes in personality, loss of consciousness, or alteration in mental state in the pregnant woman. The level of consciousness and cognitive ability can be assessed during history taking and clinical examination. The optic fundi should be inspected for papilloedema (blurring of the optic discs). The pupils, visual fields, and the presence of extraocular movements should also be assessed. The motor system should be examined with finger–nose testing, observing for the drift of outstretched hands, and heel–toe walking. The deep tendon reflexes and plantar responses should be elicited, and the presence of clonus assessed.

Investigations

If, after appropriate history and neurological examination and in the absence of any of the warning features in Box 2, the woman has no persistent neurological symptoms or signs and the headache resolves, she can be followed clinically without performing further investigations. Diagnostic testing is required if there is a suspicion of an underlying cause for the headache. The purpose of testing is to make the diagnosis, exclude other causes of headache, and to rule out diseases which might complicate headache or its treatment, such as diabetes and pre-eclampsia. The nature and extent of the investigations will be determined by the clinical possibilities after history and examination.

As discussed before, pre-eclampsia is the most common cause of secondary headache in pregnancy and must be excluded first. Severe, persistent headache in a pre-eclamptic woman is a warning of imminent eclampsia and immediate action should be taken to reduce the blood pressure and start anti-convulsion prophylaxis. After pre-eclampsia,

cerebral thrombosis, a vascular anomaly, and intracranial bleeding are the most likely serious diagnostic possibilities requiring exclusion in women presenting with a significant, new onset headache in pregnancy. Thrombosis is more likely if there is an underlying hypercoagulable state such as pre-eclampsia or thrombophilia. Blood should be taken for a complete blood count, liver function tests, urea and electrolytes, creatinine, prothrombin time, partial thromboplastin time, and thrombophilia screen if a secondary cause is suspected. Severe headache in the immediate postpartum period is most likely to be a result of a dural puncture during epidural or spinal anaesthesia. However, this is mostly a straightforward diagnosis with the context of possible dural puncture and the remarkable improvement in the headache when the woman lies down. A lack of improvement with change of posture should prompt further investigation.

Lumbar puncture

Lumbar puncture is necessary in:

- severe headache with suspicion of infection (meningitis) or subarachnoid haemorrhage;
- severe, rapid-onset, recurrent headache;
- progressive headache (increasing headache with little or no remission);
- atypical headache disorder.

If raised intracranial pressure is suspected (if papilloedema is detected), lumbar puncture should be delayed until after neuroimaging, unless meningitis is the likely cause, in which case it should be performed as soon as possible.

Radioimaging

Non-contrast computed tomography (CT) is recommended for the assessment of bony structures and detection of acute intracranial haemorrhage (subarachnoid, subdural following head trauma, intraparenchymal) but its sensitivity declines with time from the initial haemorrhage. For all other indications, including angiography, magnetic resonance imaging (MRI) is preferred but should be performed after consultation with a neurologist (Fig. 1). To date there is no evidence of harmful fetal effects with head CT or MRI, as the fetus is not directly exposed. Gadolinium should be avoided if possible in pregnancy, particularly in the first trimester, although there is no evidence for fetal damage in humans. While concern for fetal welfare is appropriate, in this clinical setting the importance of an accurate diagnosis outweighs the minimal potential for fetal harm.

With all radiological investigations in pregnancy both parents and health workers will be concerned about the effects on the fetus. It is believed that fetal exposure up to 5 rad does not result in miscarriage, anomalies, or impaired growth. The exposure to the uterus from a standard head or cervical spine CT is less than 1 mrad, and MRI does not use ionising radiation (see Breathlessness in pregnancy: respiratory causes).

Primary headaches

Migraine

Migraine is usually a severe, unilateral throbbing headache aggravated by activity with associated

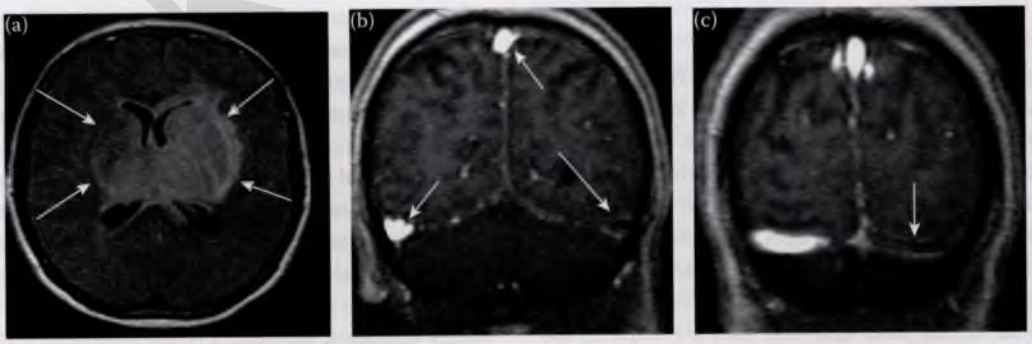

Figure 1 This 39-year-old woman with a history of antiphospholipid syndrome presented with severe, constant headache and focal neurological signs 2 weeks postpartum. (a) This FLAIR image shows bithalamic venous ischaemia (area marked by arrows) due to occlusion of the internal cerebral veins by thrombus. (b) On time of flight MR venography, increased signal confirming blood flow is seen in the superior sagittal sinus (arrowed at the top of the image) and the right transverse sinus (arrowed at 7 o'clock), but there is thrombus visible in the left transverse sinus (large arrow at 4 o'clock). (c) A similar image more posteriorly in the brain to that in (b) confirms these findings and demonstrates a clot in the left transverse sinus (dark line arrowed).

nausea, vomiting, photophobia, phonophobia (sensitivity to sound) and sometimes, but not always, an aura. Migraines can last from hours to days and often develop in a crescendo pattern. The nausea and vomiting may be severe and more debilitating than the headache. Migraines without an aura are more common (common migraine) and usually more disabling than those with an aura (classic migraine). The aura is a neurological symptom, typically visual change with scotomata (an area of loss or impairment of visual acuity surrounded by a field of normal or relatively well-preserved vision) or, less commonly, visual field loss, sensory changes (numbness or tingling), or speech changes. The symptoms of the aura develop over 15–20 minutes and precede the headache by less than one hour. Migraines are often preceded by neck stiffness, fatigue, and nausea though these symptoms do not constitute an aura.

To establish the diagnosis of migraine the woman must experience five or more similar episodes. In addition, considerable improvement in, or disappearance of, migraine is reported by 70–80 per cent of women in pregnancy, probably as a result of the sustained rise in oestrogen levels. In women with a history of migraine, improvement occurs early in pregnancy, is maintained through pregnancy, with recurrence in the first week postpartum in 60 per cent of women. Therefore the diagnosis of new onset migraine in pregnancy, especially with aura, must be made with great caution and only after exclusion of more serious causes of headache with transient neurological symptoms. If there are persisting neurological signs or the headache becomes progressive or recurrent, then further investigation is necessary.

Tension-type headaches

In comparison to migraines, tension-type headaches have few characteristic features. They are not affected by activity, are often diffuse and bilateral, and may be localised to either head or neck. There is no associated nausea or vomiting but there may sometimes be photo- or phonophobia. They may develop in association with neck or back pain or with facial neuralgias. Typical descriptions include 'a tight band around my head' or 'my head in a vice'. They are worse in the evenings and with stress and may last from hours to days. If they are present more than half the month they are termed chronic.

Tension-type headaches have not been studied extensively in pregnancy. There have been reports of both improvement and no differences in pregnancy in retrospective studies.

Secondary headaches

Head trauma

In pregnancy this is most likely to occur after vehicular accident and is usually the result of a direct injury to the head. It should also be suspected where domestic violence has occurred, and it is important to realise that domestic violence increases 3 to 4-fold during pregnancy.

Vascular disorders

Hypertension in pregnancy

The headache associated with pre-eclampsia and eclampsia is thought to be due to cerebral arterial vasospasm. This leads to either ischaemia or hypertensive encephalopathy, both of which may be associated with headache. It is usually bilateral, throbbing, and worsened by activity and rising blood pressure. It may be associated with blurred vision, flashing lights and scotomata and, as such, is a warning of imminent eclampsia, suggesting an urgent need for seizure prophylaxis and control of blood pressure.

Brain haemorrhage

The classic presentation of subarachnoid haemorrhage is the sudden onset of severe, incapacitating headache, neck stiffness, and collapse. However, at least 50 per cent will have a less dramatic onset with a progressive, severe, unremitting headache. This is caused by the rupture of either an arteriovenous malformation or a saccular or berry aneurysm. It is a widely held belief that subarachnoid haemorrhage is more common in pregnancy, but this is unlikely. Subarachnoid haemorrhage accounts for 50 per cent of cerebral haemorrhages in pregnancy, occurring in 1 in 10,000 pregnancies with a 50 per cent maternal mortality.

Intracerebral haemorrhage is a rare event that may be more common in pregnancy. It also presents with sudden, severe headache, often accompanied by rapidly progressive neurological signs. In pregnancy it is most often seen with a hypertensive disorder, usually eclampsia, although it is also associated with cocaine and alcohol abuse.

Brain CT is the preferred diagnostic modality if brain haemorrhage is suspected. However, the deteriorating clinical state of the mother often requires rapid neurosurgical intervention and delivery of

the baby because of risks to mother and baby. If the mother is clinically stable, the diagnostic workup should begin immediately with a brain CT. If this is not helpful, lumbar puncture should be performed to look for blood in the cerebrospinal fluid.

Cerebral venous thrombosis

Although rare, the risk of stroke in young women increases 13-fold in pregnancy with the most common cause being cerebral venous thrombosis. It is thought to be more common in hypercoagulable states such as underlying thrombophilia and pre-eclampsia. The usual presentation is with focal neurological symptoms and signs, but thrombosis of the superior sagittal sinus is reported to cause severe progressive headache without focal signs. It may be associated with the development of hypertension, which can delay the diagnosis because the neurological condition is incorrectly attributed to pre-eclampsia.

Benign intracranial hypertension

Benign intracranial hypertension is 10 times more common in obese women of childbearing age compared to the general population. Women may already have the condition when they become pregnant, or it may develop anew during pregnancy. It is a syndrome with the symptoms and signs of raised intracranial pressure without a cause detectable on CT or MRI. It may be due to increased production or impaired resorption of cerebrospinal fluid. It presents with a global headache that may be worse lying down, and with progressive diplopia and visual loss if untreated. There is a 10 per cent risk of permanent visual impairment in this condition, but this risk is not affected by pregnancy and there is no increased risk to the mother or fetus in pregnancy.

On testing, diplopia and papilloedema will be present, and there may be impairment of visual fields and acuity. Cerebral venous thrombosis also has this type of presentation and will need to be excluded by brain MRI. If the diagnosis is still not clear, lumbar puncture will be necessary to demonstrate an abnormally raised opening pressure.

Brain tumour

Although most pregnant women who present with severe or new onset headache will fear that they have a brain tumour, only half of brain tumours are associated with headache and such headaches are often mild. Pregnancy does not increase the risk of developing a brain tumour; however, it may worsen symptoms from vascular tumours, such as meningiomas and acoustic neuromas.

Postpartum headache

About 40 per cent of women develop headache in the first week postpartum. The cause is uncertain but, given that women with pre-existing migraine may experience an improvement in pregnancy, it is likely to be due to the rapid drop in oestrogen.

Another major cause of postpartum headache is inadvertent dural puncture, which occurs in about 1–2 per cent of women during lumbar epidural insertion. About 15 per cent of women will also complain of headache following obstetric spinal anaesthesia. The headache is similar in both and is usually tolerable when the woman is lying down. However, it is often severe on standing and this may necessitate treatment so that the woman may care for her baby. The dramatic effect of posture in the context of a history of spinal or epidural anaesthesia/analgesia usually makes the diagnosis straightforward. If the diagnosis is not clear, other rarer complications which may cause headache in this setting, such as subdural haematoma and septic meningitis, need to be excluded.

Systemic and other conditions

Headache can occur in a variety of other medical conditions in pregnancy. Examples include hypoglycaemia with the treatment of diabetes and fever due to any intercurrent infection. Other substances can cause headache in both pregnant and non-pregnant women, such as monosodium glutamate ('Chinese restaurant headache'), nitrates in processed meats ('hot-dog headache'), and alcohol soon after ingestion (in contrast to a hangover). Chocolate and cheese can cause headaches in both migraineurs and others. Headaches are also seen with the use of, and withdrawal from, illicit drugs such as amphetamines, cocaine, barbiturates, and opiates. Daily headaches attributed to medication overuse may be the diagnosis, if a drug is used for symptoms most days, and in the absence of any worrying features and with a normal examination.

Other demands of pregnancy

Finally, it is important to remember that pregnancy is often a time of profound change in a woman's or couple's life. This may cause emotional stress, and

'broken' sleep may cause tiredness, both of which can contribute to headache development. This can be especially problematic when the woman has difficulty in sleeping owing to her increasing abdominal size and discomfort or the presence of other young children in the family.

HEARTBURN DURING PREGNANCY

Sivatharjini Sivarajasingam and Baha Khan

Introduction

The prevalence of heartburn in the normal population is approximately 7 per cent. In pregnancy 45–85 per cent of women report gastro-oesophageal reflux disease (GORD) and heartburn.[1] This increase is thought to be due to the relaxation of the lower gastro-oesophageal sphincter secondary to circulating levels of progesterone. Progesterone is also thought to reduce the peristaltic activity of the stomach. The situation is compounded by the increasing size of the gravid uterus causing pressure on the stomach, thus symptoms usually worsen in the third trimester of pregnancy.

Heartburn is associated with diseases other than GORD, as illustrated in Box 1. *Helicobacter pylori* infection does not have a direct relationship with heartburn. Most women have heartburn for the first time in pregnancy. In women with a past history of GORD, pregnancy can exacerbate symptoms. The typical symptoms of heartburn and GORD are given in Box 2. The majority of women presenting with these symptoms can be confidently diagnosed without need for specific investigations. Further investigation is very rarely warranted, except in women who have 'red flag' and atypical symptoms, as described in Box 3. Upper gastrointestinal (GI) endoscopy will be then indicated. Upper GI endoscopy can be safely performed with conscious sedation and the careful monitoring of the mother and fetus.

In pregnant women with GORD, symptoms usually resolve with the delivery of the baby. However, GORD can cause significant morbidity not only from the pain but also as a result of sleep disturbances. In most women, explanation of the temporary nature of GORD in pregnancy with reassurance and life style modification may be all that is required. This can include using an extra pillow at night, avoiding large meals and spicy food especially late at night, wearing loose fitting clothes, and avoiding stooping. Cabbage, broccoli, and lettuce are all high in raffinose, a sugar that produces gas in the stomach, which may aggravate symptoms and should only be taken in moderation. Since the stomach

Box 1 Causes of heartburn

- Gastro-oesophageal reflux disease (GORD)
- Gastritis
- Peptic ulceration
- Achalasia
- Cancer of the gastro-oesophageal junction
- Gallstones

Box 2 Heartburn and symptom variation with GORD

Typical symptoms of GORD

- Heartburn
  - retrosternal chest pain, originating in epigastrium and radiating to the neck
  - exacerbated after meals
  - exacerbated by changes in posture such as lying down and bending forwards
- Regurgitation

Symptoms that are associated with GORD

- Epigastric pain
- Nausea and bloating
- Abdominal discomfort

Box 3 Symptoms that require further investigation of heartburn

Symptoms that may be due to GORD but need exclusion of other disease

- Red flag symptoms – odynophagia, dysphagia, iron deficiency anaemia, and weight loss
- Odynophagia – sensation of pain behind the sternum on swallowing food or fluid
- Dysphagia – painful or difficult swallowing
- Atypical symptoms – angina-like chest pain, chronic cough, hoarseness and asthma

empties to the right side, sleeping on the right side (rather than on the left) in itself can sometimes help. A drug history should be taken and non-steroidal anti-inflammatory drugs (NSAIDs) stopped. Other drugs that aggravate GORD include calcium antagonists, which should be avoided and alternatives used if required. Smoking and alcohol should be avoided. Many women find relaxation techniques, herbal medicines, acupuncture, acupressure, aromatherapy, and homeopathy useful.

If these measures do not alleviate the symptoms, then drug therapy may be indicated. The benefits and risks of drug treatment should be discussed, as none of the drugs used in the treatment of GORD have been evaluated in pregnancy by large randomised controlled trials. Fetal safety has been extrapolated from animal study data and cohort studies. Use of the smallest dose to achieve symptom control is the therapeutic aim; therefore, unlike the non-pregnant woman, the drug treatment in pregnancy should follow a step-up algorithm.

Antacids and sucralfate (an aluminium-containing compound) are considered the first-line drug therapy. They have little systemic absorption, and therefore do not pose much risk to the fetus. Over-the-counter remedies for neutralising stomach acid can be helpful. However, using them too often and for too long can cause constipation (if they contain aluminium) or diarrhoea (if they contain magnesium). Antacids that contain sodium bicarbonate should be avoided as they can cause maternal alkalosis and fluid overload. Women should be advised to take antacids at a different time from when they take oral iron supplements, as hydrochloric acid is required for iron absorption. Sucralfate is also poorly absorbed, inhibits pepsin and locally protects against ulcers. Alginates are used for the symptomatic treatment of heartburn and oesophagitis, and appear to act by a unique mechanism, which differs from traditional antacids. Gaviscon is an alginate, which in the presence of gastric acid precipitates to form a gel. Both in vitro and in vivo studies have demonstrated that alginate-based rafts can entrap carbon dioxide, thus providing a relatively pH-neutral barrier. Several studies have demonstrated that the alginate raft can preferentially move into the oesophagus in place, or ahead, of acidic gastric contents during episodes of gastro-oesophageal reflux; furthermore they can act as a physical barrier to reduce reflux episodes.[2]

If symptom control is still not obtained then second line treatment includes promotility drugs, such as metoclopramide and the use of histamine-2 receptor antagonists, such as ranitidine. Metoclopramide acts by increasing the pressure in the region of the lower oesophageal sphincter as well as increasing clearance from both the oesophagus and the stomach. No teratogenic side effects have been reported with this drug, which has been used more commonly in the treatment of hyperemesis gravidarum.

Histamine-2 receptor antagonists include cimetidine, famotidine, and nizatidine in addition to ranitidine. Ranitidine is the only drug that has been specifically studied for use in the pregnant woman. It is associated with significant symptom score improvement and no specific teratogenic side effects. Furthermore it is not anti-androgenic, as opposed to cimetidine, and consequently the drug of choice in this group of drugs. There is little safety data on famotidine and nizatidine.

Proton pump inhibitors (PPI) are the most effective drug group to produce a significant and long lasting reduction in gastric acid production. Even though teratogenic side effects have not been specifically demonstrated, due to the lack of safety data its use in pregnancy is limited to women with intractable symptoms or complicated reflux disease. Of this group, lansoprazole may be preferred because of its safety profile in animals and case reports of safety in human pregnancies.

Most drugs are excreted in breast milk, and only the histamine-2 receptor antagonists (with the exception of nizatidine) are safe to use in lactation.[3]

The step-up algorithm for the management of women with heartburn in pregnancy is depicted in Fig. 1.

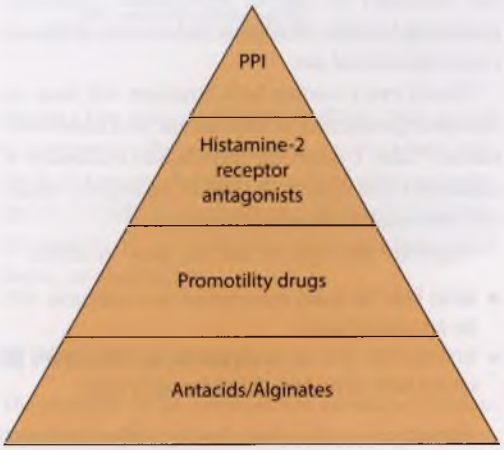

Figure 1 The step-up algorithm for the medical treatment of GORD in pregnancy. PPI, proton pump inhibitor.

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HIRSUTISM/VIRILISM

Anne Clark, revised by Harry Gibson

Hirsutism is defined as excessive body hair growth in women where it is not normally found, usually with a central body distribution. In about 10–15 per cent of hirsute women, hormone levels are within the normal range and a diagnosis of 'idiopathic hirsutism' is made.[1] Excessive facial and body hair caused by excess androgen production is usually associated with anovulatory ovaries and a loss of cyclical menstrual function.

The more severe state of virilism (defeminising symptoms: clitoromegaly, deepening of the voice, balding, increased muscle mass, and changes to a male-like body habitus) is rarely seen and is usually secondary to adrenal hyperplasia, androgen-producing tumours of adrenal and ovarian origin, or exogenous steroid use.

Nearly every woman with hirsutism will have an increased production of testosterone and androstenedione.[2] Table 1 shows the sources and incidences of conditions that result in increased androgens, which can then result in hirsutism/virilism.

There are two types of hair that grow in adults:

- vellus hair: the downy unpigmented hair associated with the prepubertal years;
- terminal hair: the coarse pigmented hair that grows on various parts of the body during the adult years.

Hirsutism occurs when resting vellus hairs are transformed to terminal hairs following exposure of the hair follicles to increased androgen levels. Androgens, particularly testosterone, initiate growth and increase the diameter and pigmentation of hair. Oestrogens essentially act in the opposite way to androgens, and progestins have minimal direct effects on hair. Once the transformation from vellus to terminal hair occurs, the terminal growth pattern persists, even if the increased androgen levels stop. Hirsutism is clinically distinct from hypertrichosis, in which there is an excess of generalised vellus hair growth, which is either hereditary, or secondary to anorexia, certain medications, or malignancy.

It is also important to note that a woman's total number of hair follicles is determined by 22 weeks' gestation and thereafter no new follicles will be produced de novo. The concentration of hair follicles laid down per unit area of facial skin differs little between men and women, but does differ between races and ethnic groups. For example, Asian women with androgen-secreting tumours are rarely hirsute because of their low concentration of hair follicles per unit skin area.

The diagnosis of hirsutism/virilisation may seem daunting, but a basic history, examination, transvaginal ultrasound scan of the ovaries and a few laboratory investigations will give the diagnosis in the majority of cases. The diagnostic evaluation of hirsutism/virilism is shown in Figure 1.

Medical history

The focus should be on the onset and duration of the symptoms of hirsutism/virilisation, and menstrual and medication history. Hirsutism associated with a history of menstrual irregularity since the teenage years or early 20s, or an increased body weight with a long gradual worsening of the condition, is polycystic ovary syndrome (PCOS) unless proven otherwise. Box 1 gives the revised diagnostic criteria of polycystic ovaries and PCOS,[5] the commonest cause of hirsutism.

Constellations of symptoms may suggest other sources of endocrinopathy. Hirsutism associated with central weight distribution, excessive sweating, and skin atrophy with purple striae suggests Cushing's syndrome. Fatigue, poor concentration, feeling cold, constipation, weight gain, and menorrhagia point towards hypothyroidism.

If there is a history of sudden onset and rapid progression of androgen excess leading to virilisation,

Table 1 Differential diagnoses and incidence of hirsutism/virilism

Polycystic ovary syndrome	10% of all women
Idiopathic hirsutism	10–15% of hirsute women
Ovarian	
Benign tumours: the vast majority of ovarian androgen-secreting tumours are benign.	<1% of all ovarian tumours, of which 75% are benign; usually occur in the younger age group
The most common in premenopausal women is a Sertoli–Leydig tumour; others include cystic teratomas and luteinised thecomas	
Malignant tumours: these can arise from the hilus, Leydig cells, or sex cords (Sertoli and granulosa cells) or epithelial cells	25% of all these types of tumour are malignant (i.e. 25% of the 1% above)
Adrenal	
Tumours (benign and malignant)	2/1,000,000 per year
Late onset congenital adrenal hyperplasia	1–5% of hirsute women
Cushing's syndrome (excessive cortisol secretion)	Overall incidence of 1 per 100,000 per year
Pituitary adrenocorticotrophic hormone (ACTH) overproduction: the most common diagnosis	Female to male ratios 5:1 with a peak incidence 30–50 years of age
ACTH, cortisol or corticotrophin-releasing hormone production by a tumour	
Increased adrenal cortisol secretion	
Other endocrine	
Hereditary insulin pathway defects: hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN syndrome)[3]	
Exogenous drug related	
Anabolic steroid use	Usually athletes or body builders[4]
Overdose of androgens	Usually postmenopausal women on hormone replacement therapy
Hair-stimulating drugs: phenytoin, diazoxide, danazol, cyclosporine, minoxidil	
Pregnancy	
Luteoma	Unilateral in 45% of cases, associated with a normal pregnancy
Theca-lutein cysts	Bilateral, associated with trophoblastic disease or multiple pregnancy
Ovarian cancer	Solid, unilateral ovarian lesions

a tumour needs to be excluded, particularly if the woman develops hirsutism later than the age of 25 years. Ovarian tumours are more common than adrenal tumours.

If the woman is pregnant, then development of virilisation is most likely due to a luteoma, which is not a true tumour but an exaggerated reaction of the ovarian stroma to normal levels of chorionic gonadotrophin. The solid lesion is unilateral in 45 per cent of cases, causes virilisation in 35 per cent of women, and regresses postpartum. Signs of masculinisation occur in 80 per cent of female fetuses. The other virilising condition that occurs in pregnancy, theca-lutein cyst, occurs when high levels of human chorionic gonadotrophin are present as a result of trophoblastic disease or multiple pregnancy; 30 per cent of women will have some degree of virilisation.

Physical examination

The purpose of the physical and laboratory evaluations are to rule out adrenal and ovarian tumours, assess the severity of androgen excess, and evaluate

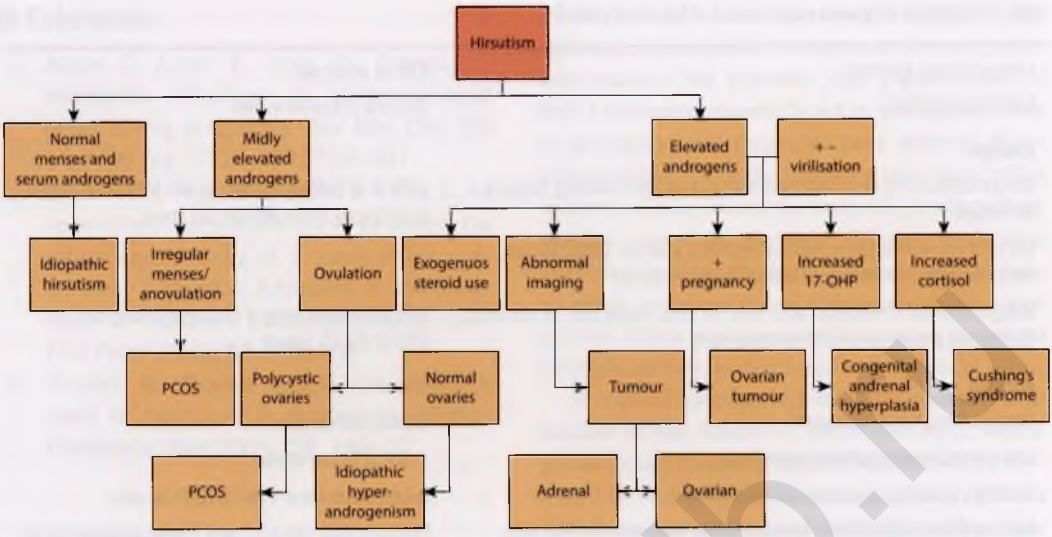

Figure 1 Differential diagnosis of hirsutism/virilisation. 17-OHP, 17-OH progesterone; PCOS, polycystic ovary syndrome.

Box 1 Revised diagnostic criteria of polycystic ovary syndrome (2003 Rotterdam PCOS Consensus)

Revised 2003 criteria (2 out of 3)

- Oligo- or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries[a]

and exclusion of other aetiologies (congenital adrenal hyperplasia, androgen-secreting tumours, Cushing's syndrome)

[a] Using ultrasound criteria, polycystic ovaries are defined by the presence of 12 or more follicles in each ovary, each measuring 2–9 mm in diameter, and/or increased ovarian volume (>10 mL).

the source of the hyperandrogenism (ovarian vs. adrenal). The presence or absence of the following should be assessed.

- Signs of androgen excess:
  - degree of hirsutism – this was traditionally quantified by the Ferriman–Gallwey scoring system, but it is now of little practical use clinically;
  - acne;
  - if anovulatory, also assess breasts for galactorrhoea;
- Signs of virilisation:
  - clitoromegaly, deepening of the voice.
- Signs of increased insulin levels:
  - acanthosis nigricans – this grey–brown velvety discoloration of the skin can be found in the neck, groin, axillae and vulva.
- Signs of an ovarian lesion on pelvic examination: unilateral or bilateral
- Signs of Cushing's syndrome:
  - moon facies, buffalo hump, abdominal striae, centripetal fat distribution, hypertension.

Investigations

The investigations will include blood tests and imaging designed to look for the underlying diagnosis.

- Blood tests for androgen excess. There is no absolute level that is pathognomonic for a tumour; however, a serum testosterone >5 mmol/L is highly suggestive.
  - total testosterone;
  - dehydroepiandrosterone sulphate (DHEAS; if raised suggests adrenal cause);
  - unbound testosterone (measure sex hormone binding globulin SHBG);
  - 17α-hydroxyprogesterone (raised in congenital adrenal hyperplasia; if baseline level is equivocal, a rise following a short Synacthen test will confirm diagnosis);
  - testosterone/epitestosterone (T/E) ratio, if exogenous testosterone suspected.
- Blood tests in addition to androgen testing if the cycles are considered to be anovulatory:
  - prolactin levels;
  - thyroid function.
- Blood tests if acanthosis nigricans or insulin resistance suspected:

  - SHBG (low in insulin resistance);
  - 2-hour glucose and insulin levels after a 75 g glucose load (glucose tolerance test).
- Blood tests if an ovarian tumour is suspected:
  - ovarian tumour markers – CA-125, inhibin, and Müllerian-inhibiting substances (sex cord tumours).
- Tests if excessive cortisol secretion (Cushing's syndrome) is suspected:
  - single-dose overnight dexamethasone test: initial test of choice;
  - confirm an abnormal result with a 24-hour urinary free cortisol excretion.
- Transvaginal ultrasound scan of ovaries:
  - polycystic ovary pattern;
  - ovarian tumour or cysts.
- Computed tomography is preferable as it gives better resolution than magnetic resonance imaging, if an adrenal tumour is suspected.
- Retrograde venous catheterisation may be required to determine the location (ovary vs. adrenal) and site (left vs. right) of the excess hormone production.

Treatment

The treatment of idiopathic or PCOS-related hirsutism (once other causes have been excluded) depends on the woman's lifestyle choices and current fertility wishes. Many patients with idiopathic hirsutism whose self-esteem is not affected will be satisfied with simple reassurance. In PCOS, a 5 per cent reduction in weight will restore ovarian cycle and androgen balance in the majority of patients,[6] and while this will not reverse terminal hairs back to vellus, it will prevent any new transformation. Bleaching, shaving, chemical washes, and mechanical depilation will physically remove unwanted hairs; laser therapy is expensive but permanent.

The combined oral contraceptive pill is the first-line medical treatment, reducing ovarian androgen production and increasing SHBG, further reducing free circulating androgens. The more recent progestogens cyproterone acetate (Dianette®) and drosperinone (Yasmin®) have anti-androgenic effects and are most effective; however, they carry a higher risk of venous thromboembolism compared to earlier generation pills. Aldosterone antagonist spironolactone and androgen antagonist flutamide compete with circulating androgens and are second- and third-line options. Finasteride (a 5a reductase inhibitor reducing peripheral conversion of testosterone to dihydrotestosterone) has also been used. All three reduce libido and cause feminisation of a male fetus, and therefore careful contraception is crucial.

Other options include eflornithine (Vaniqa®), which inhibits ornithine decarboxylase at the hair follicle and thus preventing growth. If it has no effect after three months, it should be discontinued, and it may cause rash or worsen acne. Finally, metformin improves peripheral insulin sensitivity and has been shown to have a role, although studies disagree over its benefits in specifically treating hirsutism.

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Further reading

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HOT FLUSHES

Matthew Toal

Hot flushes of varying severity are common in women leading up to and during their menopause. However, it is important to remain aware of the other causes of flushing. Reviewing the differential diagnosis will help in detecting other 'red flag' conditions and avoid inappropriate administration of hormone

replacement therapy (HRT) in those where the aetiology is different.

Definition

Hot flushes are episodes of redness of the skin together with a sensation of warmth or burning moving down the body from the face, scalp, and neck, and less frequently, the upper trunk and abdomen. They may be associated with sweats, chills, or vasomotor symptoms such as palpitations. These attacks are transient, lasting between seconds to minutes, which differentiates them from the persistent erythema of photosensitivity or acute contact dermatitis. Repeated flushing over a period of time can lead to telangiectasia and occasionally to classical rosacea of the face.

A hot flush is associated with an increase in core body temperature and pulse rate. It is followed by a decline in temperature and profuse perspiration over the area of the flush distribution. Visible changes occur in about 50 per cent of women. The attacks may occur hourly or much less frequently.

Differential diagnosis of hot flushes

1. *Physiological flushing* is associated with anger, embarrassment, drinking warm beverages, or being in a warm room temperature.
2. *Menopausal flushing* due to the increased pulsatile secretion of follicle-stimulating hormone (FSH) causing peripheral vasodilation of the skin.
3. Flushing as a symptom of an *underlying systemic disorder*, including:
   - Hyperthyroidism.
   - Phaeochromocytoma.
   - Carcinoid tumours.
   - Pancreatic cell tumours – insulinoma and VIPoma (a pancreatic endocrine tumour producing vasoactive intestinal peptide [VIP]).
   - Mastocytomas – benign proliferative disorders of the reticuloendothelial system owing to a hyperplastic rather than a neoplastic process. This condition may be associated with headache, shortness of breath, wheezing, palpitations, abdominal pain, diarrhoea, and syncope. This type of flushing lasts more than 30 minutes, unlike the carcinoid or menopausal flush, which lasts less than 10 minutes.
   - Paraneoplastic syndrome.
   - Diabetes.
   - Tuberculosis.
   - Anxiety disorders.
4. *Gustatory flushing* – associated with the consumption of alcohol, hot beverages, and spicy or sour foods; and additives such as monosodium glutamate, sodium nitrate, nitrites or sulphites. Rarely, this type of flushing can be associated with scombroid food poisoning from ingesting spoiled or decaying mackerel or tuna.
5. *Drug-associated flushes* are associated with:
   - Vasodilators – nitroglycerine, prostaglandins.
   - Calcium channel blockers.
   - Nicotinic acid.
   - Selective serotonin reuptake inhibitors.
   - Cholinergic drugs (metrifonate, antihelminthic drugs).
   - Cephalosporins.
   - Anti-oestrogens such as tamoxifen and clomiphene.
   - Danazol.
   - 4-Hydoxyandrostenedione.
   - Luteinising hormone-releasing hormone agonists or antagonists.
   - Aromatase inhibitors.
   - Niacin.
   - Chlorpropamide.
   - Glucocorticoids.
   - Cortisol/corticotrophin-releasing hormone.
   - Bromocriptine.
   - Thyrotrophin-releasing hormone.
   - Rifampicin.
   - Doxorubicin.
   - Cyclosporine.
   - Sildenafil citrate.
   - Opioids.
6. Flushing reactions *associated with alcohol*:
   - Drugs
     - disulfiram.
     - chlorpropamide.
     - phentolamine.
     - griseofulvin.
     - metronidazole.
     - ketoconazole.
     - chloramphenicol.
     - quinacrine.
     - cephalosporins.
   - Eating *Coprinus* species of mushrooms.
   - Fermented alcoholic beverages (beer, sherry) that may contain tyramine or histamine.
   - Occupational 'degreaser's' flush in consuming alcohol following exposure to industrial solvents (trichloroethylene vapour, carbon disulphide, xylene, etc.).
   - Genetic susceptibility in Asian populations.
7. *Dumping syndrome* usually following gastric outflow surgery.
8. Frey's syndrome – auriculotemporal nerve syndrome following parotid surgery, trauma, infection, or facial herpes zoster.
9. *Harlequin syndrome* – hemifacial flushing and sweating with or without warmth and anhidrosis of the contralateral limbs. It may be associated with lung cancer and Pancoast syndrome, which is an apical tumour affecting

the adjacent anatomical structures and can cause a Horner's syndrome.

10 *Neurological flushing:*
- Spinal cord injury.
- Migraine.
- Parkinson's disease.
- Brain tumours – due to a rise in intracranial pressure.
- Cholinergic erythema.

11 *Familial monoamine oxidase* (MAO) deficiency.

Diagnostic approach to a patient with hot flushes

A diagnostic approach to hot flushes should be similar to how one would assess a patient's experience of pain. The character of the flushing and its frequency, severity, and location help to determine the impact on a patient's life. It is always important to assess the symptoms in the context a patient's quality of life and how the symptoms impact on her everyday activities. Whether the flushing is patchy or confluent in distribution will help to distinguish the symptoms of menopausal hot flushing from other dermatological causes such as dermatitis.

Identification of exacerbating or relieving factors may help to develop strategies to better manage and avoid causes of flushing. In particular, avoidance of certain foods can reduce carcinoid flushing and avoidance of alcohol can reduce flushing secondary to mastocytosis and medullary thyroid carcinoma. A useful diagnostic for identifying causative agents would be to get the patient to complete a 2-week food diary to determine whether certain foods cause symptoms. This can then be followed by a trial period of exclusion of suspected foods to see whether symptoms resolve.

Seeking out associated symptoms is also useful. Sweating and palpitations occur with menopausal hot flushes. Cardio-respiratory symptoms such as shortness of breath, chest pain, and hypertension and gastrointestinal symptoms such as nausea, vomiting, and diarrhoea, as well as other symptoms such as headache, urticarial, and facial oedema, do not occur with menopausal hot flushes and should warrant further investigations of other differentials.

Diagnostic or metabolic work-up

- FSH values of >10 IU/L are indicative of declining ovarian reserve. FSH values >20 IU/L are suggestive of menopause in the perimenopausal age group in the absence of menstruation.
- Prolactin: hyperprolactinaemia is a cause of cessation of menstruation.
- LH values >30 UI/L are found 1–3 years after cessation of menstruation.
- Urinary 5-hydroxyindoleacetic acid (5-HIAA) values above 30 mg/24 hours (normal range in 24 hours is 2–10 mg) are confirmatory of carcinoid except in those who have an inability to convert serotonin to HIAA.
- Serotonin: values raised in carcinoid syndrome. However, it is important to ensure the patient has had a diet free of substances that may compound these results prior to testing.
- Chromogranin-A, substance P, and neurokinin A are other tests useful in identifying the non-endocrine causes of flushing, though not requested by a general gynaecologist.

Management of hot flushes

Lifestyle measures

Adopting certain lifestyle changes may help decrease the severity of hot flushes and a woman's ability to cope with its inconvenience. It is recommended that all women be counselled regarding these changes, including:

- taking regular exercise;
- avoidance of triggering factors such as caffeine, alcohol, spicy foods and hot beverages;
- avoidance of smoking;
- avoidance of stressful situations;
- sleeping in a cooler room;
- drinking cold drinks, bathing in cool water, using fans, using cotton sheets and dressing in lighter clothing;
- aiming for a BMI of <30 kg/m^2.

Non-pharmacological measures

- Behavioural interventions.
- Relaxation therapies – meditation, yoga and massage.
- Cognitive behavioural intervention and diversion techniques.
- Progressive muscle relaxation, or biofeedback or applied relaxation.
- Hypnosis.
- Acupuncture.
- Deep breathing – paced abdominal respiration and muscle contraction relaxation of all muscle groups.

Pharmacological measures

Once the underlying cause of hot flushes has been identified, the use of pharmacological measures to control the symptoms can be considered. Hot flushes will eventually abate even without treatment.

The difficulty is in not being able to predict when this will occur. Hence, the type of treatment is guided by the severity of the symptoms and the impact this has on a patient's quality of life.

1. If symptoms are mild, then lifestyle modifications should be the mainstay of treatment. Vitamin E supplementation may be considered in addition.
2. If symptoms are more severe, then HRT may be considered if appropriate and there are no absolute contraindications.
3. If the patient is unwilling to commence HRT or is unresponsive after a 3-month trial, then the following may be considered:
   - 2-week trial of paroxetine (20 mg OD), fluoxetine (20 mg OD), citalopram (20 mg OD), or venlafaxine (37.5 mg BD);
   - 2–4-week trial of clonidine (50–75 µg BD);
   - progestogen, such as norethisterone or megestrol – seek specialist advice if this is considered.
4. NICE does not recommend the use of herbal or complementary therapies (for example, soy, red clover, or black cohosh). If complementary therapies are being used, the patient should be advised that:
   - the efficacy of these products it not yet established;
   - there is very little control over the quality of these products;
   - some of the products (such as ginseng, black cohosh, and red clover) have oestrogenic properties and should not be used by women with contraindications to exogenous oestrogens;
   - the long-term safety of these products has not been tested;
   - some products may be dangerous (such as liver toxicity with black cohosh and kava);
   - dong quai extracts and some species of red clover contain coumarins, which make them unsuitable for women on anticoagulants.

Websites

http://cks.nice.org.uk/menopause#!scenariorecommendation:45

http://www.nhs.uk/Conditions/Menopause/Pages/Selfhelp.aspx

http://www.rcog.org.uk/files/rcog-corp/uploaded-files/SIP_No_6.pdf

http://www.rcog.org.uk/womens-health/clinical-guidance/menopause-and-hormone-replacement-study-group-statement

HYDROPS FETALIS

Mala Arora and Win Win Khine

Hydrops fetalis refers to the presence of two or more of the following abnormal fetal fluid collections (Figs 1–3):

- ascites;
- pleural effusion;
- pericardial effusion;

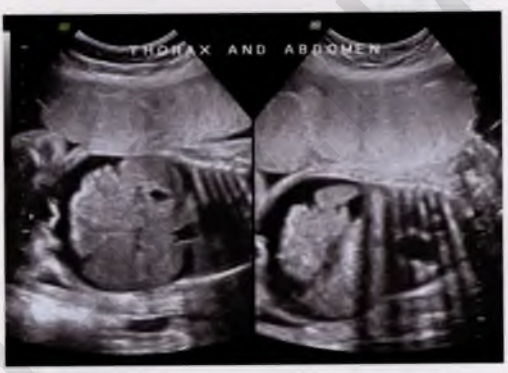

Figure 1 Hydrops fetalis.

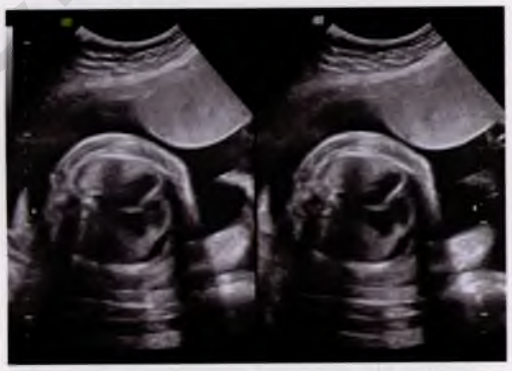

Figure 2 Fetal hydrothorax.

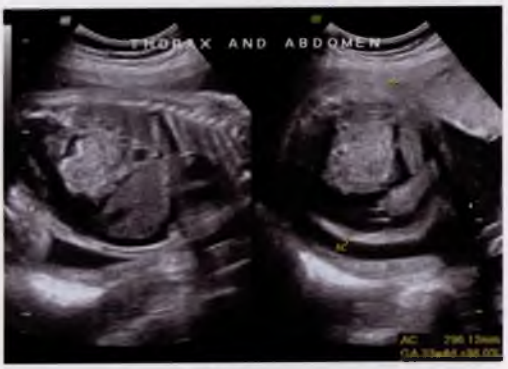

Figure 3 Transverse and sagittal ultrasound scan pictures of fetal ascites.

- skin oedema;
- polyhydramnios.

The condition is subdivided into immune and non-immune hydrops. Immune hydrops is caused by red cell antibodies (red cell alloimmunisation). Non-immune hydrops fetalis (NIHF) comprises the subgroup of cases not caused by red cell alloimmunisation.

The immune hydrops is more common in developing countries, while the non-immune variety is more common in developed countries.[1]

Mirror syndrome (Ballantyne's syndrome)

This refers to a condition of generalised maternal oedema often with pulmonary involvement that mirrors the oedema of the hydrops fetus and placenta. Although it is usually associated with non-immune hydrops fetalis, it can also occur in any immune hydrops. Mirror syndrome can occur at any time during the antenatal period and may persist postpartum, which can be life threatening. However, intervention that results in reversal of fetal hydrops can also reverse the maternal disorder. Spontaneous resolution of mirror syndrome may occur after spontaneous resolution of fetal hydrops related to parvovirus B19 and after fetal death.[2]

Immune hydrops

The best-studied immunological cause of hydrops fetalis is pregnancy with rhesus positive fetus in a rhesus negative mother who is already sensitised by either a previous pregnancy or blood transfusion. The immunoglobulin G (IgG) antibodies to the rhesus-positive red blood cells (RBCs) cross the placenta and destroy the fetal RBCs, leading to fetal anaemia and hydrops. This was first reported by Levine in 1941.[3] The first pregnancy proceeds normally, as the rhesus-negative mother is not sensitised. Fetomaternal haemorrhage occurs at placental separation and sensitises the mother.

Other procedures during pregnancy that can sensitise the mother are abruptio placentae, external cephalic version, and amniocentesis. In subsequent pregnancies, the fetal red cells are destroyed by the maternal IgG antibody that can cross the placenta. In mild cases, the fetus has anaemia and haemolytic disease of the newborn, but in severe cases it develops hydrops fetalis. If the antibody titres are high, hydrops will manifest at an earlier gestation.

Rhesus (Rh) immunoglobulin was introduced in 1966. Widespread use of Rh-D immunoglobulin has dramatically decreased the prevalence of Rh-D alloimmunisation and associated hydrops. As a result NIHF now accounts for almost 90 per cent of hydrops cases in developed countries. However, rhesus isoimmunisation continues to be the single most common cause of immune hydrops fetalis in developing countries.

Non-invasive fetal genotyping using maternal blood (cell-free fetal DNA) is now possible for D, C, c, E, e, and K antigens. This should be performed in the first instance for the relevant antigen when maternal red cell antibodies are present. For other antigens, invasive testing (chorionic villous sampling, CVS, or amniocentesis) may be considered if fetal anaemia is a concern or if invasive testing is performed for another reason (e.g. karyotyping).[4]

The risk of fetal anaemia is greatest with anti-D, anti-c, and anti-K. Other antibodies that potentially cause significant fetal anaemia include anti-E, -Fy, -JK, -C, and -Ce.[4]

Non-invasive Doppler ultrasonographic assessment of the peak velocity of systolic blood flow in the middle cerebral artery (MCA PSV) can predict severe fetal anaemia. If MCA PSV rises above the 1.5 multiples of median (MoM) threshold or if there are other signs of fetal anaemia, referral should be made to a fetal medicine specialist with expertise in *in-utero* blood transfusion.[4]

In the UK, all pregnant women are screened for blood group disorders at the time of booking and at 28 weeks' gestation.[4] Anti-D immunoglobulin is given to RhD-negative women with non-anti-D antibodies for routine antenatal immunoprophylaxis at 28 weeks, for potential antenatal sensitising events and postnatal prophylaxis. Once significant antibodies are detected, levels should be measured every 4 weeks up to 28 weeks of gestation and then every 2 weeks until delivery.[4]

Non-immune hydrops fetalis

The incidence of NIHF is 1/1500 to 1/3800 births. NIHF carries a higher fetal mortality rate (see Box 1).[5]

Examinations for the differential diagnosis include:

- serum screening of the mother based on previous obstetric history, ethnic background, family history of heritable disorders, and recent exposure to infectious agent;
- detailed ultrasound examination to look for fetal structural abnormalities; a fetal echocardiogram is useful

Box 1 Causes of non-immune hydrops fetalis

Chromosomal
- Down's syndrome and other trisomies
- Turner syndrome
- Mosaicism
- Translocation 18q+, 13q–
- Duplicated 11p
- Triploidy

Cardiovascular
- Structural anomalies
- Arrhythmia
- High output failure

Haematologic
- Alpha thalassaemia
- Arteriovenous shunts
- In utero haemorrhage
- Glucose-6-phosphate dehydrogenase deficiency
- Pyruvate kinase deficiency
- Red cell enzyme deficiencies
- Red cell aplasia
- Thrombosis of major vessels
- Congenital leukaemia

Infections
- Parvovirus
- TORCH pathogens (toxoplasma, rubella, cytomegalovirus, herpes)
- Syphilis
- Varicella
- Adenovirus
- Coxsackie virus
- Leptospirosis
- Listeria
- *Trypanosoma cruzi*

Chondrodysplasias
- Thanatophoric dysplasia
- Osteogenesis imperfecta
- Achondrogenesis
- Hypophosphatasia
- Campomelic dysplasia
- Lethal chondroplasia

Twin pregnancy
- Twin-to-twin transfusion syndrome
- Acardiac twin

Thoracic
- Congenital cystic adenomatoid malformation of lung
- Diaphragmatic hernia
- Intrathoracic mass
- Pulmonary sequestration
- Chylothorax
- Pulmonary lymphangiectasia
- Pulmonary neoplasia
- Bronchial cyst

Malformation and genetic syndrome
- Congenital lymphoedema, e.g. Noonan's syndrome
- Arthrogryposis
- Myotonic dystrophy
- Fanconi's syndrome, type III

Metabolic
- Gaucher's disease
- GM1 gangliosidosis
- Hurler syndrome
- Mucopolysaccharide (MPS) IVa
- Mucolipidosis types I + II
- Sialidosis
- Galactosialidosis

Gastrointestinal
- Midgut volvulus
- Malrotation of intestines
- Meconium peritonitis
- Hepatic fibrosis
- Cholestasis/biliary atresia
- Hepatitis/hepatic necrosis
- Hepatic vascular malformation
- Liver tumours or cysts

Genitourinary
- Urethral atresia or stenosis
- Posterior urethral valve
- Congenital nephrosis (Finnish type)
- Prune belly syndrome

if there is any suspicion of a cardiac abnormality or arrhythmia;
- determining fetal karyotype and genetic microarray molecular testing (chorionic villous sampling, amniocentesis, or fetal blood sampling).

The cause of hydrops can be determined antenatally in 50–85 per cent of cases, most of the remaining cases are determined postnatally, although 5–8 per cent are classified as idiopathic, even after an autopsy.

Chromosomal

Aneuploidy is responsible for approximately 10 per cent of NIHF. The most common chromosomal cause is monosomy X (XO, Turner's), which accounts for 42–67 per cent; 23–30 per cent of cases were caused by trisomy 21 (Down's), and 10 per cent were trisomy 13 (Patau) and 18 (Edwards). The mechanism for fluid collection in these fetuses may involve obstruction or incomplete formation of the lymphatic system in the neck or abdomen, leading to lymphatic dysplasia. Other mechanisms include cardiac failure related to associated congenital heart disease (15–20 per cent of aneuploid fetuses).[6]

The prognosis is poor, with a mortality rate approaching 100 per cent.[7]

Cardiovascular

Abnormalities of the cardiovascular system are responsible for as many as 40 per cent of NIHF. Numerous causes have been implicated.[6]

The three major subgroups are as follows.

Structural anomalies

The most commonly accounted cardiac lesions associated with hydrops are atrioventricular septal defect (AVSD), hypoplastic left and right heart, an isolated ventricular or atrial septal defects.[8]

Other less common anomalies include tetralogy of Fallot and premature closure of the ductus arteriosis.[8] Many of these lesions are also associated with aneuploidy. Most structural lesions are not amenable to in-utero therapy. If the hydrops is early onset, the prognosis for these pregnancies is poor, with mortality rates close to 100 per cent. Patients should be offered genetic counselling, as recurrent risk of congenital heart defects is as high as 2–5 per cent.[7]

Arrhythmias

Both tachy- and bradyarrhythmias can lead to hydrops.

High output cardiac failure (arteriovenous malformations or venous malformations)

Neuroblastoma, sacrococcygeal teratoma, large fetal angioma, placental chorioangioma, cardiac tumours, and cardiomyopathy can cause high output failure. Endocardial fibroelastosis has been reported with thickening of the endocardium in response to chronic prenatal myocardial stress.[6]

Haematologic

Fetal anaemia accounts to 10–27 per cent of hydrops. There are a variety of possible causes, including haemorrhage, haemolysis, defective RBC production, and production of abnormal haemoglobins (Hb). The mechanism of hydrops is thought to be high output failure.

Alpha thalassaemia major is the most common cause of NIHF among southeast Asians. A Hb electrophoresis of fetal blood will show greater than 80 per cent of Hb Barts, which is a non-functioning Hb. Hb Barts binds oxygen but cannot release it to the tissues because its affinity to oxygen is greater than that of Hb A. Profound acidosis and hydrops develop early in the mid trimester, followed by intrauterine fetal demise.[6,9]

Infection

Infections are responsible for 8 per cent of NIHF.

Parvovirus B19 is the most common infection associated with hydrops.[10–14] This virus attacks fetal RBC, hepatocytes, and myocardial cells, causing transient aplastic crisis, hepatitis, and myocarditis. Since these processes are self-limited, the prognosis is generally good if the fetus is supported by intrauterine blood transfusion until the disease remits.

B19 viraemia begins approximately 6 days after exposure and lasts for 1 week in immuno-competent individuals. An infected person is contagious before the onset of symptoms. Patients with normal immune system probably are not infectious after the onset of rash, arthralgias, or arthritis.

Individuals with B19 IgG generally are considered immune to recurrent infection. However, if they become viraemic, reinfection is possible.

Negative IgG and positive IgM result indicate recent infection. However since the viraemia is transient and the hydrops may develop 3–12 weeks after maternal infection, the serology may be unhelpful. In these cases the presence of virus can be confirmed by polymerase chain reaction (PCR) studies on the amniotic fluid.

The largest prospective study of B19 infection in 1018 pregnant women reported that the risk of fetal loss in pregnancies infected before and after 20 weeks of gestation is 11 per cent and 1 per cent respectively.

Three other studies suggest that the B19 infection in late trimester has a very low fetal death rate.

In contrast, the development of fetal hydrops with a TORCH infection (see Box 1) involves multisystem failure and is a poor prognostic indicator.

Therapy in these cases is directed toward the infectious agents.

Twin pregnancy

Monochorionic twin pregnancies are at risk for twin-to-twin transfusion syndrome and twin reversed arterial perfusion (TRAP). Hydrops may develop in one or both twins.

Thoracic abnormalities

These abnormalities account for up to 10 per cent of hydrops. These lesions increase intrathoracic pressure and can obstruct venous return to heart, leading to peripheral venous congestion, or they may obstruct the lymphatic duct, resulting in lymphoedema.[6]

The prognosis depends on the gestational age at the time of lung lesion developed. The presence of a pleural effusion prior to 20 weeks can compromise lung growth and function and have a poor prognosis.

Gastrointestinal malformation

Ascites and polyhydramnios are characteristically observed with these disorders. More widespread oedema may be present when the fetus is aneuploid. The prognosis is dependent upon the karyotype and the presence of other associated disorders such as cystic fibrosis.[6,7]

Genitourinary malformation

Abnormalities of the genitourinary tract represent a very small proportion of NIHF. Disorders such as posterior urethral valves leading to prune belly syndrome may cause intra-abdominal obstruction of venous return. Congenital Finnish-type nephrosis leads to hypoproteinaemia and decreased oncotic pressure, which in turn causes peripheral oedema.[6]

Inborn errors of metabolism

These are rare enzyme disorders that lead to defective metabolism. The most common disorder described is recurrent fetal hydrops in mucopolysaccharidosis type VII, in which there is a deficiency of the enzyme beta glucuronidase. Other disorders are listed in Box 1. The prognosis in all such fetuses is poor.[15,16]

Idiopathic

In spite of extensive investigations after cordocentesis, the cause of fetal hydrops may not be diagnosed in up to 15 per cent of cases. There are accounts where no diagnosis can be made, which makes counselling the parents extremely difficult.[5,6]

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Useful websites

http://www.rcog.org.uk/guidelines
http://www.uptodate.com

HYPERTENSIVE DISORDERS OF PREGNANCY

Peter Muller and Anwen Gorry

Hypertensive disorders in pregnancy are the most common medical problems in pregnancy. They are an important cause of morbidity and mortality, both to the mother and fetus, occurring in 12–22 percent of all pregnancies. The last Confidential Enquiry into Maternal Deaths[1] showed that 22 women died of eclampsia or pre-eclampsia, giving a mortality rate of 0.83 per 100,000 maternities. This was the second most common cause of direct maternal death in this triennia. The UK Obstetric Surveillance System from 2005 and 2006 gives an estimated incidence of eclampsia of 27.5 cases per 100,000 maternities.

Hypertensive disorders in pregnancy are classified as:

- chronic hypertension;
- gestational hypertension;
- pre-eclampsia/eclampsia.

Blood pressure measurement

Gestational age dependent

Blood pressure in pregnancy starts to decrease as early as the seventh week of pregnancy[2] because of peripheral vasodilatation, and it reaches its nadir in the second trimester. Maternal blood pressure gradually returns to pre-pregnancy levels by the third trimester. There is a fall immediately post-delivery and a gradual increase over the first 5 postnatal days. This pattern must be considered when interpreting any changes in blood pressure occurring during the pregnancy.

Position

Blood pressure readings should not be taken in the supine position. In the outpatient setting, the patient should be sitting upright or at 45 degrees. In a hospital setting, blood pressure may be taken in the left arm while in the lateral recumbent position, ensuring that the arm is at the level of the heart.

Cuff size

The appropriate size cuff can be determined by using a cuff length at least 1.5 times the upper arm circumference or the cuff bladder encircling 80 per cent or more of the arm. Others suggest using a large cuff when the upper arm circumference is greater than 33 cm.

Korotkoff sounds

The diastolic pressure recorded is the level at which the sound disappears (Korotkoff phase V).[3]

Chronic hypertension

This is diagnosed when a woman is already taking anti-hypertensives at booking, or is found to have a blood pressure of greater than 140/90 mmHg at booking or prior to 20 weeks' gestation. It can be primary ('essential') or secondary to other causes. It should not be presumed to be primary until other causes (endocrine, renal, cardiac, etc.) have been excluded.

Any teratogenic medications should be stopped prior to or on discovering pregnancy and changed to an appropriate antihypertensive; labetalol is first line. The target blood pressure should be <150/100 or <140/90 if there is already end-organ damage.

The chance of developing superimposed pre-eclampsia on a background of chronic hypertension is up to 20–25 per cent.[4] If there is no superimposed pre-eclampsia, then delivery should occur after 37 weeks and be scheduled according to consultation between mother and obstetrician.[5,6]

Gestatational hypertension

This is new hypertension presenting after 20 weeks gestation without significant proteinuria. It should resolve within 3 months of delivery. Perinatal and maternal complications are generally low with gestational hypertension. However, gestational hypertension diagnosed prior to 30 weeks progresses to

pre-eclampsia in approximately 40 per cent of cases. This incidence falls to 10 per cent when gestational hypertension is found after the 37th week.[7]

Diligent surveillance of both mother and fetus is required when non-proteinuric hypertension is discovered in pregnancy regardless of the gestation because of the risk of progression to pre-eclampsia.

Treatment of hypertension should be commenced if blood pressure is ≥150/100, with the first line being labetalol. There is no indication for delivering the fetus prior to 37 weeks if the blood pressure is well controlled. After this time, delivery is based on clinical circumstances.

Pre-eclampsia/eclampsia

This is new hypertension presenting after 20 weeks' gestation together with the presence of significant proteinuria. If there are associated seizures with no other attributable cause, this is eclampsia. More than 30% of seizures occur postnatally, so women developing pre-eclampsia in the antenatal period also require close postnatal surveillance.

The aetiology of pre-eclampsia is multifactorial and poorly understood. It certainly has a genetic component with significantly increased risk in first-degree relatives. The primary pathology seems to be placental in nature, with poor placentation in the first and second trimesters leading to placental ischaemia. There is a maternal inflammatory response with endothelial dysfunction, increased capillary permeability, and microvascular vasoconstriction.

Hypertension

- Mild hypertension: diastolic 90–99 mmHg, systolic 140–149 mmHg.
- Moderate hypertension: diastolic 100–109 mmHg, systolic 150–159 mmHg.
- Severe hypertension: diastolic ≥110 mmHg, systolic ≥160 mmHg.

Proteinuria

Significant proteinuria is defined as ≥300 mg protein/24 h or a spot protein/creatinine ratio (PCR) of ≥30 mg/mmol. Bedside urine dipsticks for protein can be used for screening in the antenatal clinic or community, but a random urine dipstick of 1+ or greater requires quantification with either a urine PCR or 24-hour collection. While the 24-h urinary protein analysis has traditionally been the gold standard for the diagnosis of significant proteinuria, spot protein/creatinine ratio has shown correlation to the 24-h study[8,9] and results can be obtained much more quickly.

Symptoms and signs

Symptoms and signs can be vague and non-specific but may include:

- oedema (classically non-dependent – face/hands);
- headache;
- visual disturbance and 'flashing lights';
- epigastric or right upper quadrant pain;
- vomiting;
- shortness of breath (pulmonary oedema);
- hyper-reflexia and multiple beats of clonus;
- oliguria;
- papilloedema (cerebral oedema);
- neurological symptoms secondary to haemorrhagic or thrombotic stroke;
- seizure (eclampsia) – usually a self-limiting grand-mal seizure;
- signs of fetal compromise including reduced movements, reduced symphysio-fundal height, placental abruption and in-utero death.

It is important to remember that some of these symptoms are common in pregnancy and may have other causes; however, a high index of suspicion should always be maintained. Equally, it is not uncommon that a woman's first presentation may be with an eclamptic seizure, with having had no features of the disease previously.

Investigations

In addition to quantifying the urinary protein, the following investigations may be helpful.[10]

Biochemical investigations

- Elevated serum urate – traditionally used to aid diagnosis, although levels correlate only weakly with severity of disease.[11,12]
- Elevated haemoglobin and haematocrit levels – suggestive of haemoconcentration.
- Elevated serum creatinine – which is normally low in pregnancy.
- Falling platelet count – may be a feature of HELLP syndrome with evidence of haemolysis.
- Liver function abnormalities – particularly elevated transaminases.
- Lactate dehydrogenase elevation – suggestive of haemolysis.

Fetal investigations

- Fetal heart rate monitoring – may show signs of acute compromise.

- Fetal ultrasound – may show signs of chronic placental dysfunction:
  - growth restriction;
  - reduced liquor volume;
  - abnormal fetal Dopplers (umbilical artery, middle cerebral artery, and ductus venosus).

Management of pre-eclampsia

The definitive cure for pre-eclampsia is delivery of the fetus and placenta. The challenge involves balancing the risks of continuation of the pregnancy to both the mother and the fetus against the risks of prematurity to the fetus. Ultimately maternal well-being supersedes fetal rights, and in very severe cases delivery may be warranted with the knowledge that the fetus is non-viable. Once 37 weeks' gestation is reached, delivery is recommended even if pre-eclampsia is mild.

Once the diagnosis of pre-eclampsia is made, an assessment of the severity of the disease must be carried out. If the pre-eclampsia is felt to be mild, then a senior clinician may consider allowing careful out-patient management, with frequent surveillance via day assessment units; however, in most cases the diagnosis of pre-eclampsia warrants in-patient care.

Management involves the following.

Blood pressure control

- Pharmacological treatment is warranted if the blood pressure is greater than 150/100 mmHg.
- If systolic blood pressure is >160 mmHg there is significantly increased risk of stroke.
- First line treatment is labetalol (oral or intravenous).
- Nifedipine or methyldopa may be considered.
- Hydralizine can be used if blood pressure is very high but use with care as it can cause acute hypotension.

Seizure treatment/prophylaxis[13]

- Magnesium sulphate:
  - bolus of 4 g followed by 1 g/hour for 24 hours;
  - recurrent seizures can have a repeat bolus of 2–4 g.
- Consider prophylaxis if there are features of severe pre-eclampsia:
  - severe hypertension;
  - severe headache/ visual disturbance/papilloedema;
  - severe epigastric pain;
  - clonus (≥3 beats);
  - hepatic tenderness;
  - HELLP syndrome;
  - very abnormal biochemistry.

Supportive treatment

- Multidisciplinary care:
  - Support from senior obstetricians, anaesthetists, and intensivists may be required;
  - Level of care depends on severity of disease – Level 1, 2, or 3.
- Fluid balance:
  - in severe pre-eclampsia;
  - to reduce the risk of pulmonary oedema reduce fluid intake to 80 mL/hour and monitor urine output;
  - invasive monitoring may be required.

Corticosteroids for fetal lung maturation

- If pre-term and delivery is anticipated within 7 days.

Delivery

- Mode of delivery depends upon clinical situation and parent's wishes.
- Consider parity and Bishop's score.
- If there is concurrent fetal growth restriction, particularly in the presence of abnormal fetal Dopplers, then delivery by caesarean section may be preferred,
- If attempting vaginal delivery, then continuous fetal heart rate monitoring should be in place.
- Unless the blood pressure is very poorly controlled, there is no need to limit the second stage of labour.

HELLP syndrome

Haemolysis, elevated liver enzymes, and low platelets is part of the spectrum of pre-eclamptic disease, occurring in 2–12 per cent of patients with pre-eclampsia. It is characterised by:

- haemolysis;
- abnormal peripheral blood smear;
- elevated transaminases;
- raised serum bilirubin;
- raised lactate dehydrogenase (usually >600 IU/L);
- thrombocytopaenia (usually <100,000/mm^3).

Management is as per management of severe pre-eclampsia and is supportive.

Prevention of pre-eclampsia

All women should be risk assessed at their booking appointment as to their likelihood of developing pre-eclampsia. If they have one high-risk factor or two or more moderate risk factors, then they should be started on low-dose aspirin (75 mg), as this is only measure that has been shown to improve outcome.

High-risk factors

- Chronic hypertension.
- Chronic renal disease.
- Previous pregnancy affected by hypertensive disease.
- Type 1 or Type 2 diabetes.
- Chronic autoimmune conditions, including systemic lupus erythematosus (SLE) and antiphospholipid syndrome.

Moderate-risk factors

- Primigravida.
- Pregnancy interval >10 years.
- Multiple pregnancy.
- Maternal age >40 years.
- Body mass index >35.
- Family history of pre-eclampsia in first-degree relative.

Uterine artery dopplers

Consider offering a uterine artery Doppler scan at 23 weeks' gestation to patients deemed at high risk of developing pre-eclampsia. The results of this will allow further risk assessment as to how likely the mother is to develop pre-eclampsia and how likely the fetus is to develop growth restriction.[14] Ongoing antenatal care can be tailored based on the result of this scan.

Differential diagnosis

There are other disease processes that may mimic or even coincide with pre-eclampsia. Although the presentation can be similar, there may be subtle differences for each disease that will assist the clinician in instituting a specific treatment strategy.

Thrombotic thrombocytopenic purpura (TTP) and haemolytic-uraemic syndrome (HUS)

These two disease processes present with microangiopathic haemolytic anaemia (MHA) and severe thrombocytopenia, thus the confusion in relation to the HELLP syndrome.

Thrombotic thrombocytopenic purpura is commonly described as a pentad of findings: MHA, thrombocytopenia, neurological symptoms (headache, confusion, and seizures), fever, and renal dysfunction. However, the pentad presents in only 40 per cent of cases. The majority will usually present with MHA, thrombocytopenia, and neurological findings.[15]

Presentation in the mid-trimester should lead the clinician to suspect TTP. The haemolytic-uraemic syndrome (HUS) commonly presents postpartum with the characteristic acute renal disease, thrombocytopenia, and MHA.[16]

HUS is rare in adults but must be considered when the HELLP syndrome does not resolve in the first few days postpartum. Since these conditions can lead to rapid maternal deterioration, accurate diagnosis and early treatment is essential. Plasma exchange has been advocated as the first-line treatment in pregnancy.[17]

Acute fatty liver of pregnancy

Patients present, generally in the third trimester, with non-specific symptoms such as nausea, vomiting, headache, malaise, or abdominal pain. Some patients may describe symptoms suggestive of a viral illness. Physical and laboratory findings may include jaundice, hypertension, hypoglycaemia, hyperbilirubinaemia, coagulopathy, elevated creatinine, and elevated transaminases. Compared to the HELLP syndrome, proteinuria is less commonly present. Transaminases are elevated to the levels seen in the HELLP syndrome, but not commonly to those levels seen in acute viral hepatitis. Liver biopsy can be diagnostic, but is infrequently required for the diagnosis. (See Jaundice and liver disease in pregnancy.)

Systemic lupus erythematosus (SLE)

Systemic lupus erythematosus (SLE) is more common in women of reproductive age.[18] This may present for the first time in pregnancy. SLE may manifest itself with renal, haematological, or neurological alterations. Hypertension is common in association with renal dysfunction, making distinguishing it from pre-eclampsia difficult in early gestations. Evidence of dermatologic (malar or discoid rash) and arthritic complaints in conjunction with the other clinical findings, as well as an atypical presentation for pre-eclampsia, will commonly suggest this alternative diagnosis. A high titre of antinuclear antibodies and positive autoantibodies to double-stranded DNA will allow the clinician to suspect the diagnosis further. The diagnosis of SLE is based on clinical and laboratory criteria.[19]

Acute renal disease

An atypical presentation of acute renal insufficiency and hypertension should lead the clinician to include acute renal disease in the differential diagnosis of hypertension in pregnancy. The differential diagnosis of acute renal failure should be divided into three categories: pre-renal, intrinsic, and post-renal. Pre-renal failure may be secondary to hypovolaemia, such as from haemorrhage or increased vascular

resistance from non-steroidal anti-inflammatory drugs. Intrinsic renal disease may be from acute tubular necrosis or glomerulonephritis. Post-renal disease may be from bilateral urinary obstruction from the gravid uterus (especially in multiple pregnancy).

The clinician should review the clinical history of risk factors or exposures, consider a renal ultrasound for evidence of obstruction, determine the fractional excretion of sodium from urinary electrolytes, and review the urinary sediment for evidence of hyaline (pre-renal), renal tubular (acute tubular necrosis), or red-cell casts (glomerulonephritis).

Seizures

If a pregnant patient presents with a first seizure, it must be presumed to be eclampsia until proven otherwise. However, if the clinical features are not consistent with a pre-eclamptic pathology (that is, there is no hypertension, proteinuria, or additional biochemical features of the disease), then other causes must be considered. Electrolyte abnormalities and hypoglycaemia are easily diagnosed with initial biochemical screen. A first presentation of epilepsy may occur in pregnancy, as this diagnosis is often made in young women of reproductive age. Referral to a first seizure clinic under the care of neurologists is appropriate where additional investigations such as electro-encephalograms can be performed and where trials of anti-epileptics may be considered. Additionally, rarer causes of seizures must be considered. Intra-cranial imaging (usually magnetic resonance imaging (MRI) scan in pregnancy) must be carried out to exclude space-occupying lesions such as tumours and abscesses. The presence of cerebral venous sinus thrombosis usually presents with headache, but may present as a seizure. This is a rare but serious condition and must appear on the differential diagnosis list of any pregnant patient with unexplained seizure owing to the innate pro-thrombotic state of pregnancy. Investigation is with cranial magnetic resonance venography, and treatment is as per any venous thrombosis, with low-molecular-weight heparin and referral to haematology for investigation of any additional thrombophilias.

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Useful websites

www.NICE.org.uk/CG107
www.rcog.org.uk – Green-top Guidelines 10A

INCONTINENCE, FAECAL, AND PREGNANCY

Madura Jayawardane and Dilip Visvanathan

Faecal incontinence may be defined as 'any involuntary loss of faeces or flatus, or urge incontinence that adversely affects the quality of life'.[1] It is an embarrassing condition and therefore goes largely underreported. The prevalence of faecal incontinence on direct questioning of women before pregnancy, at 34 weeks' gestation, and after delivery was found to be 0.7 per cent, 6.0 per cent, and 5.5 per cent, respectively.[2] A multicentre study found that the prevalence of persistent faecal incontinence was 3.6 per cent.[3]

Faecal continence is maintained by the coordinated action of several anatomical and physiological elements. Continence depends on rectal sensation, capacity, and the anal sphincter strength (internal and external anal sphincters and the puborectalis muscle; see Fig. 2 in Birth injuries, maternal). These local factors are controlled by the cerebral cortex. Dysfunction of any of these components may lead to faecal incontinence. It is easy to appreciate that diarrhoea would make incontinence worse.

Incontinence may be passive (where the woman in unaware), urge (where it occurs despite active attempts to prevent it), and faecal soiling (staining of the underwear without much faecal material).

Box 1 Faecal continence scoring scale

0 Never
1 Rarely (<1/mo)
2 Sometimes (1/wk to 1/mo)
3 Usually (1/d to 1/wk)
4 Always (>1/d)

The severity of incontinence can be classified depending on the frequency of incontinent episodes (Box 1). However, the effect on the quality of life will also depend on the type (fully formed stool, liquid stool, or flatus) and volume of stool lost.

Causes of faecal incontinence

There are many causes of faecal incontinence and a complete classification is given in Box 2.[4] Advancing age and high body mass index (BMI) increase the risk. The commonest cause in women is considered to be sphincter injury as a result of childbirth.[4,5] Asian women are more likely to suffer sphincter injury compared with Caucasians and Afro-Caribbean women. The exact reason is unknown.

Damage may occur during childbirth in three ways:

Direct mechanical injury

Direct external or internal anal sphincter muscle disruption can occur in with a clinically obvious third- or fourth-degree perineal laceration, or as an occult injury subsequently noted on ultrasound scan of the anus.

Neurological injury

Neuropathy of the pudendal nerve may result from forceps delivery or persistent nerve compression from the fetal head.[6] Traction neuropathy may also occur with:

- fetal macrosomia;
- prolonged pushing during the second stage in successive pregnancies;
- prolonged stretching of the nerve owing to persistent poor tone of the pelvic floor postpartum.

Injured nerves often undergo demyelination but usually recover with time.

Box 2 Classification of the causes of faecal incontinence

Normal sphincters and pelvic floor

- Faecal impaction
- Causes of diarrhoea (e.g. infection, inflammatory bowel disease)
- Faecal fistula/colostomy

Abnormal sphincters and/or pelvic floor

Minor incontinence

Internal sphincter deficiency
- Previous surgery
- Rectal prolapse
- Third-degree haemorrhoids
- Idiopathic
- Minor denervation of external sphincter and pelvic floor

Major incontinence

Congenital anomalies of the anorectum

Trauma
- Iatrogenic
- Obstetric
- Fractures of the pelvis
- Impalement

Denervation
- Obstetric
- Rectal prolapse
- Peripheral neuropathy (e.g. diabetic mellitus)
- Cauda equina lesion (tumour or trauma)
- Tabes dorsalis (syphilis)
- Lumbar meningomyelocele (spina bifida)

Upper motor neuron lesion
- Cerebral
  - Multiple stroke
  - Metastases and other tumours
  - Trauma
  - Dementia and other degenerative disorders

Spinal
- Multiple sclerosis
- Metastases and other tumours
- Degenerative diseases (e.g. vitamin B12 deficiency)

Rectal carcinoma
- Anorectal infection (e.g. lymphogranuloma)
- Drug intoxication (particularly in the elderly)

Combined mechanical and neurological trauma

Neuropathy more commonly accompanies mechanical damage.

Box 3 Factors in pregnancy and delivery associated with faecal incontinence

- Nulliparity (primigravidity)
- Instrumental delivery, overall
- Forceps-assisted delivery
- Vacuum-assisted delivery
- Midline episiotomy
- Episiotomy, even mediolateral
- Prolonged second stage of labour
- Epidural analgesia
- Birth weight >4 kg
- Persistent occipitoposterior position
- Previous anal sphincter tear

Factors in childbirth contributing to faecal incontinence

These are summarised in Box 3. The most significant factors that cause sphincter damage include forceps delivery and a previous sphincter injury. A randomised control trial found clinical third-degree tears in 16 per cent of women with forceps-assisted deliveries, compared with 7 per cent of vacuum-assisted deliveries.[7]

Prevalence of anal symptoms

The prevalence of anal symptoms in women who have undergone third- and fourth-degree tear repair ranges from 25 to 57 per cent. In these studies, the type of incontinence is mainly of flatus (30 per cent) and leakage of liquid stool (8 per cent), while leakage of solid stool occurred in 4 per cent. Faecal urgency occurred in 26 per cent of women.[8]

Prevention

Avoiding obstetrical injury to the anal sphincter is the single biggest factor in preventing faecal incontinence among women. The strategies for prevention of this problem are outlined in Box 4.[9,10] Elective caesarean section appears to be the only preventive measure to avoid sphincter and pelvic floor damage; however, it has been reported that there was no reduction in the prevalence of persistent faecal incontinence in women following elective caesarean section when compared to a normal vaginal delivery.

Box 4 Strategies for preventing sphincter damage at childbirth

Primary prevention

- Spontaneous over instrumental vaginal delivery
- Vacuum extraction over forceps delivery
- Restrictive use of episiotomy
- Mediolateral episiotomy over medial episiotomy
- Antepartum pelvic floor exercises and antepartum perineal massage
- Consider caesarean section

Secondary prevention

- Early detection and proper repair of perineal injury

Tertiary prevention

- Consider lower segment caesarean section for women with childbirth injuries to the pelvic floor in future pregnancies

Repair

Repair of sphincter damage at delivery is best done immediately. Failed repairs should be diagnosed early and specialist help enlisted.

Immediate repair

It is standard practice to repair a damaged anal sphincter immediately or soon after delivery. All women having a vaginal delivery should have a systematic examination of the perineum, vagina, and rectum to assess the severity of damage prior to suturing. Repair of the perineum requires good lighting and visualisation, proper surgical instruments and suture material, and adequate analgesia.

Two commonly used methods of external anal sphincter repair are:

- end-to-end approximation of the cut ends;
- overlapping the cut ends and suturing through the overlapped portions.

There is no significant difference in outcomes between these methods. The preoperative, intraoperative, and postoperative standards for the successful outcome of the procedure have been described in the RCOG guidelines.[11]

Secondary sphincter repair

All women who have had a third- and fourth-degree tear repaired should be offered a planned follow-up at 6–12 months by a gynaecologist with an interest in anorectal dysfunction or by a colorectal surgeon. If symptomatic, they should be offered endoanal ultrasonography with anorectal manometry and referral to a colorectal surgeon for consideration of secondary sphincter repair.

Management in a subsequent pregnancy

Subsequent vaginal deliveries may worsen anal incontinence symptoms. These women are also at increased risk of repeat injury to the anal sphincter complex. All women who have had a third- and fourth-degree tear in their previous pregnancy should be counselled regarding the risk of developing anal incontinence or worsening symptoms with subsequent vaginal delivery. If they are symptomatic or with abnormal endoanal ultrasonography or manometry, the option of elective caesarean section should be discussed. If asymptomatic, there is no clear evidence as to the best mode of delivery.[1,12]

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Useful website

www.rcog.org.uk/guidelines

INCONTINENCE, URINARY

James Green

At least a quarter of women will experience some form of incontinence in their adult life.[1] The incidence increases with age, so prevalence in the elderly is around 50 per cent.[2] The causation is multifactorial, and the aetiology can be divided into anatomical and physiological causes. The latter can then be subdivided into bladder and/or outlet dysfunction (see Table 1).

Anatomical causes include:

- congenital – ectopic ureter, spina bifida occulta;
- acquired – fistula, which can be due to tumour, infection and childbirth, or be iatrogenic (surgical).

Physiological causes include:

- bladder dysfunction;
- urethral/outlet dysfunction;
- a mixture of both of the above.

Table 1 Terminology and classification of urinary incontinence

Detrusor		Outlet		Classification
Normal	+	Normal	=	Continent unless 'functional or situational'
Overactive	+	Normal	=	Urge urinary incontinence
Underactive	+	Normal	=	Retention —> overflow incontinence
Normal	+	Overactive/ stenosed	=	Retention —> overflow incontinence
Normal	+	Underactive	=	Stress urinary incontinence

Anatomical causes often result in continuous leakage of urine, whereas leakage tends to be episodic if the cause is dysfunction. Transient causes of urinary incontinence (UI) include urinary tract infection, restricted mobility, constipation, acute illness, confusion, dementia, diabetes mellitus or insipidus, and cardiac failure, as well as some drugs, in particular, diuretics, tranquillisers, and anticholinergic agents.

Neurological causes of UI (e.g. multiple sclerosis) should always be considered a possible differential cause. These range from continuous 'overflow' caused by an atonic bladder (see Urinary retention) to 'functional' problems, where there is an inability to perform toileting functions due to mental or mobility problems. More rarely, 'situational' causes of incontinence can occur on intercourse or giggling.

Primary evaluation of UI is directed towards categorising the type of incontinence. This is often difficult, as a mixed pattern of UI, involving a component of urge and stress, is more common than either urge or stress incontinence on their own. The second aim is to identify any treatable causes of the incontinence.

A thorough history should explore severity (pad usage) and quality of life issues. Voiding diaries should be completed for at least 3 days and urinalysis undertaken to exclude diabetes, infection, and neoplasia. A measurement of post-void residual urinary volume is useful. A cystometrogram should be considered if the type of incontinence is not clearly defined. This is desirable, if any surgical intervention is planned, as the exact form of incontinence has to be clearly defined preoperatively because inappropriate surgery on a unstable bladder may aggravate the situation, making urge incontinence worse.

Table 1 describes the types of incontinence; however, mixed forms of incontinence, such as urge and stress, can often coexist in varying degrees. This classification system is based on whether the detrusor muscle in the wall of the bladder is functionally overactive (sometimes termed 'unstable' or 'irritative') or reflexive (underactive), and depends on whether the bladder outlet, which includes the sphincter mechanism, is dyssynergic (overactive; see Urinary retention), stenosed, or incompetent (underactive).

Urge urinary incontinence

The definition of urge urinary incontinence (UUI) is 'the involuntary loss of urine resulting from an increase in bladder pressure secondary to a bladder contraction'. The main symptom is the loss of urine with the feeling of urgency, voiding before the ability to get to the toilet. It can be a difficult problem to treat, with varying levels of success.

The treatment for UUI is given in Box 1.

Stress urinary incontinence (SUI)

The definition of stress urinary incontinence (SUI) is 'the involuntary loss of urine resulting from an increased intra-abdominal pressure, which overcomes the resistance of the bladder outlet in the absence of a true bladder contraction'. The main symptom is the involuntary loss of urine with activity (coughing, laughing, sneezing, lifting, or straining). SUI can be caused by hypermobility of the bladder neck and proximal urethral, or loss of the posterior urethral support mechanism.

The treatment for SUI is given in Box 2. However, if SUI occurs with a well-supported pelvic floor, then intrinsic sphincter deficiency should be considered. Treatment of this condition involves coapting the urethral mucosa at the level of the bladder neck and proximal urethra (Box 3). The success rate for surgical treatment of SUI is 75–90 per cent.

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Box 1 Treatment of urge urinary incontinence

Treat any underlying cause
- Infection, inflammation, obstruction, calculus, neoplasm, neurological disease, etc.

Behavioural therapy
- Timed voiding (approx. every 2–3 hours) or bladder retraining for a period of at least 6 weeks

Pharmacologic therapy
- Muscarinic cholinergic antagonists
- Tricyclic antidepressants

Surgery
- Botulinum injections
- Sacral nerve stimulation
- Augmentation cystoplasty
- Other alternatives, including subtrigonal rhizolysis, autoaugmentation

Box 2 Treatment of stress urinary incontinence

Behavioural therapy
- Biofeedback
- Pelvic floor exercises (Kegel) for at least 3 months' duration
- Vaginal cones/weights

Pharmacologic therapy
- Alpha-adrenergic agonists
- Tricyclic antidepressants
- Oestrogen replacement (intermittent) may help some individuals

Surgery
- Tension-free transvaginal/obturator mid-urethral tape procedures
- Bladder neck suspension techniques

Box 3 Treatment of intrinsic sphincter deficiency

Surgery
- Intraurethral bulking agents
- Tension-free transvaginal/obturator mid-urethral tape procedures
- Artificial urinary sphincter implantation

INFERTILITY/SUBFERTILITY

Anne Clark, reviewed by Rashna Chenoy

Involuntary infertility, which affects one in six couples, is defined as the lack of conception after 1 year of unprotected regular intercourse, by which time 85 per cent of couples attempting to conceive will have been successful. Intercourse should occur 2–3 times in the week prior to ovulation: though the oocyte (egg) will be capable of fertilisation for only 24 hours, the sperm will retain potency for up to 72 hours. Intercourse prior to the day of ovulation also encourages remodelling of the endometrial lining, making implantation more likely.

Primary infertility is defined as when a couple has not had a pregnancy together, although one or both might have had a pregnancy in another relationship. *Secondary infertility* is when the couple has had at least one pregnancy together, irrespective of the outcome.

Early assessment (<12 months infertility) should be considered in the following situations:

- The woman has a history of irregular menstrual cycles (oligomenorrhoea or amenorrhoea).
- The woman has a known or suspected history of pelvic pathology, such as tubal disease or endometriosis.
- The man has a known or suspected reproductive tract pathology, such as an undescended testis.
- The couple present because they have not conceived as quickly as they had expected.
- A couple are in their 30s, as increased age affects their chance of conceiving. Therefore, if the woman is over 35 and/or the man is over 40, investigations should start after only 6 months of attempting to conceive.

Some of the distress associated with fertility problems can be reduced by prompt investigation and providing appropriate factual information if a problem exists. It is important to emphasise that establishing a diagnosis or cause of the infertility does not commit the couple to any further management.

For a couple to conceive normally, the following are required:

- The woman needs to produce and release a mature, healthy egg (oocyte) on a regular basis (ovulation).
- The man needs to have a certain number of normally shaped, healthy, motile sperm in his ejaculate with a sperm DNA fragmentation rate below 20 per cent.
- The egg and sperm need to be able to get together (there is no tubal disease, sperm antibodies, or sexual dysfunction).
- The embryo needs to be able to hatch out and implant without interference (there are no intrauterine adhesions, submucosal fibroids or hydrosalpinges).
- The couple have avoided lifestyle factors that may affect egg and/or sperm quality.

As fertility is a 'couple issue', it is not uncommon for more than one pathology to be affecting their likelihood of conceiving.

The causes of infertility are classified in Box 1.

Box 1 Classification of causes of infertility

Female factors
- Ovulation disorders
- Tubal pathology
- Uterine pathology
- Endometriosis
- Antibodies to sperm
- Age

Male factors
- Sperm-production problems
- Azoospermia (no sperm in the ejaculate)
- Sperm DNA fragmentation
- Antibodies to sperm
- Sexual problems
- Hormonal problems
- Age

Lifestyle factors
- Smoking
- Increased weight – raised body mass index (BMI)
- Increased alcohol intake
- Increased caffeine intake
- Recreational drugs (marijuana decreases sperm count) and anabolic steroids

Unexplained infertility

Female factors

If a couple presents for fertility investigations, the woman should also have her rubella status checked so that if immunisation is required it will not significantly delay any treatment, as conception is not recommended within 1 month of vaccination.

Ovulation disorders

Ovulation disorders are present in more than 25 per cent of women with fertility problems. They range from amenorrhoea (see Menstrual periods, absent) through oligomenorrhoea (see Menstrual periods, infrequent) to irregular cycles. The majority of these women have polycystic ovary syndrome (PCOS). The initial diagnosis is made by taking a history about the regularity of the menstrual cycle length and taking blood for a serum progesterone level in the mid-luteal phase (7 days prior to when menstruation is expected to commence). A serum progesterone level of >30 nmol/L is consistent with a normal ovulatory cycle. Basal body temperature charts are not helpful and should be avoided, particularly as they can increase the woman's stress and thereby exacerbate any ovulatory disorder.

Polycystic ovaries

Polycystic ovaries, which occur in one in five women, can be diagnosed by ultrasound scanning. Box 1 in Hirutism/virilism shows the 2003 consensus statement on the diagnosis of polycystic ovaries, which can be made on transvaginal ultrasound scan alone, and PCOS, which occurs in one in ten women. The investigations for the assessment and management of hirsutism, which is associated with hyperandrogenic conditions causing infertility, are dealt with in Hirutism/virilism.

If the woman has a history or physical signs consistent with increased insulin levels – a family history of late-onset diabetes, body mass index (BMI) >30, or acanthosis nigricans (a grey-brown, velvety discoloration of the skin found at the neck, groin, axillae, and vulva) – a 2-hour glucose tolerance test should also be done.

Weight gain or loss

Weight gain or loss also results in ovulatory disorders. If a woman has polycystic ovaries and her BMI increases, she is more likely to develop or exacerbate the PCOS, although this may be reversed by a weight loss of only 5–7 kg.

A woman with a BMI of <18 will often become anovulatory (does not release oocytes).

Hyperprolactinaemia

Hyperprolactinaemia (prolactin >1000 IU/L) as a consequence of a pituitary adenoma results in anovulation and is associated with galactorrhoea in 30–50 per cent of cases. It may be diagnosed clinically with changes in the visual field, but is more likely on imaging using magnetic resonance imaging or computerised tomography of the pituitary fossa. However, the prolactin levels should be repeated initially to confirm the raised concentration, as stress alone can increase levels. Moderately raised prolactin levels are present in 15 per cent of women with PCOS.

Hypothyroidism should be excluded by checking thyroid-stimulating hormone levels.

Ovarian failure

Ovarian failure needs to be considered if there is a history of anovulation for some months, particularly if there is a family history of early or premature (<40 years of age) menopause. It can be diagnosed by a raised serum level of follicle-stimulating hormone (>20 IU/L) and low serum oestrogen level on more than one occasion.

Tubal pathology

Damaged Fallopian tubes are present in 10 per cent of women with fertility problems who have never been pregnant and in 20 per cent of those who have, irrespective of the outcome of the pregnancy. It is uncommon for a woman to be aware she has had a pelvic infection unless it is related to an infection following pregnancy. Tubal disease should always be suspected in women with a history of secondary infertility, particularly if there has been a previous history of retained products of conception.

Diagnosis can be made by watching the passage of fluid through the Fallopian tubes using X-ray (hysterosalpingogram, HSG) or ultrasound technology (hysterosalpingo-contrast sonography: Hy-Co-Sy), or through laparoscopy and dye studies (Figs 1 and 2).

A hydrosalpinx if present can be visualised on a pelvic ultrasound. A history of an ectopic pregnancy

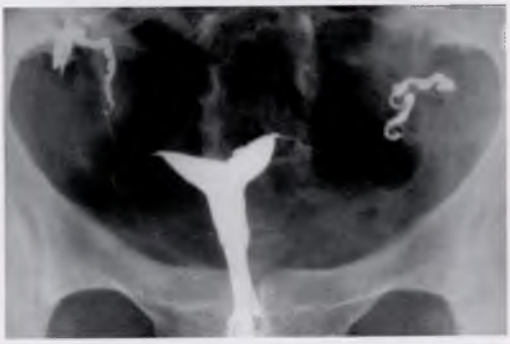

Figure 1 Normal hysterosalpingogram showing passage of contrast through the Fallopian tubes.

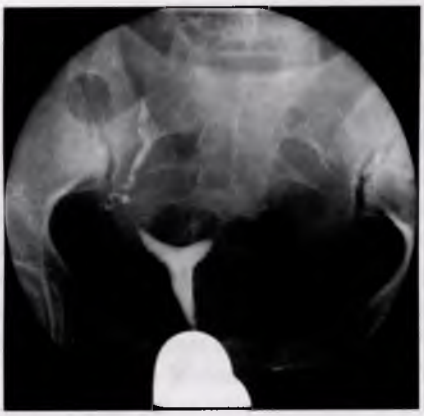

Figure 2 Hysterosalpingogram showing left tubal blockage at cornua.

is also suggestive of bilateral tubal damage. It is important to remember that a normal HSG or Hy-Co-Sy does not guarantee normal Fallopian tubes. It can show only tubal patency and an internal silhouette of the tubes, but is not able to reveal damage to the lining cilia of the tubes, which alters their function to waft the fertilised egg to the uterine cavity.

Laparoscopy and dye studies are the only absolute way to assess whether a woman has damage to the tubes that impairs the passage of sperm or an embryo, or external adhesions that compromise the function of the fimbrial ends as well as movement of the Fallopian tube (Fig. 3). Similarly, proximal occlusion at HSG or Hy-Co-Sy may be due to cornual spasm, which does not occur under general anaesthesia for laparoscopy. At laparoscopy, it is very important that a good cervical seal is made for the dye studies. Often a Spackmann catheter is insufficient, and a Leech–Wilkinson catheter is required.

If pelvic infection is suspected, *Chlamydia* testing should also be performed and the tubal investigations carried out under antibiotic cover to avoid reactivation of disease.

Laparoscopy also enables the diagnosis and treatment of unsuspected endometriosis during the same procedure.

Uterine pathology

Uterine pathology should be detected at the same time as the tubal assessment and may require hysteroscopy. Types of pathology encountered include polyps, uterine fibroids, uterine septa, and occasionally Asherman's syndrome (intrauterine adhesions – most likely occurring after a curettage for previous retained products of conception.)

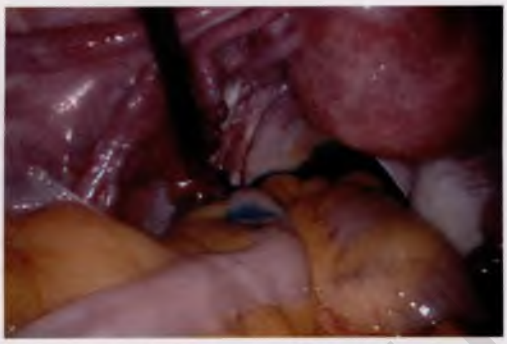

Figure 3 Laparoscopic view of the pelvis showing passage of dye through normal Fallopian tubes.

Endometriosis

Endometriosis is found in up to 30 per cent of women with fertility problems, particularly if the woman is in her 30s. It is reported that it takes 8–11 years from the time a woman first presents to a doctor with symptoms before a diagnosis is made. However, a likely diagnosis can be made on history alone in many cases. The following factors may point to a diagnosis of endometriosis in an infertile woman:

- family history of endometriosis;
- if the woman complains of 'old blood' or brown premenstrual spotting, and/or pain with menstruation, especially if it starts several days before menstrual flow and these are symptoms that have developed over time, rather than being present since her teenage years;
- increased lifetime history of menstruation, e.g. early menarche, shorter menstrual cycles, prolonged or heavier periods, few or no pregnancies, minimal or no use of hormonal contraception;
- history of deep dyspareunia;
- if no other cause for the couple's fertility problem can be found, there is a strong likelihood that the woman has endometriosis.

It is important to remember that a third of women with endometriosis have no pain with their periods and only one in eight will have an endometrioma visible on pelvic ultrasound. Therefore, in the majority of cases, diagnosis can only be made by laparoscopy, but that does enable surgical removal to occur during the same operation, with histology confirming the diagnosis of endometrial glands in the biopsies. Having made the diagnosis, if there is ureteric and/or bowel involvement at laparoscopy, referral to a laparoscopic specialist should be undertaken.

Antibodies to sperm

Up to 6 per cent of women can develop antibodies to sperm over time, which impair sperm function and transport in the woman's reproductive tract. As sperm are foreign to all women, it is unclear why most sexually active women do no produce anti-sperm antibodies.

Age

It is important to remember that it is not just the woman's age that affects a couple's chances of conceiving. Although it is known a woman's fertility decreases with age, particularly after the age of 35, it is also important to remember that a woman in her late 30s is likely to be partnered with a man of a similar age or older. If a woman in her mid- to late 30s is trying to conceive with a partner five years older than herself, she has half the chance of conceiving each month compared to a woman whose partner is the same age or younger.

A good guide for timing the reduced ovarian reserve is to ascertain the age of menopause of the woman's mother or any older sisters. An ultrasound scan to assess the number of antral follicles present (>6) at one time and absence of any reduction in ovarian size is a good indicator of normal ovarian reserve.

Table 1 covers the investigations and their interpretations for female fertility factors.

Male factors

The known causes of male infertility are outlined in Box 2 and Table 2. A total of 40–50 per cent of couples with fertility problems will have a male factor contributing to their infertility. The most common are sperm production problems; therefore, a semen analysis is the first step in assessing a man's fertility.

Table 3 outlines a normal semen analysis. The period of abstinence prior to the sample should be no longer than 3 days, because abnormal morphology and DNA fragmentation rates can rise if the sperm have been sitting in the epididymis too long. This is in contrast to advice given only a few years ago to increase periods of abstinence in the hopes of increasing the sperm count. The number of normal, functioning sperm is now recognised as a more important indicator of a man's fertility than the total number per ejaculate. A reduced number of sperm in ejaculate is called *oligospermia*, as opposed to a complete absence of sperm in the ejaculate, which is *azoospermia*.

A man's age is important in fertility assessments, as even in an in-vitro fertilisation (IVF) treatment,

Table 1 Interpreting the results of investigation of female partners

Test	Result	Interpretation
Progesterone	<30 nmol/L	Anovulation: but check cycle length and timing correct in mid-luteal phase; complete other endocrine tests; scan for polycystic ovaries – glucose tolerance test if obese; advise weight gain or loss; may need ovulation induction; clomifene should not be started without tubal patency test
	10–30 nmol/L	Likely ovulation, but timing of test incorrect
Follicle-stimulating hormone	>10 IU/L	Reduced ovarian reserve: may respond poorly to ovulation induction
	>20 IU/L	May need egg donation
Luteinising hormone	>10 IU/L	May be polycystic ovaries: ultrasonography to confirm
	>5 nmol/L	Congenital adrenal hyperplasia: check 17-OHP and DHEAS
Testosterone	>2.5 nmol/L	May be polycystic ovaries: ultrasonography to confirm
	>5 nmol/L	Congenital adrenal hyperplasia: check 17-OHP and DHEAS

Table 1 Continued

Test	Result	Interpretation
Prolactin	>1000 IU/L	May be pituitary adenoma: repeat prolactin to confirm raised concentration; exclude hypothyroidism; arrange magnetic resonance image or computerised tomography of pituitary gland; if confirmed hyperprolactinaemia, start dopamine agonist
Rubella	Non-immune	Offer immunisation and 1 month of contraception
HSG or Hy-Co-Sy	Abnormal	May be tubal factor: arrange laparoscopy and dye test to evaluate further May be intrauterine abnormality, e.g. fibroid or adhesions: evaluate further by hysteroscopy
Laparoscopy and dye	Blocked tubes	Tubal factor confirmed: possibly suitable for surgery or in-vitro fertilisation (decision also depends on semen quality and couple's age)
	Endometriosis	Assess severity: may benefit from surgical excision; medical suppression not helpful for fertility; may need in-vitro fertilisation after excision

DHEAS, dihydroepiandrosterone sulphate; HSG, hysterosalpingogram; Hy-Co-Sy, hysterosalpingo-contrast sonography; 17-OHP, 17-hydroxyprogesterone.

Table 2 Blockage of sperm transport

Cause	Obstructive	Non-obstructive	Hypothalamic–pituitary
	Post-testicular	Testicular	
Congenital	Cystic fibrosis or cystic fibrosis carrier, Müllerian cysts	Genetic causes, cryptorchidism, anorchia, Sertoli cell only	Kallmann's syndrome, isolated FSH deficiency
Acquired	Sexually transmitted diseases (gonorrhoea, chlamydia), tuberculosis, prostatitis, vasectomy	Radiotherapy, chemotherapy, orchitis, trauma, torsion	Craniopharyngioma, pituitary tumour or ablation, anabolic steroid use, hyperprolactinaemia
Testicular size	Normal	Small, atrophic	Small, prepubertal
FSH	Normal	Raised	Low
Testosterone	Normal	Low	Low

FSH, follicle-stimulating hormone.

if a man is over 40, his partner's chance of conceiving can be half that compared to the man being in his 30s.

Just because a man has fathered a pregnancy in the past does not mean he can be excluded from investigations. Men's fertility, as well as women's, changes over time, and unless DNA testing has been done, it is only an assumption that he is the father of any previous pregnancies. Studies have shown that 10 per cent of children have not been fathered by the person named on the birth certificate.

Lifestyle factors

Lifestyle factors play a significant part in a couple's chance of conceiving and having an ongoing healthy pregnancy.

It is estimated that smoking alone causes 13 per cent of fertility problems. For women, it reduces the chance of conceiving each month 2–3-fold and doubles the risk of miscarriage. Men who smoke increase sperm DNA fragmentation rates and increase the risk of the resulting child developing cancer in childhood by four times. Studies have

Table 3 A normal semen analysis[a]

Parameter	Normal	Abnormal
Volume	2–5 mL	If volume is low, check the collection was complete. The majority of sperm are in the first part of the ejaculate.
Count	20–250 × 10^6/mL	Repeat sample. Check no acute illness has occurred in the 2 months before the sample was taken. If total count <5 × 10^6, consider testing for chromosomes and Y chromosome deletions.
Motility	>25% rapidly	If reduced, check if the time between ejaculation and assessing of progressive sample is <1.5 hours. Repeat the sample and check lifestyle factors
Morphology	>15% normal	A very important parameter. Even if there are sufficient motile sperm, if they do not have a shape that gives 'the key to the door' of the egg, the couple can have fertility problems. Repeat the sample, and check lifestyle factors and abstinence.
Sperm antibodies	<50% binding	Prevalence in the general population cannot be estimated; 50–70% of men with vas deferens obstruction (surgical or congenital) are positive.
DNA fragmentation	<20%	Increased fragmentation does not affect fertilisation but does result in decreased pregnancy and increased miscarriage rates. Specialised assays (TUNEL or SCSA) are required.

[a]If an assay is not available, advise men >39 years, plus those that smoke, take marijuana, drink alcohol and/or caffeine heavily, or have a poor diet to take antioxidant supplements (vitamin E and C 1000 mg/d plus a good-quality multivitamin/mineral tablet).

Box 2 Known causes of male infertility

Sperm production problems
- Chromosomal or genetic causes
- Undescended testes (failure of the testes to descend at birth)
- Infections
- Torsion (twisting of the testes in the scrotum)
- Heat
- Varicocoele
- Drugs and chemicals
- Radiation damage
- Unknown cause

Blockage of sperm transport (azoospermia; see Table 2)

Sperm DNA damage or fragmentation
- Male age >40 years
- Long periods of abstinence
- Lifestyle factors (e.g. smoking, alcohol, poor diet, medications)

Sperm antibodies
- Vasectomy
- Injury or infection in the epididymis
- Unknown cause

Sexual problems (erection and ejaculation problems)
- Retrograde and premature ejaculation
- Failure of ejaculation
- Infrequent intercourse
- Spinal cord injury
- Prostate surgery
- Damage to nerves
- Some medicines, such as antihypertensives

Hormonal problems
- Pituitary tumours (hyperprolactinaemia)
- Congenital lack of LH/FSH (pituitary problem from birth)
- Anabolic (androgenic) steroid abuse

Male age
- >40 years
- Lifestyle factors (e.g. smoking, alcohol, poor diet and medications) can exacerbate the problem

FSH, follicle-stimulating hormone; LH, luteinising hormone.

also shown passive smoking decreases a woman's chance of conceiving to a similar level as if she were a smoker herself.

Increased weight affects both male and female fertility. An increase of just 9 kg has been reported as significantly reducing a man's fertility. If a woman's BMI rises to just 27 (normal BMI is 18–25) she is three times more likely to have ovulatory problems. However, a loss of just 5–7 kg can reverse ovulatory and miscarriage problems.

The evidence for alcohol affecting fertility is less secure. However, women may drink a maximum of three drinks/units a week (not in the same night), and men can average ten drinks/units a week, provided there is no binge drinking.

Studies have shown that women who consume more than 100 mg of caffeine a day (one cup of percolated coffee or two instant) can halve their chance of conceiving and double their risk of miscarriage in that month. Information is less certain in relation to male fertility, so 'all things in moderation' is the best advice.

Recreational drugs, such as marijuana, have an impact on sperm, conception, and sexual function, and so should be avoided. Anabolic steroids can render a man azoospermic or a woman anovular. Depending on the dose and length of use, these changes are not always reversible, so they also should be avoided.

Unexplained infertility

Unexplained infertility is a diagnosis of exclusion, when all the above investigations or lifestyle factors are normal. It can occur in up to 25 per cent of couples. It does not mean there is no cause for the couple's infertility, only that the cause has not been found in the investigations available. For example, a woman with abnormal oocytes would have that diagnosis made only if she proceeded to have an IVF treatment cycle. Similarly, if the sperm were unable to penetrate the shell of the egg (zona pellucida) and fertilisation it, this diagnosis could be made only at the time of an IVF treatment cycle.

It is important to reassure a couple that all fertility problems can potentially be solved with current fertility treatments. It is the man's sperm and the woman's Fallopian tubes that will most determine their choices. If eggs and/or sperm are absent, then a pregnancy is still possible with the use of donor gametes. If the uterus is absent, surrogacy is possible. Finally, most couples plan on having more than one child. Therefore, the couple's age in relation to the last pregnancy should be taken into account when considering the timing of investigations and/or referral to a specialist centre.

Useful websites

http://www.nice.org.uk/guidance/CG156 – Fertility: assessment and treatment for people with fertility problems. Feb 2013.

www.rcog.org.uk – Green-top Guidelines. Fertility: assessment and treatment for people with fertility problems. 2004.

INTRAUTERINE FETAL DEATH AND MID-TRIMESTER PREGNANCY LOSS

Manish Gupta

In the UK, intrauterine fetal death (IUFD) is defined as fetal death after 24 completed weeks' gestation. Any fetal loss before that time is classed as a miscarriage.

The Confidential Enquiry into Maternal and Child Health defines stillbirth as an in-utero death delivering after the 24th week of pregnancy, and defines late fetal loss as an in-utero death delivering between 20 weeks and 23 weeks 6 days of gestation. Using this classification, in the UK in 2003 there were 642,899 live births, 2764 late fetal losses and 3730 stillbirths, giving a stillbirth rate of 5.77 per 1000 live births and stillbirths. In 2007 the rate was 5.2 per 1000 live births, a rate that has stayed largely unchanged since 2000.

Pregnancy is arbitrarily divided into trimesters, although it is really a continuum. It has been said that the common causes for fetal loss in the first trimester are genetic, infective in the second, and placental in the third. However, this is by no means invariable. Fetal death in the second and third trimester can be due either to a single cause or to multiple factors which may be acute, subacute, or chronic in onset.

In addition to any physical effects, stillbirth often has profound emotional, psychiatric, and social effects on the parents and their relatives and friends.

Most commonly the pregnant woman may have no other symptoms, the diagnosis being made at a routine antenatal clinic visit. However, the woman may have noted an absence of fetal activity with abdominal pain, as in placental abruption.

Auscultation of the fetal heart by Pinard stethoscope or Doppler ultrasound is not sufficiently accurate for diagnosis. Auscultation can also give false reassurance: maternal pelvic blood flow can result in an apparently normal fetal heart rate pattern with an external Doppler. Real-time ultrasound scanning is essential for diagnosing IUFD. Real-time ultrasound allows direct visualisation of the fetal heart. Imaging

can be technically difficult, particularly in the presence of maternal obesity, abdominal scars, and oligohydramnios, but views can often be augmented with colour Doppler of the fetal heart and umbilical cord. A second opinion should always be sought if possible.

General risk factors include:

- maternal age – both teenage and over 40 years;
- single parent status;
- multiple pregnancy (increased 3.5-fold);
- high parity.

History

A history is not always helpful in pointing to the cause of a fetal death.

Aspects specific to the pregnancy include:

- a history of pain;
- a history of bleeding;
- concerns from previous ultrasound scans e.g. growth restriction;
- fetal number i.e. gestational order and also multiple pregnancy.

Aspects specific to the patient include:

- pre-existing medical conditions including diabetes, hypertension, renal disease and thromboembolic disease;
- recent exposure to any infectious illnesses, e.g. malaria, toxoplasmosis and parvovirus;
- any recent use of any prescribed or recreational drugs;
- the possibility of trauma especially domestic violence, uterine massage or recent road traffic accident.

Examination

General examination of the woman should include vital signs to exclude sepsis and shock from bleeding, and to look for signs of pre-eclampsia, including urine testing for proteinuria is essential.

Abdominal examination may be unremarkable or may reveal the signs of placental abruption or local signs of maternal injury implicating uterine injury. After excluding a major placenta praevia, a vaginal examination may show signs of bleeding or septic discharge. Appropriate bacteriology swabs should be taken during examination.

Causes of in utero fetal death

In approximately 50 per cent of cases, the underlying cause may not be diagnosed, which can be very upsetting and confusing for the mother and her family.

Acute

- Placental abruption.
- Umbilical cord accidents and pathology.
- Trauma.

Subacute

- Infection due to overgrowth of the normal flora can lead to cervical shortening and mid-trimester loss. Transvaginal ultrasound of the cervix in the at-risk woman and insertion of a cervical cerclage has been shown to reduce the risk of mid-trimester loss.
- Parvovirus B19, cytomegalovirus (CMV), Coxsackie virus and toxoplasmosis. This is deemed important as many women with viral-infection-associated IUFD show no clinical signs of infection during pregnancy.

Chronic

- Congenital malformations. As a group, this is a major determinant of perinatal mortality.
- Premature rupture of fetal membranes and infection.
- Fetal growth restriction.
- Maternal diabetes.
- Chronic maternal hypertension.
- Pre-eclampsia.

Investigations

The loss of a pregnancy at any stage can be devastating to the mother and her partner, causing all the phases of the bereavement reaction. Their major concerns are around whether they could have done anything to cause or prevent the loss, and whether this will happen again in a subsequent pregnancy. In order to give the best advice to women about the cause of fetal death and the possible implications on future pregnancy, the clinician requires a test protocol that is extensive and at the same time suitable for the patient population.

Maternal

Blood tests should include:

- full blood count;
- Kleihauer–Betke bloods stain, looking for fetomaternal transfusion;
- rhesus antibody status;
- clotting screen;
- lupus anticoagulant;

- anticardiolipin antibodies;
- biochemistry, including urea and electrolytes, liver function tests, glucose and HbA1c levels as well as bile acids.

Fetal

Fetal and placental examinations include:

- karyotype from either amniotic fluid, fetal blood sample or skin biopsy;
- external examination of the fetus;
- X-ray of fetus;
- magnetic resonance scan of the fetus, particularly important if there are sensitivities regarding post-mortem;
- infection screen from either fetal blood sample, fetal or placental swabs, or maternal serology including syphilis, *Toxoplasma*, parvovirus (maternal B19, IgM, and IgG levels), rubella and cytomegalovirus; some of these tests will have been undertaken early in the pregnancy and so may not need repeating;
- fetal and placental pathological examination.

Despite extensive investigation, up to 50 per cent of IUFDs will remain unexplained. It is wise to warn the woman of this possibility when the investigations are commenced, especially the postmortem examination. In the vast majority of cases, the risk of a similar event in a subsequent pregnancy is small. The woman should be reassured that she could try for a pregnancy when she and her partner feel emotionally ready to embark on another one. It is always worthwhile to warn the couple that the expected date and time of the previous delivery could possibly be emotionally difficult for them.

Further reading

Green-top Guideline 55: Late intrauterine fetal death and stillbirth. RCOG, October 2010.

ITCHING IN PREGNANCY (SEE ALSO RASHES IN PREGNANCY)

Anthony Bewley

Itching related to pregnancy

As so often in medicine, the diagnosis, when a patient presents with itching (pruritus) during pregnancy, can frequently be made from taking a history and careful examination. Investigations are rarely required. The differential diagnosis (Table 1) is made up of causes both specific to and unrelated to pregnancy.

Table 1 Common causes of itching in pregnancy

Itching related to pregnancy	Itching unrelated to pregnancy
Rashes in pregnancy[a]	**Rashes from skin disease**
Polymorphic eruption of pregnancy	Atopic eczema
Pemphigoid gestationalis	Eczema (other causes; e.g. contact)
Prurigo of pregnancy	Psoriasis
Pruritic folliculitis of pregnancy	Xerosis (dry skin)
	Lichen planus
	Pityriasis rosea
	Urticaria
Rashes from metabolic changes of pregnancy	**Metabolic causes**
Hyperthyroidism/ hypothyroidism[b]	Hyperthyroidism/ hypothyroidism
Cholestasis[c] impairment	Liver disease
Iron deficiency	Renal impairment
	Iron deficiency
	Other causes
	Scabies and infestations
	Tinea (fungal skin disease)
	HIV-related skin disease
	Localised itching
	Vulval itch[d]

[a] See Rashes in pregnancy.
[b] See Thyroid problems in pregnancy.
[c] See Jaundice and liver disease in pregnancy.
[d] See Vulval itching.

Rashes specific to pregnancy (most of which are intensely itchy) usually follow specific patterns and are discussed in Rashes in pregnancy. Both hyperthyroidism and hypothyroidism (Thyroid problems in pregnancy) may lead to itching as a primary presenting complaint; and cholestasis (Jaundice and liver disease in pregnancy) is a common cause of itching during pregnancy. Renal impairment may be exacerbated by pregnancy and iron deficiency (from poor nutrition or multiple successive pregnancies) may also present as itching.

Itching unrelated to pregnancy

A patient's pre-existing dermatological disease may improve or deteriorate during pregnancy. Most patients with pre-existing skin disease can identify the cause of their itching, or else can identify others within their family who have similar conditions.

Atopic eczema (Fig. 1) is intensely itchy and so is characterised by excoriations (scratch marks), thickening (from rubbing the skin), pigmentation changes, oozing, and scaling of, usually, flexural skin. Patients with eczema may also have hay fever, perennial conjunctivitis, and asthma.

Psoriasis (Fig. 2) usually presents as scaly, well-demarcated plaques affecting the extensors. Many patients with psoriasis also have nail, scalp, and genital (see Vulval itching) disease.

Lichen planus (Fig. 3) is a self-limiting disease, so, unlike eczema and psoriasis, the patient usually presents *de novo* with characteristic purplish, polygonal flat-topped papules affecting the anterior surfaces (especially the wrists). About 30 per cent of patients will have oral lichen planus.

Pityriasis rosea appears to be more common in pregnancy. It certainly affects young adults. It is the *herald patch* (a scaly, often annular patch, usually found on the abdomen or back, usually pre-dating the main rash) that is so helpful in ascertaining the diagnosis. The smaller, scaly, ovoid macules, which form a 'Christmas tree' pattern on abdomen, chest, and back, appear a few days after the herald patch. The rash of pityriasis rosea rarely extends below the knees and elbows, and rarely affects the head.

Scabies (Fig. 4) is usually sexually transmitted in adults. It is characterised by curvilinear, intensely itchy burrows. The total mite population of an infested individual is surprisingly small (often just 20 mites). Burrows often affect the hand's web spaces and the genital and periareolar skin. If scabies is suspected, take a look at the patient's partner, as similar lesions may help to make the diagnosis.

Tinea (ringworm) (Fig. 5) is characterised by an annular rash, which often has small pustules and scaling at the edge of individual ring-shaped lesions. Scraping of the edge may show fungal hyphae, and culture of the scrapings may identify causative organisms. Topical treatments only are safest during pregnancy.

Chickenpox (varicella) is uncommon in pregnancy but when a patient presents with chickenpox in pregnancy, it is important to recognise the condition, as transplacental spread of the virus may lead to fetal varicella syndrome. Chickenpox presents initially as 'tear drops on a rose petal' vesicles. The often intensely itchy lesions spread centripetally and usually involve mucosal membranes.

Use of zoster immune globulin (ZIG) within 24 hours of the infection may be used at various stages of the pregnancy according to national/local guidelines (in the UK, see www.rcog.org.uk). ZIG may be used when a non-zoster-immune pregnant woman comes into contact with chickenpox or shingles, or when a neonate is exposed around the puerperium. Aciclovir, although not licensed during pregnancy, is thought to be safe, and is frequently

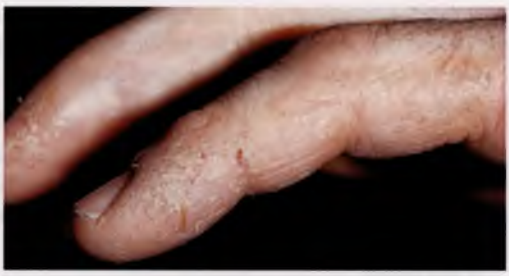

Figure 1 Atopic eczema. Note fissuring and thickening (lichenification) of the skin.

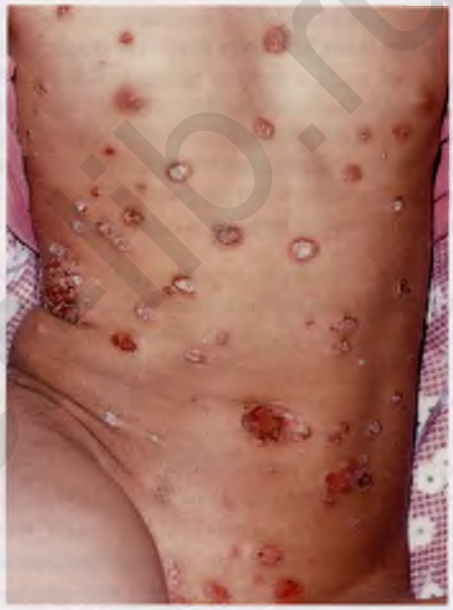

Figure 2 Psoriasis. Scaly plaques, but note that some are excoriated indicating pruritus.

Figure 3 Lichen planus (classical). Note the flat-topped, polygonal, violaceous (purple) papules affecting the flexures.

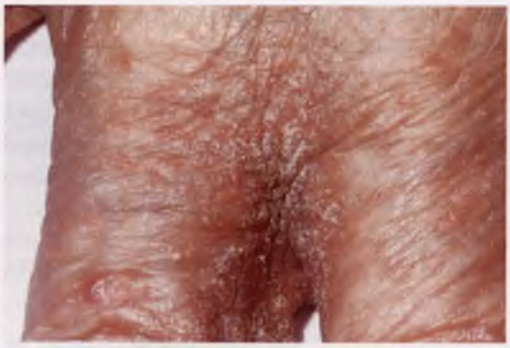

Figure 4 Scabies. Note scaling adjacent to curvilinear papules affecting the hand-web spaces.

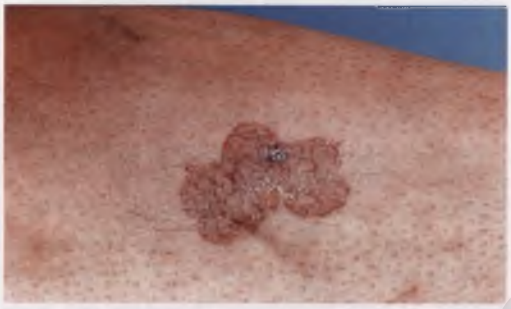

Figure 5 Tinea corporis. The scaly edge of this lesion has small studded pustules. This lesion had been mistakenly treated with steroids (tinea incognito), hence the atrophy.

used to treat pregnant women who develop chickenpox or shingles during pregnancy.

Finally, human immunodeficiency virus (HIV)-related skin disease is often itchy. The virus itself can lead to various, very itchy inflammatory dermatoses. Medication for HIV commonly leads to skin rashes, many of which are itchy and, of course, skin disease associated with opportunistic infections is more common in HIV-infected individuals.

Management of itching in pregnancy

Management of itching in pregnancy is limited and follows a stepwise pattern (Box 1). Management of specific dermatological problems may involve specific treatments together with advice from the local dermatology department. Primarily dermatological conditions such as eczema and psoriasis (which are frequently itchy despite what the textbooks say) may require ongoing treatment with topical steroids. When advocating topical steroids, it is advisable to prescribe ointments, to keep to the lowest strength possible (no stronger than betamethasone 0.1 per cent on the body and hydrocortisone 1 per cent on the face), and to use steroids for pulses of no longer than 6 weeks. Topical steroids are the treatment for inflammation (although cessation of inflammation usually means cessation of itch) and so should be stopped as soon as the disease improves.

Box 1 Management of itching in pregnancy

- Emollients (into the bath or on to the skin)
- Bath additives containing lauromacrogols (e.g. Balneum Plus® or oat extract, e.g. Aveeno®, may be additionally antipruritic)
- Topical emollients range from creamy (e.g. Diprobase) to very greasy (e.g. white soft paraffin). Let the patient decide which is best
- Avoidance of soaps and detergents. Use soap substitutes (e.g. Dermol 500)
- Non-sedating antihistamines (e.g. loratidine) are usually not licensed for pregnancy but are probably safe
- Sedating antihistamines (e.g. chlorpheniramine) have been used safely in pregnancy
- Topical steroid ointments (rather than creams) are probably safe (although not licensed) in pregnancy. Try to keep to the lowest strength possible for no longer than 6 weeks
- (Rarely) Phototherapy (usually narrow-band ultraviolet B)
- Information available at www.bad.org.uk

JAUNDICE AND LIVER DISEASE IN PREGNANCY

Alexander Evans and Margaret Myzsor

Liver diseases in pregnancy include:

- those present at conception;
- those that occur coincidentally;
- those that occur as a result of pregnancy.

Functions of the normal liver are:

- production of plasma proteins (albumin, coagulation factors, globulins);
- metabolism of amino acids, carbohydrates, and lipids;
- metabolism and excretion of bilirubin and cholesterol;
- biotransformation of drugs and toxins.

A list of liver function tests (LFTs) in the non-pregnant state is shown in Table 1.

History

If liver disease is suspected, the most important factor is to determine the gestational age of the pregnancy, as the differential diagnoses change with the stage of the pregnancy (Table 2). However, taking a careful history that includes a drug history is vitally important. Most women minimise the use of prescribed and over-the-counter medication while pregnant, but there has been a general increase in the use of alternative and herbal remedies, some of which can be associated with abnormal liver function. A history of intravenous drug use or alcohol abuse will make certain forms of liver disease much more likely (e.g. viral hepatitis). If there are abnormal LFTs, then it is important to determine whether this was also the case in any previous pregnancies, as both intrahepatic cholestasis and acute fatty liver of pregnancy can recur.

Table 1 Liver function tests in the non-pregnant state. (Note: No single test can quantify liver function, as a panel of tests is needed to help.) The following are serum blood tests

Serum level	Cause
AST ↑	Liver cell injury or necrosis
ALT ↑	
Albumin ↓	
Prothrombin time (INR) ↑	Reduced liver synthetic function
ALP ↑	Cholestasis or biliary obstruction
Bilirubin ↑	Cholestasis, biliary obstruction or haemolysis

↑, increased; ↓, decreased; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; INR, international normalised ratio.

Table 2 Differential diagnosis of abnormal liver function tests or jaundice in pregnancy

Trimester	Differential diagnosis
First	Hyperemesis gravidarum Drug-induced hepatitis Gallstones Viral hepatitis
Second	Intrahepatic cholestasis of pregnancy Gallstones Viral hepatitis Drug-induced hepatitis
Third	Intrahepatic cholestasis of pregnancy Pre-eclampsia/eclampsia HELLP syndrome Acute fatty liver of pregnancy Hepatic rupture Gallstones Viral hepatitis Drug-induced hepatitis

HELLP, haemolysis, elevated liver enzymes and low platelets.

Clinical features that can be elicited from the history include pruritus (itch). In intrahepatic cholestasis of pregnancy, pruritus initially affects predominantly the hands and feet, but will eventually become more generalised. It is usually worse at night and will usually predate abnormal LFTs. Although the commonest cause of itch and abnormal LFTs is intrahepatic cholestasis of pregnancy, other causes should be excluded, such as a gallstone in the bile duct leading to cholestasis.

Abdominal pain, particularly in late pregnancy, may be extremely important as it can be a sign of acute fatty liver, hepatic rupture, or eclampsia, or rather less worrying but more common, gallstones.

Fever and malaise may be prominent in viral hepatitis or cholecystitis, but when there are the classical clinical features of pre-eclampsia in association with abnormal LFTs, then the HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome or hepatic rupture must be considered.

Examination

Some of the clinical signs associated with chronic liver disease in the non-pregnant state are normal occurrences in pregnancy. For example, spider naevi and palmar erythema are common findings,

and should not be over-interpreted. Jaundice is rare during pregnancy, and has no prognostic importance in terms of the severity of the liver disease. Excoriations with abnormal LFTs are a sign of intrahepatic cholestasis of pregnancy or other causes of cholestasis (less common).

Abdominal tenderness, particularly over the liver, may indicate cholecystitis associated with gallstones or imminent hepatic rupture.

Investigations

- Ultrasound examination of the liver and biliary system is safe in pregnancy, and should be performed where there is any abnormality of liver function. If intrahepatic cholestasis of pregnancy is suspected, it is important to rule out other causes of cholestasis, such as gallstones with biliary obstruction.
- Serum bile acid estimation (where available) will help in the diagnosis of intrahepatic cholestasis of pregnancy.
- Low platelets and evidence of haemolysis occur in the HELLP syndrome, as can disseminated intravascular coagulation.
- If viral hepatitis is suspected, check hepatitis A, B, and C markers and, if the patient has travelled to the appropriate part of the world, check hepatitis E.

The pattern of LFTs in pregnancy-associated liver disease is shown in Table 3.

Diagnoses

Hyperemesis gravidarum

Intractable vomiting in the first trimester commonly leads to slightly abnormal LFTs. The diagnosis is usually fairly easy to make because of the clinical situation and stage of pregnancy.

Intrahepatic cholestasis of pregnancy (obstetric cholestasis)

This is characterised by intense pruritus and abnormal LFTs associated with other signs of cholestasis, such as dark urine and pale stools. It affects 0.9 per cent of pregnancies, although the incidence is higher in those from the Indian subcontinent and rare in Afro-Caribbean patients. It is also commoner in those with a family history or those who have experienced it in a previous pregnancy, and it typically occurs in the third trimester. As the pruritus is particularly severe at night, it can lead to significant sleep deprivation, and has been reportedly associated with intrauterine death (not confirmed by the most recent studies) and premature delivery. It is thought to be related to oestrogen metabolism. Jaundice occurs in a small minority of patients.

Treatment is symptomatic and sometimes unsuccessful. In recent years the bile acid ursodeoxycholic acid (15 mg/kg/d) has been widely used and is well tolerated, although there is no conclusive evidence that it works. Parenteral vitamin K should be given to those with prolonged cholestasis to minimise the effects of malabsorption of fat-soluble vitamins. There has also been a trend to deliver at 36 weeks to minimise the risk of stillbirth. Once again, there is insufficient evidence to sustain this practice, and certainly early delivery should not be undertaken for abnormal LFTs alone in obstetric cholestasis. Liver function tests return to normal within 2 weeks of delivery.

Acute fatty liver of pregnancy

This is a rare pregnancy-associated liver disease most commonly presenting in the third trimester. It occurs as a result of fat accumulation in the liver.

Table 3 Pattern of liver function tests in pregnancy-associated liver disease

Condition	Bilirubin	AST/ALT	ALP	Bile acids
Normal pregnancy	Normal	Normal	Slightly raised	Normal
Hyperemesis gravidarum	Normal	Slightly raised	Slightly raised	Normal
Intrahepatic cholestasis of pregnancy	Normal	Slightly to moderately raised	Slightly raised	Markedly raised
Acute fatty liver of pregnancy	Slightly raised	Slightly to moderately raised	Slightly raised	Normal
Pre-eclampsia/eclampsia	Normal	Slightly to markedly raised	Slightly raised	Normal
HELLP syndrome	Moderately raised	Slightly to markedly raised	Slightly raised	Normal
Hepatic rupture	Slightly raised	Slightly to markedly raised	Variably raised	Normal

Slightly raised: 1–2 × upper limit of normal.
Moderately raised: 3–5 × upper limit of normal.
Markedly raised: 5–100 × upper limit of normal.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HELLP, haemolysis, elevated liver enzymes and low platelets.

It is potentially fatal to both mother and baby, and is thought to occur as a result of an interaction between a fetus that is homozygous for long-chain 3-hydroxyacyl-coenzyme A deficiency and a heterozygous mother. The mother is frequently symptomatic with headache, malaise, nausea, vomiting, and abdominal pain, which is often located over the site of the liver. Jaundice is not common, but liver failure may develop with encephalopathy, a coagulopathy, and renal failure. In liver failure, a change in the international normalised ratio (INR) or prothrombin time is the most sensitive and rapid indicator of liver synthetic function, and hence liver failure.

Treatment is rapid delivery of the baby, which should lead to rapid improvement of the mother. However, fulminant hepatic failure may develop; therefore, the patient should be managed under the joint care of an obstetrician and hepatologist.

Pre-eclampsia and eclampsia

Elevated transaminases are fairly common in these conditions. The incidence rises with the severity of the condition, such that almost 90 per cent of patients with eclampsia will have abnormal LFTs. Treatment is for the underlying condition and no specific treatment is necessary for the liver.

HELLP syndrome (haemolytic anaemia, low platelets and elevated LFTs)

This can complicate the course of up to 10 per cent of those with pre-eclampsia and is due to microangiopathic damage, platelet activation, and vasospasm. Patients present with right upper quadrant discomfort and malaise, and typical haematological and biochemical abnormalities. There is a significant maternal mortality rate of 2 per cent with a much higher fetal mortality rate of 33 per cent; therefore, prompt delivery is vital for fetomaternal health.

Hepatic rupture

This is an exceedingly rare complication of pre-eclampsia or eclampsia, but can also be associated with acute fatty liver of pregnancy, HELLP, and hepatic adenoma. It usually occurs in the last trimester, and is characterised by sudden onset of severe abdominal pain, nausea, and vomiting. There is rapid abdominal distension and hypovolaemic shock, and the prognosis for both mother and baby is very poor. Prompt delivery is mandatory with surgical or radiological intervention to stop the bleeding from the liver.

Pregnancy in patients with chronic liver disease

Pregnancy is uncommon in patients with cirrhosis as hormonal and metabolic derangements often result in anovulation and amenorrhoea. In the absence of portal hypertension, if pregnancy does occur, the clinical course of the liver disease is generally not altered. Most of the drugs used for the treatment of liver disease are safe in pregnancy, such as ursodeoxycholic acid for primary biliary cirrhosis, prednisolone and azathioprine for autoimmune chronic active hepatitis, and penicillamine for Wilson's disease. Previously treatment of chronic hepatitis C with interferon and ribavarin has been avoided owing to teratogenicity seen in animal models, but newer direct-acting antivirals (DAATs) and the advent of interferon-free regimes may in time allow treatment of hepatitis C in pregnancy. Similarly patients with Hepatitis B who are in the immunotolerant phase of infection with a high risk of vertical transmission can be treated in the third trimester with either lamivudine or tenofovir.

If varices are present at the time of conception, there is an increased incidence of bleeding while pregnant; therefore, varices should be treated prophylactically, preferably with oesophageal variceal band ligation performed at endoscopy. Despite this, there is a reported increase in maternal mortality and stillbirth rate in these patients.

Finally, there is an increasing number of patients who have had successful pregnancies after a stable liver transplant for chronic liver disease, such as primary biliary cirrhosis, autoimmune chronic active hepatitis, Wilson's disease, and primary sclerosing cholangitis, as well as those that are transplanted in childhood for such conditions as biliary atresia. It is recommended that there be a period of 2 years between transplantation and conception to allow the likelihood of rejection to diminish and any initial problems with antirejection medications to be resolved.

Liver disease coincidental to pregnancy

Cholelithiasis in pregnancy

Gallstones can be found in as many as 6 per cent of pregnant women but are usually asymptomatic. If symptomatic, they can present with abdominal pain, fever, and a raised white cell count suggestive of cholecystitis. There are usually associated changes in the LFTs, with a rise in the transaminases. Surgery is

sometimes indicated either during or shortly after delivery (see Epigastric pain in pregnancy).

Choledocholithiasis accounts for as much as 7 per cent of patients with jaundice in pregnancy and will present as an emergency, with or without pancreatitis. Endoscopic retrograde cholangiopancreatography can be performed safely during pregnancy with adequate shielding of the fetus from radiation and minimal screening during procedure. This allows the safe removal of intraductal calculi, particularly important in gallstone pancreatitis.

Viral hepatitis

Infection with hepatitis B virus (HBV) is probably the commonest cause of liver disease in pregnancy worldwide, and screening for HBV is now universally performed as part of the antenatal screening programme in the UK. If found to be hepatitis B surface-antigen-positive (HBsAg+ve), then liver function tests, HBV serology, and HBV-DNA levels are performed to establish the phase of infection. These women should be referred to a hepatology department and should be seen within 6 weeks. Mothers in the immunotolerant phase of infection (high viral load, HBeAg+ve, often with normal LFTs) have a higher risk of vertical transmission. They may be offered treatment with lamivudine or tenofovir in the third trimester to reduce viral load and subsequent risk of hepatitis B transmission to their baby. Babies born to this latter group of mothers should receive immunoglobulin at birth, and all babies born to HBsAg-positive mothers should also receive a full course of immunisation starting shortly after birth.

Mothers infected with hepatitis C virus (HCV) have a lower risk of transmission than HBV or HIV. There is no evidence that HCV is transmitted to a baby by breast feeding, and certainly HCV-positive mothers should not be advised against breast feeding. There is currently no effective vaccine against HCV, and treatment with interferon and ribavirin (the current standard of care for HCV) is contraindicated in pregnancy. However, recent developments and the emergence of interferon-free regimes for the treatment of HCV with direct-acting antiviral therapies, such as sofosbuvir, may in the future allow treatment of HCV during pregnancy, which is currently not possible. Babies are tested for HCV between 12 and 18 months of age, depending on local policy.

Hepatitis E is a rare waterborne virus associated with high maternal mortality rates. Although relatively rare it must be considered if mothers have travelled to endemic areas.

KELOIDS AND HYPERTROPHIC SCARS

Anthony Bewley

Keloids (Fig. 1) and hypertrophic scars (Fig. 2) occur where there is exaggerated fibroblastic activity and collagenous scar deposition within the dermis of the skin. The term *keloid* tends to refer to spontaneous scar formation (although, in fact, keloids tend to be at sites of minor skin trauma, e.g. on shoulder skin from clothing friction). The tendency to develop spontaneous keloids tends to run in families and is more common in individuals of African or Caribbean heritage. Keloids are also more common in the midline of the body, especially the neck and chest.

Hypertrophic scars appear the same as keloids clinically, but have a clear precipitant cause (e.g. incisions for caesarean sections, or body piercings). Individuals who form spontaneous keloids are very likely to form hypertrophic scars as well, but a purely hypertrophic scar (such as may develop following abdominal surgery) may have a better prognosis.

Hypertrophic scars may be very itchy, and treatment of the itch may be all the patient seeks. Slow (over 5 years or more) softening of hypertrophic scars is usual. Interventional management of hypertrophic

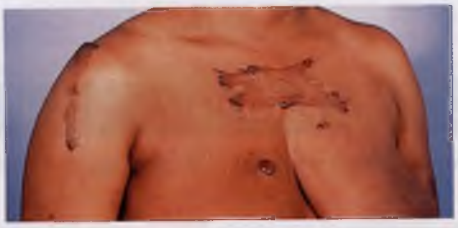

Figure 1 Keloids are more common in African or Caribbean patients and may occur spontaneously.

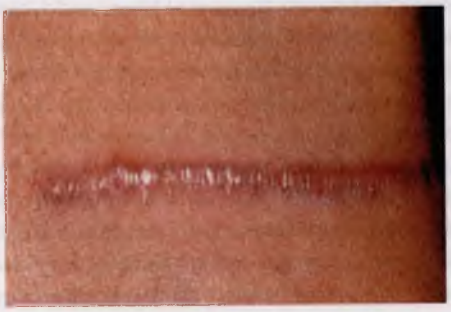

Figure 2 Hypertrophic scar on the abdomen of a woman following abdominal surgery.

Box 1 Management of hypertrophic scars following obstetric and gynaecological surgery

- Prevention is better than cure
- Reassurance that the scar will soften with time (often the best advice)
- Intralesional triamcinolone, 1 mL of 10 mg/mL, every 4 weeks for six doses (remember to get consent, as hypopigmentation and atrophy are possible, especially in Asian and African/Caribbean skin)
- Massage with emollient (e.g. vitamin E cream)
- Silicon gel and plasters (little evidence base)
- Very rarely; surgical repair sometimes with additional topical chemotherapy (recurrence and exacerbation of scarring is common)
- Some evidence for 595 nm laser treatment in combination with intralesional steroids
- Research with radiotherapy and methotrexate intralesionally
- Research with 5-flouracil imiquimod, vascular endothelial growth factor (VEGF) inhibitors, photodynamic therapy (PDT) and bevacizumab
- Information available at www.bad.org.uk

scars from obstetric and gynaecological surgery is described in Box 1.

Individuals who form keloids and hypertrophic scars are likely to have similar reactions following future trauma and should be advised accordingly.

LABOUR, PRECIPITATE

Deepa Janga and Nigel Bickerton

The definition of precipitate labour varies depending on geographical location. In the UK, midwifery texts have defined precipitate labour as an interval of one hour or less between the onset of labour and delivery. The International Federation of Obstetrics and Gynaecology (FIGO) describes precipitate labour as 1 hour or less from 3 cm cervical dilatation to delivery for primigravid women, and half an hour or less for multiparous women. More recently, the RCOG in its guidelines has adopted two hours as the cut-off point, in line with the definition most commonly used in the USA. Several countries in the Middle East use three hours or less from the start of uterine contractions until delivery as their definition. In many definitions the inclusion of the third stage is not clearly stated.

It follows that epidemiological comparisons within and between countries is, therefore, difficult. Inevitably, the diagnosis of labour is retrospective, and many women are not precise about the time of onset of their labour. Some women may not be aware of uterine contractions until labour is well established and consequently may appear to have had a precipitate labour according to a particular definition. A true precipitate labour is characterised by rapid dilatation of the cervix with rapid descent of the fetus through the pelvis, caused by frequent and strong uterine contractions. It was thought that precipitate labour was associated with fetal distress and hypoxia, but this is an extremely rare event.

Using the 2-hour definition, it is estimated that 2 per cent of women will experience a precipitate labour, which can occur in spontaneous or induced labour. Induction of labour in women of high parity may be associated with an increased incidence of precipitate labour, uterine rupture, and postpartum haemorrhage. Induction of labour to avoid a birth unattended by healthcare professionals should not be routinely offered to women with a history of precipitate labour. In a large study of outcomes of induction of labour, it was found that there was no higher incidence of fetal distress in the subgroup of babies born to women with precipitate labour.

When presented with a possible precipitate labour, the following possibilities should be considered:

- a normal labour of undetermined start time;
- a rapid labour;
- uterine hypertonus – often iatrogenic, owing to prostaglandin use;
- placental abruption.

In precipitate labour there is an adequate duration of each uterine contraction with an interval of rest between each one. In uterine hypertonus, there are contractions of prolonged duration with a reduced intervening relaxation phase. A common working definition for hypertonicity is a single uterine contraction that lasts longer than 2 minutes. A hard, tender uterus that does not relax characterises placental abruption. Tenderness may be localised or general, depending on the severity. Predisposing factors for precipitate labour include:

- increased parity/grand multiparity;
- induction of labour in women of high parity;
- placental abruption;
- some variants of Ehlers–Danlos syndrome;
- congenital hypoplasia of the cervix.

However, in the majority of cases, there is no apparent cause.

A precipitate labour may lead to delivery in an unplanned location, especially if the woman is travelling to hospital while in labour. The woman will often need emotional support during and after the event, as many women can find this type of labour very distressing.

The chance of a similar labour in a subsequent pregnancy is significant, and appropriate timing and planning should be taken into consideration in the future. There is an association with postpartum atonic uterus and primary postpartum haemorrhage. While it would appear a logical approach, there is no proven benefit in using tocolytic agents to 'normalise' the labour.

Assessment of fetal well-being in labour should follow normal practice. If fetal compromise is suspected, then it should be assessed and managed in the usual way, including fetal blood sampling to aid decision-making where indicated.

Further reading

Erkkola R, Nikkanen V. Precipitate labour. *Ann Chir Gynaecol* 1978; **67**: 150–53.

NICE Clinical Guideline 70: Induction of labour, July 2008. nice.org.uk/cg70

Sheiner E, Levy A, Mazor M. Precipitate labour: higher rates of maternal complications. *Eur J Obstet Gynaecol Reprod Biol* 2004; **116**: 43–47.

LABOUR, PREMATURE

Manish Gupta

In the UK, there are 650,000 babies born each year and of these approximately 7 per cent are born prematurely. Approximately one third are iatrogenic for causes such as pre-eclampsia, fetal growth restriction, and abruption, while the remainder are spontaneous. A preterm birth, defined as one that occurs before 37+0 weeks of gestation, is the single most important determinant of adverse infant outcome in terms of both survival and quality of life. Very preterm birth (less than 28 weeks gestation) accounts for 1.4 per cent of UK births but 51 per cent of infant deaths. Although birth at 32+0 to 37+0 weeks of gestation is associated with less risk than very preterm birth, there is growing recognition that even this moderate level of prematurity is associated with an increased risk of infant death. The risk of death or neurosensory disability increases with decreasing gestational age. Preterm birth can have huge psychosocial and emotional effects on the family, as well as being costly for health services.

Premature labour occurs when any process disrupts the normal physiology that maintains the pregnant uterus quiescent until parturition at term. The normal parturition cascade is usually inhibited until term. Removal of this inhibition plus an increase in myometrial receptors for prostaglandins and oxytocin, as well as raised levels of the myometrial gap junction component connexin-43, leads to activation of uterine activity. Long-duration, low-frequency uterine contractions change to high-intensity and more frequent contractions. At the same time, there is softening, effacement, and dilatation of the uterine cervix.

The common pathway in labour, activated through the different causes of premature labour, is prostaglandin synthesis. This occurs whether it is due to infection, cytokine activity, or bleeding in placental abruption. The physiology of the onset of premature labour is still not fully understood and remains the source of extensive research.

Clinically, the importance of premature labour is correct diagnosis so that the mother is in the optimal place for safe delivery, which will be determined by local models of care for varying levels of gestation and rationalisation of services. See Boxes 1 and 2 for risk factors.

Diagnosis

As in many areas of obstetrics, the diagnosis of premature labour is not a precise art: two-thirds of those considered in preterm labour will remain undelivered 48 hours later, and one-third will continue the pregnancy to term.

The diagnosis is made by history, abdominal palpation, and by using a uterine tocograph, if one is available. The strength, frequency, and the patient's response to the uterine contractions are recorded. Vaginal examination using a speculum may reveal some effacement or even dilatation of the cervix.

Box 1 General risk factors for premature labour

Maternal age
- <20 years
- >35 years

Weight
- Low body mass index (<18)

Obstetric history
- Relative subfertility
- Previous miscarriage 16–24 weeks
- Previous premature labour

Social
- Lower socioeconomic class
- Single parent

Lifestyle activities
- Smoking
- High caffeine intake
- Recreational drugs (cannabis, cocaine, ecstasy)

Box 2 Clinical risk factors for premature labour/delivery

Cervical surgery
- Previous termination of pregnancy, especially late dilatation and evacuation procedure
- Cone biopsy
- Large loop excision of the transformation zone (LLETZ)

Infections
- Genital tract
- Bacterial vaginosis

Fetoplacental unit
- Multiple pregnancy
- Polyhydramnios
- Fetal growth restriction
- Placental abruption

Maternal trauma
- Domestic violence

Congenital
- Uterine and cervical anomalies

There are now more objective methods of determining whether a woman who is contracting is actually in premature labour, which include:

- fetal fibronectin. A vaginal swab is taken to detect the presence of fetal fibronectin. It has good negative predictive value (99.8%) but if positive only a third of positive cases will go on to labour;
- transvaginal cervical ultrasound scan to measure cervical length. Using a cut-off measurement of 15 mm or less, 90–95 per cent will go into labour within 7 days.

These tests have provided a better method of diagnosing premature labour and have reduced the need for tocolysis and steroids.

Tocolysis

Whilst the use of tocolytics reduces the proportion of births after treatment starts, there is little available evidence about its effect on perinatal mortality or severe morbidity.

The main indications for tocolytic drugs in premature labour in the short term are:

- to allow a course of maternal steroid injections for fetal lung maturation;
- to allow transfer of the mother to a maternity unit with appropriate neonatal intensive care unit facilities for that particular gestation.

Steroids

Babies born prematurely are at risk of respiratory/ventilation problems, and this is a major cause of mortality and morbidity. Respiratory distress syndrome (RDS) will occur in 40–50 per cent of babies born before 32 weeks' gestation. Antenatal steroid treatment causes a significant reduction in the severity of RDS, intraventricular haemorrhage, and neonatal death. In addition, steroid treatment reduces the cost and duration of neonatal intensive care.

Further reading

Green-top Guideline 7: Antenatal corticosteroids to reduce neonatal morbidity. RCOG, October 2010.

Green-top Guideline 1B: Preterm labour, tocolytic drugs. RCOG, February 2011.

LABOUR, PROLONGED

Deepa Janga and Nigel Bickerton

A successful labour requires uterine contractions of adequate strength to dilate the uterine cervix and then to expel the fetus.

Labour is subdivided into the following phases/stages:

- *A latent phase of the first stage*: the softening and thinning of the cervix (effacement). This is a slow process until the cervix is 3–4 cm dilated.
- *An active phase of the first stage*: regular uterine contractions cause the cervix of the primigravid woman to dilate at approximately 1 cm per hour until the cervix is fully dilated (no cervix palpable around the fetal head).
- *A second stage*, which involves descent of the fetal presenting part through the pelvis leading to birth of the baby. This part of the labour will take about 1 hour in primigravid women. In multiparous women the time is usually less.
- *A third stage*, involving the delivery of the placenta and fetal membranes.

The process of a woman's labour is recorded on a partogram chart. These differ in their layout between countries and between units in the same country. The majority are rectangular, although in some countries a circular partogram is used (developed by the National University Hospital of Ouagadougou). The partogram is used to record the progress of a woman's labour. It can be used to alert the carer to poor progress that may warrant intervention (Fig. 1).

The World Health Organisation defines prolonged labour as a woman having experienced labour pains for 12 hours or more without delivery.[1] It is often difficult to pinpoint the time of onset of labour. It is defined as the time when uterine contractions become regular and cause cervical effacement and dilatation.

Many studies have shown that the mean times for the duration of labour differ for primigravid and multiparous women. In Europe, the mean labour time for primigravid women is 10 hours, compared with a mean time of 5.5 hours for multiparous women, but the normal range either side of these figures is wide. As a general rule, the cervix should dilate at the rate of at least 1 cm per hour once the active phase of labour has been reached.

This fact should be remembered in clinical practice. A multiparous woman whose progress in labour is slow requires particular caution in assessment. An unduly large baby or a malposition needs to be excluded. Augmentation of labour using oxytocin should proceed with caution, and regular assessment of progress is required.

Prolongation of labour can be considered accordingly:

- false labour or the misdiagnosis of labour;
- a prolonged latent phase of labour;
- a prolonged active phase of labour;
- a prolonged expulsive phase of labour.

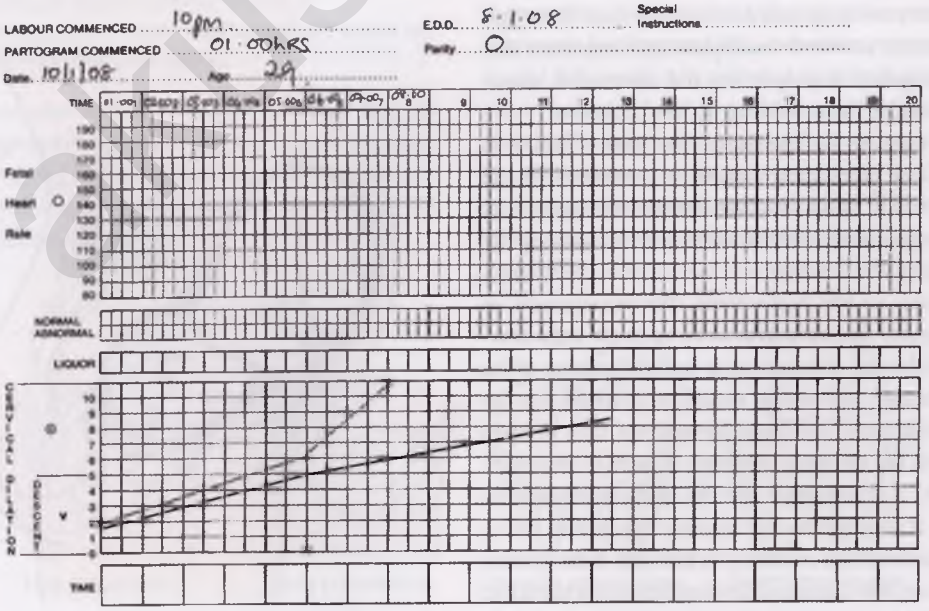

Figure 1 Partogram representation of normal labour pattern.

False labour may be suspected when abdominal palpation reveals no palpable uterine contractions or the occasional infrequent contraction only, together with a vaginal examination that shows no cervical effacement or dilatation. A *prolonged latent phase of labour* has to be made retrospectively. It is important to recognise false labour and a prolonged latent phase of labour. This will help to avoid unnecessary intervention, which may diminish patient satisfaction and carry an increased risk of operative delivery.

Prolonged labour in the active phase is more common in the primigravid woman, and is usually due to:

- ineffective uterine contractions;
- occipitoposterior position of the fetal head;
- cephalopelvic disproportion.

The assessment of the quality of uterine contractions is notoriously difficult and inaccurate by abdominal palpation. The printout on the cardiotocograph is a representation of the frequency of uterine contractions and cannot be used to infer or quantify the strength of the contractions. The use of intrauterine pressure-transducer catheters to measure the strength of a contraction and the work done per contraction is rarely performed in the UK nowadays.

Serial examination of the cervix, preferably by the same examiner, which shows progressive dilatation is reassuring of adequate uterine contractions and progress in labour, especially if an appropriate partogram path of progress is achieved. If the uterine contractions are not dilating the cervix, then, save for the rare case of cervical dystocia, it is most likely that the uterine activity is inadequate. It is important that cephalopelvic disproportion and obstructed labour are excluded before coming to this conclusion.

If delay in the established first stage of labour is suspected, amniotomy should be considered for all women with intact membranes, following explanation of the procedure and advice that it will shorten her labour by about an hour and may increase the strength and pain of her contractions. The management of inadequate uterine activity is by oxytocin augmentation following spontaneous or artificial rupture of the membranes, and women should be informed that the use of oxytocin will bring forward the time of birth but will not influence the mode of birth or other outcomes.[2] It is important that the oxytocin infusion be given at an adequate dose to cause regular and strong contractions with relaxation in between. If the woman becomes dehydrated and develops ketones in her urine, then fluid replacement can very often positively affect the efficiency of her contractions. Progress should be assessed by abdominal and vaginal examination after strong, regular uterine contractions are established.

The routine use of enemas during early labour is very much an outdated practice; however, on occasion, it can be extremely useful in facilitating descent of the presenting part if the woman has become very constipated during her pregnancy. Likewise, a full urinary bladder can affect the descent of the presenting part and catheterisation may be necessary, particularly in women with an epidural catheter in situ.

The occipitoposterior (OP) position of the fetal head is a relatively common event, occurring in approximately 10 per cent of labours, with the fetal occiput lying in the posterior part of the maternal pelvis. It can be a particular problem in women with a raised body mass index, where excess adipose tissue in the ischiorectal fossae results in poor descent of the fetal head into the pelvis. In the OP position, the fetal head presents a larger diameter to the maternal pelvis and it may be deflexed (Fig. 2).

The diagnosis may have been made antenatally by inspection and palpation. The fetal head tends to be readily palpable in an unengaged state. In Europe, this position of the fetus is the commonest cause of a high fetal head at term. During labour, the mother may complain of a gnawing and persistent backache, worsened during uterine contractions. There is an association with incoordinate uterine contractions that may require an oxytocin infusion to improve them.

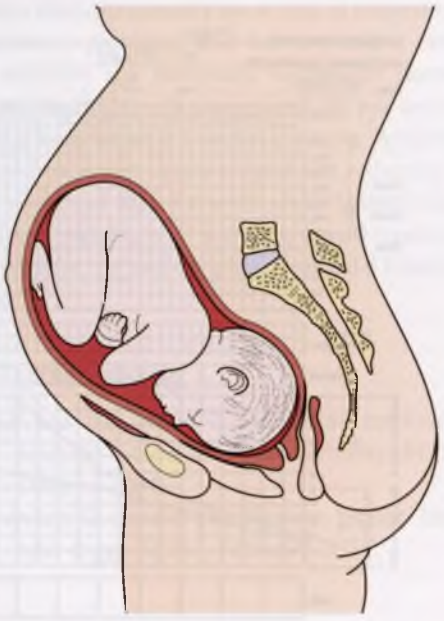

Figure 2 Diagram of the occipitoposterior position.

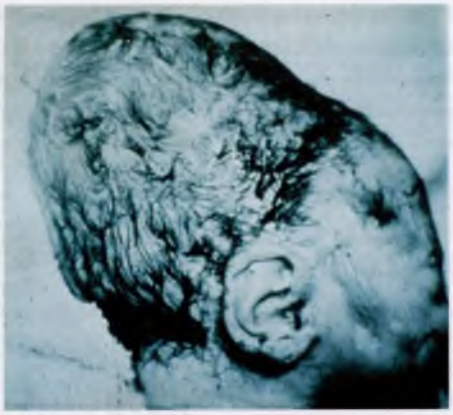

Figure 3 Caput and moulding of a baby's head.

Women who labour with an OP fetal position tend to experience the urge to bear down before completion of the first stage of labour. This in part is due to the fetal occiput pressing on the maternal rectum. Premature bearing down may cause cervical oedema together with the development of fetal caput and skull moulding (Fig. 3). This can be a trap for the inexperienced attendant, as the elongated fetal scalp often comes into view before the cervix is fully dilated. Enthusiasm in encouraging the patient to bear down at this stage can seriously demoralise the woman when subsequent examination reveals the true state of cervical dilatation.

Occipitoposterior positions are associated with:

- the need for syntocinon infusion owing to inadequate contractions in the second stage of labour;
- a prolonged second stage of labour;
- an increased need for operative delivery;
- an increased risk of failed operative vaginal delivery and second stage caesarean section.

Obstructed labour is diagnosed when there is no progressive descent of the fetal presenting part despite strong uterine contractions. Often, in primigravid women, this is associated with an eventual fall off of uterine activity.

Absolute cephalopelvic disproportion is a disparity between the fetal size and the maternal pelvis to a degree that vaginal birth is not possible. The problem of a contracted pelvis is an uncommon finding in a well-nourished population, but may be more problematic in the developing world or in young girls who find themselves pregnant before their full growth potential has been achieved. Delivery by caesarean section is required in such cases.

Relative cephalopelvic disproportion occurs when the presenting fetal head is not optimally aligned, through malposition. Management of such cases requires an experienced clinician. Following a period of satisfactory uterine contractions, re-examination will reveal either progress, or it will reveal increasing scalp oedema (caput) and moulding of the fetal skull bones with no further fetal descent at re-examination. The management for the latter is caesarean section.

Another cause for prolonged labour is deep transverse arrest – at the level of the ischial spines following incomplete rotation from an OP position. The fetal occipitofrontal diameter becomes fixed. The sagittal suture lies in the transverse plane, and usually both fontanelles are palpable. Management involves operative delivery. According to local practice, this will be by manual rotation, ventouse, or Keilland's (rotational) forceps. In all cases, the fetal head is brought on to the occipitoanterior position before delivery. Adequate analgesia is required, usually through regional anaesthesia.

It is wise to consider the possibility of other fetal presentations in cases of prolonged labour. A brow presentation or even more rarely a shoulder presentation might be diagnosed late. A shoulder presentation cannot deliver vaginally and must be delivered by caesarean section. A brow presentation rarely delivers vaginally unless there is spontaneous flexion to a vertex or extension to a face presentation (mentoanterior; Fig. 4).

Rare causes have become even rarer, as nowadays most women receive antenatal ultrasound scans. Such

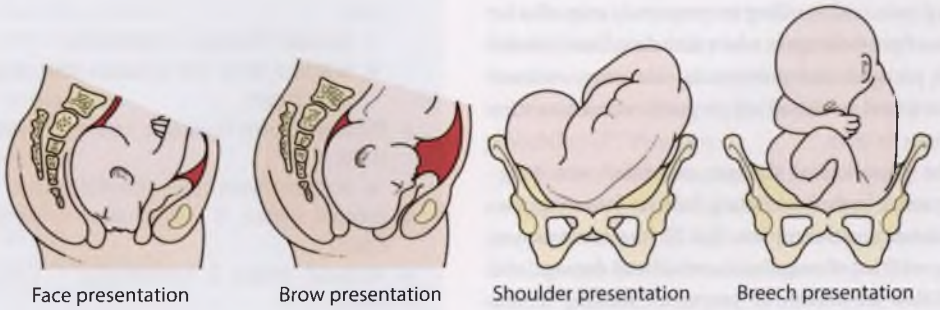

Figure 4 Diagrams of malpresentations.

rarities include hydrocephalus and conjoined twins. Abnormalities of the uterus and adnexa that may obstruct labour are usually discovered before labour, and include large or multiple fibroids in the lower segment of the uterus and large ovarian masses impacted in the pelvis. Ovarian cysts are not usually an impediment to vaginal birth, as the majority lie at the side of or above the pregnant uterus, so that they do not obstruct.

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LEG PAIN IN PREGNANCY (DEEP VENOUS THROMBOSIS)

Naim Akhtar

Deep venous thrombosis (DVT) and venous thromboembolic disease remains the leading cause of illness and death in pregnancy in the Western world. In the UK, pulmonary embolism (PE) remains the leading cause of maternal death, and obviously DVT is the underlying cause.

Leg pain and swelling in pregnancy is, however, fairly common (Box 1), and might not have a sinister cause. Leg oedema from venous insufficiency is not dangerous, with symptoms of pain, heaviness, night cramps, and paraesthesiae, but requires further investigation. Leg pain may also result from infected varicose veins and superficial thrombophlebitis. Prolonged standing and sitting (long-haul flights, car journeys) are fairly common benign causes for leg pain and swelling.

Leg pain and swelling in pregnancy may also be a sign of pre-eclampsia when associated with raised blood pressure and proteinuria. However, oedema can be found in almost all pregnant women as they get closer to term.

The physiological changes associated with pregnancy result in the haemostatic balance favouring procoagulation and thrombosis (Box 2). As a consequence, Virchow's triad of coagulation, vessel wall damage, and blood flow are affected in pregnancy, making venous thromboembolic disease a serious and potentially life-threatening complication. Therefore, the pregnant woman with leg pain/swelling or chest pain/breathlessness should be suspected and investigated appropriately for a diagnosis of DVT or venous thromboembolism (VTE). There appears to be reluctance to investigate pregnant women with suspected VTE thoroughly.

The clinical diagnosis and differential diagnoses are based on:

- clinical history (including family history, additional risk factors);
- physical examination;
- initial screening tests;
- confirmatory investigations.

Box 1 Causes of leg pain and swelling in pregnancy

- Pregnancy with increasing gestation
- Prolonged standing or sitting
- Venous insufficiency
- Pre-eclampsia (associated with hypertension, proteinuria)
- Infection (superficial thrombophlebitis)
- Ruptured Baker's cyst (popliteal bursa)
- Lymphatic obstruction (lymphadenopathy)
- Previous deep venous thrombosis (DVT)
- Previous abdominal/pelvic surgery
- Previous trauma
- Age, obesity
- Co-morbidities (heart failure, liver/renal disease)
- Drugs (e.g. calcium-channel blockers, antidepressants)
- DVT/venous thromboembolism (new onset)

Box 2 Physiological procoagulant changes in pregnancy

- Prohaemostatic changes – shortened clotting times
  - increased fibrinogen concentration
  - increased factor VIII and some other coagulation factors
- Reduced systemic fibrinolysis – slower dissolution of clot
  - increased plasminogen activator inhibitor
- Reduced protein S concentration – variable effects
- Increased protein C concentration – variable effects

Clinical history

The history will exclude other likely causes of leg pain and swelling, such as venous insufficiency and pre-eclampsia. VTE occurs in 1 per 1000 pregnancies, which is a five-fold increase from the non-pregnant state. Although the risk is carried throughout pregnancy, it is substantially higher in the last trimester and delivery, and even higher in the postpartum period.

The risk assessment for a patient is based on several factors (Table 1). A previous history of VTE, obesity, and multiparous state are major contributing risks for DVT and VTE.

The antiphospholipid syndrome poses significant risk (three-fold increase) for arterial, venous, and small vessel thromboses, in addition to the well-recognised association with pregnancy losses (Box 3).

Table 1 Thrombotic risk assessment in pregnancy

Risk factor	Risk
Pregnancy	5-fold increase (1:1000 risk)
Previous VTE	3.5-fold increase
Inherited thrombophilia	3–15-fold increase
Prothrombin variant	Estimated risk 1:200
Factor V Leiden	Estimated risk 1:400
Protein C + S deficiency	Estimated risk 1:100
Antithrombin III deficiency	Estimated risk 1:40
Obesity (BMI >30)	Significant risk factors identified in multivariate analysis but remain ill defined in terms of absolute risk
Parity (multiparous >4)	
Co-morbidities: heart failure, sickle cell disease, malignancy, myeloproliferative disorders, paraplegia, inflammatory disorders, gross varicose veins	
Antiphospholipid syndromes	
Lupus anticoagulant (strongly positive and persistent)	
Anticardiolipin antibodies (moderate levels >20 units)	
Age (risk increases with age >35)	
Additional risk factors	
Trauma	
Major surgery	
Central venous catheters/lines	
Hyperemesis	
Dehydration	
Immobilisation (including long-distance travel)	

BMI, body mass index; VTE, venous thromboembolism.

Box 3 Antiphospholipid syndromes (APS) and pregnancy

APS

- Increased risk of venous thromboembolism (arterial, venous, small vessel thrombosis)
- Pregnancy losses (early, late), fetal growth retardation
- Pre-eclampsia, abruption (poor placental perfusion)

Diagnosis

- Lupus anticoagulant (two or more times, 6 weeks apart)
- Anticardiolipin immunoglobulin G (IgG) or IgM at moderate levels (>20 U)

Therapy

- Thromboprophylaxis – low-molecular-weight heparin (LMWH) + low-dose aspirin
- Thrombosis – therapeutic anticoagulation (LMWH) + postpartum heparin or warfarin for 6 weeks

Left-leg DVT predominates (90 per cent) in pregnancy owing to the anatomical circulation of the left iliofemoral veins and the compressive effect of the gravid uterus. The postphlebitic syndrome is also fairly common. A total of 70 per cent of VTEs in pregnancy are not associated with any inherited thrombophilias, and in 25 per cent there are no obvious risk factors other than pregnancy.

Physical examination

A full physical examination is mandatory in order to exclude other potential conditions and establish co-morbid risk factors. Pain and tenderness over the deep veins is common. Leg swelling may be significant, and no other signs may be apparent. Pain on dorsiflexion of the foot (Homan's sign) has not been found to be particularly discriminatory. A clinical risk and probability score can be based on the absence or presence of significant findings on physical examination (Box 4) and is the basis of pre-test probability (PTP) scores.

Objective measurements include circumferential measurements of the leg at fixed points in comparison with the normal leg, and presence of spreading cellulitis are useful baseline recordings. The presence of varicose veins and synovial joint swellings should also be detected and recorded. The presence

Box 4 Clinical risk for deep vein thrombosis (DVT) and pulmonary embolism (PE)

DVT

- Paralysis/paresis
- Recent confinement to bed >3 days
- Major surgery within 12 weeks
- Localised deep vein tenderness
- Swelling of entire leg
- Calf circumference difference >3 cm
- Pitting oedema
- Collateral flow
- Previous DVT

PE

- Signs of DVT
- Alternative diagnosis less likely
- Heart rate >100
- Immobilisation or surgery within previous 4 weeks
- Previous DVT or PE
- Haemoptysis
- Cancer

of a haematoma and ecchymosis should alert the clinician to consider a bleeding diathesis to be a potential cause.

Screening tests

These include the following routine tests:

- *Full blood count and erythrocyte sedimentation rate* (ESR) to exclude potential secondary causes, including myeloproliferative disorders, malignancy, and infection. A normal platelet count and subsequent drop with the introduction of heparin raises the clinical suspicion for heparin-induced thrombocytopenia (HIT).
- *Coagulation profile* to establish a baseline, and exclude possibilities of a coagulopathy associated with lupus anticoagulant, consumptive thrombocytopenia in disseminated intravascular coagulopathy, and haemolysis associated with elevated liver enzymes and low platelets (HELLP syndrome).
- *D-dimers* are useful when negative to exclude a diagnosis of DVT or VTE. If elevated, D-dimers may support a diagnosis for VTE and hence further definitive investigations. Raised D-dimers, however, may result from many other causes, including inflammation and malignancy. There are some models that use D-dimers as part of a risk assessment score, which essentially raises the clinical suspicion of VTE. However, the clinical suspicion of DVT and VTE in pregnancy is high, irrespective of the D-dimer level.

The investigation of inherited thrombophilia factors is not encouraged in the acute setting. The levels of many of these factors are likely to be erroneous as a result of the dynamic situation of production and consumption in VTE. Secondly, the immediate management is not altered by the absence or presence of these factors. Pregnancy, in addition, will in any case alter the steady levels of these factors.

Definitive investigations

The diagnosis of DVT and VTE may be problematical in pregnancy. Historical venography is no longer the investigation of choice for suspected DVT and leg swelling. Venography has, therefore, been phased out in all patients owing to clinical risks associated with an invasive investigation and the complications associated with a radioactive tracer. The current imaging modalities are listed in Box 5.

In pregnant women with suspected PE or with a suspected DVT and PE, a limited ventilation/perfusion (V/Q) scan may be diagnostic. The use of a spiral

Box 5 Current imaging modalities for suspected venous thromboembolism

Venography (for DVT)

- Historic gold standard for DVT
- Significant risks (invasive, allergy, post-phlebographic DVT)

Ultrasonography (for DVT)

- Compression with transducer
- Non-compression
- Colour duplex
- Pelvic veins not accessible
- Higher sensitivity for proximal DVT

Ventilation/perfusion scan (for PE)

- ^{99}Tc-labelled albumin
- Limited perfusion scan suitable for pregnant patient

Spiral computerised tomography pulmonary angiography (for PE)

- Radiation dose to lactating breasts of concern

Invasive pulmonary angiography (for PE)

- Investigation of last resort in an emergency setting in consideration of thrombolysis

DVT, deep vein thrombosis; PE, pulmonary embolism.

computerised tomography pulmonary angiography (CT-PA) scan is now considered to be a good alternative, but both investigations are associated with modest radiation doses and inherent risks in pregnancy.

For suspected leg DVT, duplex ultrasound scan is the main diagnostic tool and is in widespread routine use (see Fig. 1 in Leg swelling in pregnancy). These later scans are useful for detecting proximal DVTs, but may miss the less clinically significant distal leg DVTs. Negative duplex scans should be repeated within a few days if the clinical suspicion remains high, and the patient should be treated for a DVT or VTE in the interim.

It is important to note that CT-PA, V/Q scanning, and limited venography have modest radiation doses, and pose negligible risks to the fetus.

Risks in subsequent pregnancies

There is substantial risk of recurrence in subsequent pregnancies for a variety of reasons, including age, parity, and veins damaged by previous VTE. Some of these risks are quantified in Table 1. Thromboprophylaxis is mandatory in subsequent pregnancies.

Management of obstetric thromboprophylaxis

Both warfarin and unfractionated heparin (UH) have side effects limiting their use in pregnancy. Warfarin is contraindicated in early pregnancy and the first trimester, as it can cross the placenta and disrupt normal bone and cartilage development (warfarin embryopathy).

Unfractionated heparin has no direct teratogenic effects, but risks to the mother include allergic skin reactions, heparin-induced thrombocytopenia and, with long-term use, significant risk of osteoporosis. Most patients are comfortable with self-injection with a longer-acting, low-molecular-weight heparin (LMWH), and with not needing the monitoring required with both UH and warfarin.

Assessment of thrombotic risk factors (Table 1) should be made in all women in early pregnancy as part of the booking procedure. High-risk women should be managed jointly with a haematologist in a thrombophilia clinic. All women should have their body mass index calculated based on early pregnancy weight. Risk reassessment should occur during pregnancy, if intercurrent problems arise.

Consider prophylaxis with LMWH (enoxaparin 40 mg daily subcutaneously) if three or more of the risk factors (Table 1) are present. For specific recommendations based on risk categories, see Box 6.

Box 6 Obstetric thromboprophylaxis

(a) High risk

- Antiphospholipid syndrome (previous VTE or fetal loss)
- Recurrent VTE
- Antithrombin deficiency

Recommendations

- Antenatal: enoxaparin 0.75–1 mg/kg twice a day SC + aspirin 75 mg daily
- Intrapartum: enoxaparin 40 mg/d SC
- Postpartum: enoxaparin 0.75–1 mg/kg twice a day SC until 6 weeks postpartum

(b) Intermediate risk

- Personal history VTE (spontaneous or precipitated)
- Thrombophilia
- Family history of VTE (first-degree relatives)

Recommendations

- Antenatal: enoxaparin 40–80 mg/d SC from 10 to 16 weeks
- Intrapartum: enoxaparin 40 mg/d SC
- Postpartum: enoxaparin 40–80 mg/d SC until 6 weeks postpartum

(c) Low risk

- No personal history of VTE but with thrombophilia
- Previous VTE, precipitated now resolved
- Family history

Recommendations

- Antenatal: aspirin 75 mg daily
- Intrapartum: enoxaparin 40 mg/d SC
- Postpartum: enoxaparin 40 mg/d SC until 6 weeks postpartum

SC, subcutaneously; VTE, venous thromboembolism.

Treatment of VTE in pregnancy

Low-molecular-weight heparin is recommended for treatment of suspected or proven VTE in pregnancy. A twice-daily dose is recommended in view of the rapid clearance in pregnancy (Table 2). The guidance is based on enoxaparin, but would be equally applicable to other low-molecular-weight heparins.

Monitoring is required using anti-Xa levels (target 1 IU/dL 3 hours post dose). Continue treatment throughout pregnancy and the puerperium, with

Table 2 Treatment of venous thrombosis in pregnancy

Early pregnancy weight (kg)	Initial enoxaparin dose
<50	40 mg SC twice daily
50–69	60 mg SC twice daily
70–89	80 mg SC twice daily
>90	100 mg SC twice daily
Target anti-Xa levels	1 IU/dL

SC, subcutaneously.

a minimum of 3 months anticoagulation following VTE in pregnancy. Women may breast feed with both LMWH and warfarin.

LEG SWELLING IN PREGNANCY

Anwen Gorry and Nigel Bickerton

Leg swelling is very common in pregnancy. By term, over 60 per cent of women will have noticed it to some degree. The clinical difficulty with leg swelling is to distinguish between the physiological and the pathological in order to decide whether treatment is necessary and if so, its degree of urgency. Leg swelling is most commonly due to oedema, but enlargement of any of the tissues of the leg may give the clinical impression of swelling. Box 1 gives a broad summary of the causes of leg swelling, both acute and chronic, which may occur irrespective of pregnancy.

A brief summary of the physiology of peripheral fluid homeostasis may be helpful.

Physiology

Tissue capillaries are porous rather than watertight. In the normal state, there is tissue fluid exchange from the capillaries into the interstitial space. This is a filtration of liquid with the hydraulic pressure in the capillaries determining the rate of flow. There are different forces at work during this process, and an imbalance will lead to oedema. Hydraulic pressure moves fluid through the capillary wall in the direction of the interstitial tissues. The hydraulic force in the capillary is countered by the pressure in the interstitial fluid and by the osmotic suction in the capillary fluid. Under normal circumstances, the direction of fluid flow is towards the interstitial tissues. Older physiology texts describe a significant distal capillary reabsorption of water. However, in

Box 1 Causes of leg swelling

Acute leg swelling

Oedema
- Physiological of pregnancy
- Pre-eclampsia

Thrombotic
- Thrombophlebitis
- Deep vein thrombosis (DVT)

Infective/inflammatory
- Cellulitis
- Dermatitis
- Necrotising fasciitis

Traumatic
- Fracture
- Dislocation
- Disrupted joint – effusion or haemarthrosis
- Ligamentous tear
- Torn leg muscles
- Ruptured Achilles' tendon
- Ruptured popliteal fossa cyst (Baker's cyst)
- Sunburn
- Insect bite

Chronic leg swelling

Congenital lymphoedemas
- Hereditary lymphoedema Type I
  - Milroy's disease
  - presents after birth
  - may initially be unilateral
  - well known accounts for about 2–5 per cent of cases
- Hereditary lymphoedema Type II
  - Meige lymphoedema – familial
  - lymphoedema praecox
  - presents at puberty
  - accounts for 80 per cent of cases
- Hereditary lymphoedema Type III
  - hereditary lymphoedema tarda
  - presents at 35 years
  - accounts for 10–15 per cent of cases

Acquired
- Traumatic
  - post lymphatic dissection
  - post radiotherapy
- Venous
  - chronic insufficiency
  - venous obstruction
  - post DVT syndrome
  - pelvic tumour obstructing venous return

- Cardiac
- Congestive heart failure
- Pericardial effusion
  - valvular disease
  - tricuspid valve regurgitation/stenosis
  - pulmonary stenosis

Low serum albumin
- Production
  - malnutrition
  - cirrhosis
  - enteropathy
  - malabsorption
- Loss
  - nephrotic syndrome

Drugs
- Calcium-channel blockers
  - amlodipine
  - diltiazem
  - felodipine
  - nifedipine
- Steroids
- Monoamine oxidase inhibitors
  - phenelzine
- Tricyclics
  - amitriptyline
  - desipramine
  - nortriptyline

most tissues, the majority of fluid is returned to the body's circulation by way of the lymphatic system.

The lymphatic drainage of fluid away from the tissue starts at the cellular level, and then the lymph fluid flows towards small collecting tubules that in turn convey the lymph into the main trunks. These trunks mirror the layout of the major arteries. Lymph movement at this level is by muscular contraction in the lymph trunks, and one-way flow is ensured by a series of valves. In the pregnant woman, up to 10 L of lymph is transported daily. The lymph returns to the circulation by two routes, the lymph nodes and the thoracic duct.

Understanding the process will help to appreciate ways that the steady state may be altered. An increase in capillary hydrostatic pressure, a fall in plasma osmotic pressure, or a fall in lymph drainage rate will all lead to oedema formation. Most cases of clinical oedema occur after the capillary filtration rate exceeds the handling capacity of the lymphatic system, even though this has some degree of biological reserve.

Assessment

Assessment of the pregnant woman with leg swelling starts with taking a history of events. Some useful questions are:

- When did the swelling start?
- Has the onset been gradual or acute?
- Has the swelling arisen during the pregnancy or did it predate pregnancy?
- Is there associated swelling of face or hands?
- Is the swelling dependent (lower limbs/ feet/ sacral area)?
- Is the swelling painful?
- Have there been any skin changes?
- Has there been any associated trauma?
- Is the swelling unilateral or bilateral?
- Are there any systemic symptoms?
  - shortness of breath;
  - chest pain;
  - orthopnoea and paroxysmal nocturnal dyspnoea;
  - joint pains;
  - fever/malaise;
  - rash;
  - symptoms of pre-eclampsia (headache, vomiting, epigastric pain, visual disturbance, reduced fetal movements).

Examination

Examination should be carried out in good light and with both of the patient's legs at the same level. Ideally, the patient should be lying down to allow examination of the abdomen and groin. The urine should be tested for proteinuria, and the blood pressure checked. The examiner should look for any asymmetry of swelling, for skin changes (rash, erythema, trauma, ulceration, varicosities), and for the degree of oedema. Testing for pitting oedema should involve gentle and prolonged pressure over a bony area, for example, 2 cm above the medial malleolus. Bilateral leg circumference measurement should be undertaken and should be standardised. One approach is to measure the circumference at 10 cm below the tibial tuberosity. A girth increase of more than 3 cm is clinically significant. In deep vein thrombosis (DVT), there may be marked pain induced by palpation over the deep venous system. However, the classical features of increased skin warmth and increased venous collateral circulation may not be present. Peripheral pulses should be assessed and the skin temperature noted bilaterally. A systemic examination should be carried out to look for signs of systemic fluid overload (pulmonary oedema, ascites), cardiac disease and systemic sepsis. The abdomen and groin should be examined to look for masses in addition to the gravid uterus. If the blood

pressure is elevated or if there is proteinuria (raising the suspicion of oedema related to pre-eclampsia), the peripheral reflexes should be assessed. The oedema related to pre-eclampsia is classically bilateral and may affect non-dependent areas (the face and hands) as well as dependent areas (feet and legs). See Hypertensive disorders in pregnancy for further details.

Deep vein thrombosis (DVT)

The presence of unilateral leg swelling in pregnancy and the puerperium must be considered to be a deep vein thrombosis until proven otherwise.

Venous thromboembolism (VTE) is up to 10 times more common in pregnant women than non-pregnant women of the same age, in part due to the physiological adaptations of pregnancy that lead to a hypercoagulable state and in part due to the abdominal mass that is the gravid uterus. Approximately one in four women with untreated DVT will go on to develop a pulmonary embolism, and it is estimated that one in seven of those may die as a direct result. All women should undergo risk assessment for VTE in early pregnancy, continuously throughout pregnancy, and in the puerperium. Consideration should be given for starting prophylactic low-molecular-weight heparin (LMWH) if the woman is deemed to be at high risk. Box 2 lists the additional factors that increase this risk of DVT during pregnancy.

Four-fifths of DVTs are left sided and 7 of 10 are ileofemoral in pregnancy. This is a remarkably high proportion compared with the non-pregnant rate.

Clinical findings alone are not reliable for diagnosis of DVT in pregnancy, and only a minority of women in whom DVT is suspected will have a proven VTE. Compression duplex ultrasound scanning is the investigation of choice for making the diagnosis of DVT (Fig. 1) Women should be commenced on low-molecular-weight heparin at treatment doses until a negative ultrasound has excluded the diagnosis. However, if clinical suspicion remains high, the treatment should continue and the duplex ultrasound should be repeated after 1 week. If there is unilateral swelling of the whole leg, then an ileo-femoral DVT may be suspected and magnetic resonance venography can be considered. D-dimer testing should not be performed to diagnose acute DVT, as in pregnant women D-dimer is often elevated due to the physiological changes to the coagulation system.

Once the diagnosis of DVT has been made, women will require therapeutic doses of LMWH for the remainder of their pregnancy and for at least 6 weeks postnatally (to ensure a minimum of 3 months treatment time). They will also require follow up and investigation for underlying thrombophilia at least 6 weeks postnatally (thrombophilia screens are notoriously difficult to interpret during pregnancy due to the changes in the coagulation system). These women will

Box 2 Additional risk factors increasing the risk of DVT in pregnancy

- Personal history of VTE
- Family history of VTE
- Thrombophilia
- Age >35 years
- Certain medical co-morbidities (heart or lung disease, SLE, cancer, sickle cell disease, inflammatory conditions, nephrotic syndrome)
- High parity (>2)
- Obesity (BMI >30)
- Varicose veins
- Immobility (paraplegia, long distance travel, prolonged labour)
- Pre-eclampsia
- Sepsis
- Dehydration (including hyperemesis gravidarum and ovarian hyperstimulation syndrome)
- Multiple pregnancy or assisted reproductive therapy
- Smoking
- Intravenous drug use
- Operative procedure in labour or the puerperium (including emergency/elective caesarean section and mid-cavity operative delivery)
- Postpartum haemorrhage

BMI, body mass index; DVT, deep vein thrombosis; SLE, systemic lupus erythematosus; VTE, venous thrombo embolism.

Figure 1 A sagittal scan through the femoral vein (FV) showing lack of compressibility and absence of Doppler signal. A tributary vessel shows marginal flow around the recent sonolucent clot. Reproduced by kind permission of Dr Carl Wright FRCR, Department of Radiology, Ysbyty Glan Clwyd, Bodelwyddan, North Wales.

need prophylactic doses of LMWH during any subsequent pregnancy and for 6 weeks postnatally. In addition women diagnosed with DVT should be advised to wear a compression stocking on the affected leg for 2 years to avoid the post thrombotic leg syndrome (persistent swelling, pain, chronic pigmentation and sometimes ulcers and varicose veins).

LIBIDO, LOSS OF

Zoe Moatti and Tony Hollingworth

Libido is a person's overall desire for sexual activity, and is determined by hormonal as well as physical and motivational-affective factors in both sexes.

Circulating androgens are promoters of sex drive and are derived largely from the testes in men and the suprarenal glands in women. Thus hypothalamic or pituitary disease, which reduces gonadotrophin levels in men and adrenocorticotrophic levels in women, will deprive each sex, respectively, of its main source of androgen. Similarly, testicular damage or disease in a male and primary suprarenal failure in a female will achieve the same effect.

A number of endogenous substances regulate libido, which include cortisol, serotonin, oestrogens, dopamine (inhibiting prolactin secretion), alpha-melanocyte-stimulating hormone, norepinephrine (positively or negatively), oxytocin, progesterone (negatively affects libido, increased during the week following ovulation), and sex-hormone-binding globulins. Imbalance of these substances, whether iatrogenic or secondary to a medical condition, may result in a down-regulation of libido.

Psychological factors can impact on libido, namely, interpersonal relationship, loss of intimacy, stress, fatigue, and bereavement. Other causes include experience of sexual abuse, assault, trauma or neglect, negative body image, and anxiety about engaging in sexual activity. Psychiatric disorders, such as depression and schizophrenia, reduce sex drive both through biochemical imbalances and the side effects of medications. See Table 1.

The categories of desire problems are:

- Primary low libido where a woman never experiences sexual desire. This can be a difficult challenge and no therapies have been found to be helpful.
- Secondary inhibited sexual desire. These are summarised in the table of causes (Table 1). Strategies to overcome the problems will be dependent on the underlying cause.

Table 1 Causes of loss of libido and their mechanism

Condition	Mechanism
Endocrine	
Hypothalamic disease Pituitary disease	Reduced adenocorticotrophic hormone
Hypothyroidism	Psychomotor retardation, lethargy
Addison's disease	Decreased adrenal androgens
Menopause	Decreased circulating oestrogens vaginal dryness and atrophy
Premature ovarian failure	(Increased circulating androgens may increase libido)
Psychological	
Interpersonal relationships causes Socio-cultural influences Anxiety Depression Hypoactive sexual desire disorder (lack of sexual desire for a period of time)	Loss of affective-motivational drive
Medical conditions	
Pelvic and breast neoplasms	Raised prolactin
Coronary heart disease Hypertension Diabetes mellitus Renal failure Anorexia/ malnutrition Chronic lung disease Parkinson's disease Obesity/metabolic syndrome Chronic alcohol or drug use	Biochemical imbalance
Pelvic and perineal causes	
Endometriosis Vaginitis (trichomonas, yeasts, bacteria) Pelvic inflammatory disease Chronic pelvic pain Irritable bowel syndrome Pelvic surgery	Dyspareunia
Human immunodeficiency virus (HIV)	Advanced HIV giving rise to ovarian failure
Vulvitis Post-radiation vaginal atrophy Infection of Bartholin's gland	Dyspareunia
Hymenal obstruction Relaxed vaginal musculature (after vaginal delivery)	Reduced sexual enjoyment

Table 1 Continued

Condition	Mechanism
Iatrogenic:	
Selective serotonin reuptake inhibitors	
Anti-depressants (paroxetine)	Imbalance between excitatory neurotransmitters and stimulatory neurotransmitters such as serotonin
Anti-psychotics (clozapin, olanzapine)	
Cryptoterone acetate	
Alpha and beta blockers	
Opiates	
Combined oral contraceptive pill	Additional cosmetic side effects (weigh gain, hair loss, allergic reactions)
Anti-epileptic drugs (valproate, vigabatrin, gabapentin, topiramate)	

- Desire discrepancy, where there is a mismatch with desire frequency between the woman and her partner. This may be inevitable in long-term partnerships and counselling may be appropriate.

In cases of low libido, it is important for the woman to describe the problem, including when it first started and how it has developed. She should be asked what she believes to be the cause of the problem, what she has tried to do to resolve it, and what are her expectations and goals from seeking help.

Management of this condition may prove difficult unless there is an underlying cause (Table 1) that can be treated or medication changed. Lifestyle changes may be helpful, especially reviewing alcohol consumption, smoking, and weight and stress management. Pharmacological agents may include vaginal lubricants and the use of androgenic progestogens (levonorgestrel, norgestrel, or desogestrel). Pubococcygeal exercises can increase blood flow to the perineum and can improve the sensation of arousal. However, if these measures are ineffective, then the help of a psychosexual counsellor should be recommended.

Further reading

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MENSTRUAL PERIODS, ABSENT (AMENORRHOEA)

Ismail Wong and Tony Hollingworth

Amenorrhoea can be defined as the absence of menstruation, which can be either temporary or permanent. It may occur as a normal physiological event before puberty, as a result of pregnancy and subsequent lactation, or as the onset of the menopause. It may be a symptom of a non-physiological problem which may be systemic or gynaecological in origin.

Primary amenorrhoea is the failure to menstruate by the age of 16 years, when the girl has developed normal secondary sexual characteristics, or failure to menstruate at the age of 14 years in the absence of any secondary sexual characteristics. This definition aids the diagnostic identification of causes, which include reproductive tract anomalies, gonadal quiescence, and gonadal failure. Primary amenorrhoea may result from congenital abnormalities in the development of the ovaries, genital tract, or external genitalia, or disturbance of the normal endocrinological events at the time of puberty. Some of these structural abnormalities may lead to cryptomenorrhoea, where menstruation is taking place but the menstrual flow is unable to escape owing to some closure of part of the genital tract (see Puberty).

Most causes of secondary amenorrhoea can cause amenorrhoea if the problem occurs before puberty. Delay in the onset of puberty is often constitutional. It is important to exclude the possibility of primary ovarian failure or dysfunction of the hypothalamic–pituitary axis. As a general rule, 40 per cent of cases of primary amenorrhoea are caused by endocrine disorders and the remainder (60 per cent) are from developmental abnormalities.

The definition of *secondary amenorrhoea* has usually been taken to be the cessation of menstruation for six consecutive months in a woman who has had regular periods, although recently it has been suggested that cessation of periods for 3–4 months may be considered pathological and warrant investigation.

Irrespective of the type of amenorrhoea, a thorough history and examination should be undertaken. Examination needs to include the stature and body form of the individual; the height and weight should be measured and converted into a body mass index (BMI = weight in kilograms divided by the square of

one's height in metres, or kg/m^2). Inspection should concentrate on the presence or absence of secondary sexual characteristics and the appearance of the external genitalia. It is essential that this be undertaken before requesting any investigations. Most cases of secondary amenorrhoea by definition would exclude congenital anomalies unless the individual had been using the oral contraceptive pill, which would induce a withdrawal bleed each month. Vaginal examination may be inappropriate in someone under the age of 16 years or who had not been sexually active. Abdominal ultrasound scanning is very useful for defining the anatomy. It is *always* important to exclude pregnancy. Serum investigations should include prolactin, gonadotrophins (follicle-stimulating hormone (FSH) and luteinising hormone (LH)), and thyroid function tests.

Raised serum prolactin levels (>1500 IU/L) may indicate the need for a magnetic resonance imaging (MRI) scan of the pituitary fossa to exclude a pituitary tumour and hypothalamic pituitary disease. Serum FSH levels >40 IU/L usually suggest irreversible ovarian failure. Raised serum FSH and LH levels usually suggest ovarian failure, but raised LH levels alone may indicate polycystic ovarian syndrome (PCOS), which can be confirmed by ultrasound scan of the ovaries. Amenorrhoea in PCOS is secondary to acylical ovarian activity and continuous oestrogen production. Abnormally low serum levels of FSH and LH suggests failure at the level of the hypothalamus and pituitary, leading to hypogonadotrophic hypogonadism. Kallmann's syndrome is associated with hypogonadotrophic hypogonadism; such patients will have hyposmia and possibly colour blindness. Hormonal patterns in amenorrhoea with their associated diagnoses are shown in Table 1.

Table 1 Hormonal patterns in amenorrhoea with their associated diagnoses

Condition	Serum biochemistry
Ovarian failure	Raised FSH and LH Low E2
Polycystic ovarian syndrome	Normal/low FSH Raised/normal LH, Raised/normal E2 Raised free androgen index
Hypogonadotrophic hypogonadism	Low FSH, LH Low E2

E2, oestradiol; FSH, follicle-stimulating hormone; LH, luteinising hormone.

The free-androgen index is the relationship or ratio of the total testosterone concentration (slightly raised) to the sex-hormone-binding globulin concentration, which is lowered in PCOS. This is on a molar/molar basis and may be rescaled by a factor of 10, 100, or 1000. It is often raised in severe acne, male androgenic alopecia, and hirsutism, as well as PCOS, for which it can be a sensitive and specific indicator if elevated in the early follicular phase.

Chromosomal abnormalities (e.g. Turner's syndrome 45XO) can be diagnosed by karyotyping. Autoantibody screens should be undertaken in women with a premature menopause. Premature menopause can be associated with an increase risk of heart disease and, consequently, it may be useful to check serum cholesterol levels in these patients. Women with PCOS and prolonged amenorrhoea have an increased risk of endometrial hyperplasia and carcinoma; endometrial sampling may be useful if any abnormal bleeding occurs.

Primary amenorrhoea

Chromosomal

Turner's syndrome (gonadal dysgenesis), in which there is also dwarfism, web neck, cubitus valgus, and an XO sex-chromosome pattern (Fig. 1) is the commonest form of gonadal dysgenesis. These women may develop spontaneous menstruation; however, premature ovarian failure is common. The gonadotrophin levels may be raised, and such women may require hormone replacement therapy (HRT). Although spontaneous conceptions have been reported, some form of assisted conception is likely to be required, if pregnancy is desired.

Testicular feminisation (which is, in reality, androgen insensitivity) in which the form is female with well-developed breasts, but with absent or sparse pubic and axillary hair, and the gonad, which may be found in the groin or in the abdomen, is a testicle. The gonadal tissue should be removed because of the increased risk of malignancy.

In *ovarian dysgenesis*, there are streak ovaries, an infantile uterus and absent secondary sexual characteristics. In these cases, a buccal smear for sex chromatin and a chromosome analysis on a sample of peripheral blood are indicated.

In ovarian dysgenesis, there is a chromatin-negative smear but only 45 chromosomes – a single X chromosome (XO). In testicular feminisation, the smear is also chromatin negative, but there are

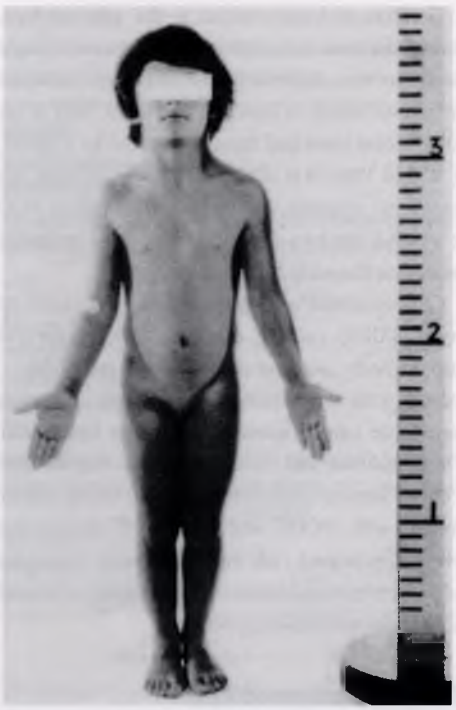

Figure 1 Turner's syndrome. (Courtesy of Professor Paul Polani.)

46 chromosomes (XY). Gonadal biopsy is also helpful in diagnosis.

Müllerian duct abnormalities

The Wolffian ducts regress in the embryo after the sixth week if the Y chromosome is lacking. The Müllerian ducts will develop into the tubes and uterus, and fuse caudally with the urogenital sinus to produce the vagina (Fig. 2). Abnormalities may occur in the process of fusion; these may be medial or vertical and give rise to primary amenorrhoea. Complete or partial Müllerian agenesis may occur. In these cases, the genotype is 46XX with normal secondary sexual characteristics and normal ovarian tissue, but the vagina is short and may require surgery. There may also be associated urinary tract abnormalities.

The commonest form of abnormality is that of an imperforate hymen, which leads to primary amenorrhoea or cryptomenorrhoea (hidden menses). The secondary sexual characteristics are normal, but the individual may complain of cyclical lower abdominal pain and abdominal distension. It is not unusual for these cases to present with retention of urine and,

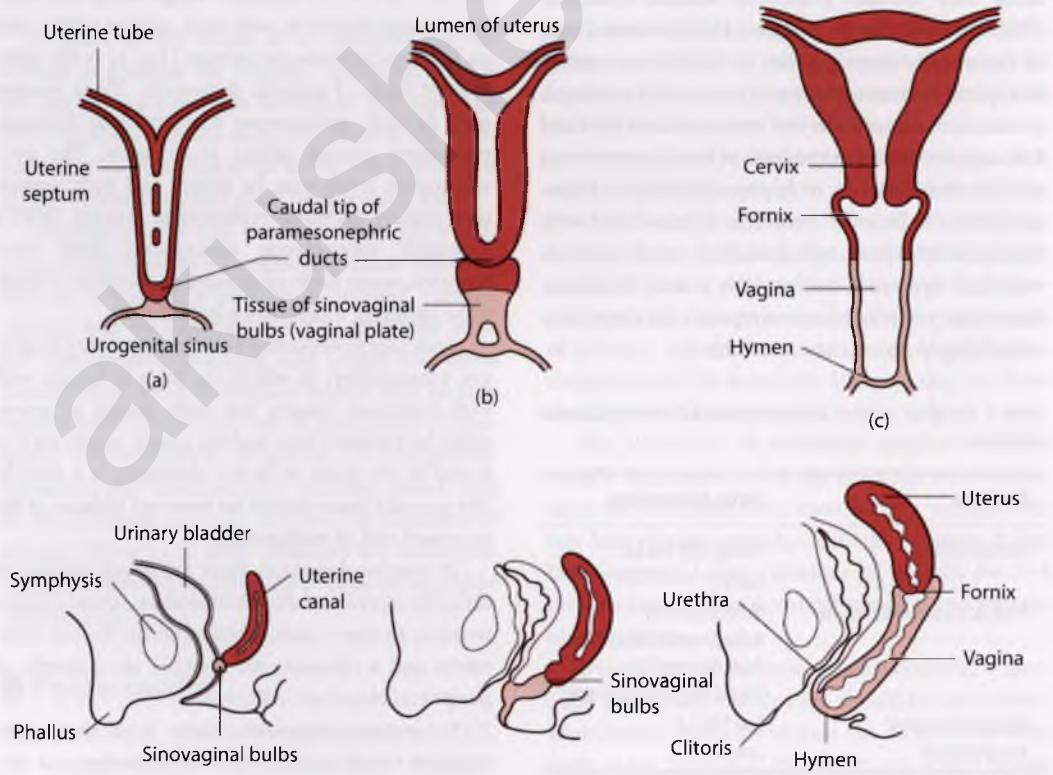

Figure 2 Development of the genital tract.

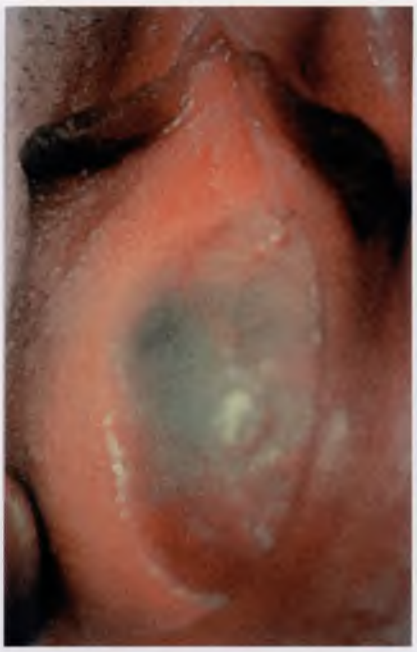

Figure 3 Imperforate hymen.

on inspection, have a bulging hymen (Fig. 3). A cruciate incision releases the menses, and that is all that is necessary.

Secondary amenorrhoea

Genital tract abnormalities

There is a potential for scarring anywhere within the genital outflow tract. Ashermann's syndrome is a condition where intrauterine adhesions develop which prevent normal endometrial growth. It is an uncommon condition, and usually occurs following vigorous curettage at the time of an evacuation of the uterus or suction termination of pregnancy. Cervical stenosis can cause cryptomenorrhoea with development of a haematometra, and may result from repeated treatment of the cervix for precancerous lesions. Radiotherapy may have an effect on the cervix and uterus if used for advanced cancer of the cervix, and may cause vaginal stenosis. In these cases, the amenorrhoea is more likely to be related to the radiotherapy effect on the ovaries than outflow obstruction.

Systemic disorders

Chronic disease may cause menstrual disorders as a consequence of the general disease state, weight loss, or effects on the hypothalamic–pituitary axis. Certain disorders will affect gonadal function directly. Chronic renal disease will act by increasing the serum LH level and also prolactin levels, possibly due to reduced renal clearance. Other causes would include systemic conditions in the form of tuberculosis or sarcoid.

Weight-related amenorrhoea

Body weight and BMI can have a significant effect on the regulation and release of serum gonadotrophins. Menstruation will not occur regularly if the BMI falls below 19, and it is estimated that 22 per cent of female body weight should be fat to ensure ovulatory cycles. Fat in the form of adipose tissue is a source of oestrogen by the aromatisation of androgens to oestrogen. This ensures the appropriate feedback mechanism of the hypothalamic–pituitary–ovarian axis. The weight loss may a result of illness, exercise, or dieting. Potential sequelae of a low BMI include the long-term effects on bone mineralisation.

Stress in itself is unlikely to give amenorrhoea lasting longer than 2 months unless associated with debilitation. Exercise, particularly in the endurance events, is a common cause of amenorrhoea, and this is also usually related to the BMI and body fat content, as described above.

Hypothalamic causes

These causes are uncommon and include craniopharyngioma, gliomas, and dermoid cysts. The mechanism of action may be to destroy local tissue or disrupt dopamine production, resulting in hyperprolactinaemia. Treatment is usually surgical, and possibly radiotherapy. HRT may be necessary together with other hormonal supplementation depending on the extent of the local damage in the pituitary. Head injury or irradiation may have a similar effect.

Pituitary causes

The commonest pituitary cause of amenorrhoea is hyperprolactinaemia, which may be physiological due to lactation, or iatrogenic, or pathological. A non-functioning tumour or pituitary adenoma may affect dopamine secretion levels, as may prothiazines and metoclopramide. The consequence is a rise in the serum prolactin level. Galactorrhoea may occur in up to a third of patients and, very occasionally, there may be visual field impairment.

Unless the serum prolactin is markedly raised, it is unlikely to show any effect on the sella turcica on a lateral skull X-ray. MRI scanning may be a more appropriate investigation.

Treatment involves the use of a dopamine antagonist, usually bromocriptine or a related drug. This should be discontinued if the patient becomes pregnant: a quarter of adenomas will increase in size during pregnancy.

Profound hypotension following delivery can cause Sheehan's syndrome, which can affect the pituitary, causing necrosis, as the pituitary has an end artery with no collateral supply to protect it in such a circumstance. Appropriate induction agents will be needed to induce ovulation.

Treatment needs to be given to correct the amenorrhoea and oestrogen deficiency, improve libido and effect tumour shrinkage in cases with hyperprolactinaemia. It is safe for these women to use the combined oral contraceptive pill if they require contraception.

Ovarian causes

Premature ovarian failure is defined as the cessation of periods before the age of 40 years. This may be due to chromosomal abnormalities, which have already been discussed, or to chromosomal mosaicisms. The most common causes include autoimmune disease, as well as infection, previous surgery, chemotherapy, and radiotherapy.

Tumours are an unusual cause of amenorrhoea, but arrhenoblastomas can cause virilism as well as amenorrhoea, atrophy of the breasts, and hirsutism.

Iatrogenic causes

The obvious causes include radiotherapy and chemotherapy for malignant disease. Others that may need to be considered are forms of contraception, including the Mirena coil and progesterone-only pills such as Depo-Provera, as well as post-pill amenorrhoea and gonadotrophin-releasing hormone analogues. A list of drugs that have also been associated with secondary amenorrhoea is shown in Box 1.

Classification of amenorrhoea

Although the basic classification is primary and secondary, amenorrhoea can also be classified as shown in Box 2.

Box 1 Drugs associated with secondary amenorrhoea

- Amoxapine
- Carbenoxolone
- Cyclophosphamide
- Danazol
- Domperidone
- Fluvoxamine
- Glucocorticoid
- Imipramine
- Isoniazid
- Leuprorelin
- Methyldopa
- Neuroleptic agents
- Procainamide
- Tamoxifen

Box 2 Classification of amenorrhoea

Physiological
- Before puberty
- After the menopause
- During pregnancy
- During lactation

Hypothalamic
- Primary hypothalamic–pituitary failure
- Following oral contraceptives (post-pill)
- Anterior pituitary failure (Sheehan's disease)

Pituitary

Ovarian
- Congenital absence of ovaries (rare)
- Ovarian agenesis
- Gonadal dysgenesis (Turner's syndrome)
- Destruction of both ovaries by double ovarian growths
- Polycystic ovarian disease
- Resistant ovarian syndrome
- Certain rare functioning tumours of the ovary: arrhenoblastoma, granulosa-cell tumour

Genital outflow (uterine, cervix, vagina and vulva)
- Imperforate vagina
- Imperforate hymen
- Absence of the vagina

- Imperforate cervix
- Double uterus with retention
- Congenital absence of uterus
- Uterine hypoplasia of infantile type
- Uterine hypoplasia of adult type
- Haematocolpos
- Haematometra
- Haematosalpinx

Acquired

- Ashermann's syndrome
- Pelvic inflammation
- Closure of the vagina:
  - due to specific fevers
  - due to injury
- Closure of the cervix
  - due to injury
  - following operations, e.g. loop cone biopsy

Endocrine

- Myxoedema
- Addison's disease
- Thyrotoxicosis
- Adrenal hyperplasia
- Adrenal cortical tumours
- Acromegaly

Iatrogenic

- Pelvic irradiation
- Hysterectomy
- Depo-Provera
- Progesterone-only contraception
- Mirena coil
- Drugs mentioned earlier (see Box 1)

General

- Anaemia
- Leukaemia
- Hodgkin's disease
- Malignant growths
- Tuberculosis
- Prolonged suppuration
- Diabetes
- Late stages of nephritis
- Late stage of some forms of heart disease
- Late stage of cirrhosis of the liver
- Dietetic deficiencies, the result of attempts to lose weight
- Toxic
- During and after specific fevers
- Chronic poisoning by lead, mercury, morphine, alcohol
- Anorexia nervosa or loss of weight
- Obesity
- Dystrophia adiposo-genitalis (Frohlich's syndrome)
- Cretinism
- Stress

MENSTRUAL PERIODS, HEAVY AND/OR IRREGULAR (MENORRHAGIA/METRORRHAGIA)

Fredric Willmott and Tony Hollingworth

Heavy menstrual bleeding (HMB), also known as *menorrhagia*, refers to excessive menstrual flow whereby the patient is free from bleeding during the intermenstrual period. The terms irregular uterine bleeding and intermenstrual bleeding are used for bleeding that occurs between periods; this condition is also called *metrorrhagia*. HMB is an important symptom of many well-defined conditions, which may or may not be associated with irregular cycles. As a rule, delayed menstruation is often associated with an increase in the menstrual blood flow. These terms are limited to patients who menstruate and must not be used for bleeding after the menopause.

Heavy menstrual bleeding is a subjective symptom which hampers a woman's physical, emotional, social, and material quality of life. Any treatment should aim to improve quality of life. The menstrual loss consists of blood, but can include other tissue and secretions. Objectively, periods are considered to be heavy if there is more than 80 mL blood loss per month, which will result in iron-deficiency anaemia. The diagnosis of heavy menstrual bleeding is of necessity a self-diagnosis, although even mild anaemia (haemoglobin <12 g) is a good indication of the severity. Sleep disturbance, clots, and flooding all provide some indication that menstruation is excessive. Heavy bleeding is the second most common cause for hospital referrals, and up to one-third of women may consult their primary care physician about this symptom.

An excess of menstrual loss in women without evidence of pathology is sometimes called abnormal uterine bleeding (AUB), or unexplained HMB. Acute endometritis of gonococcal or pyogenic origin

tends to cure itself, owing to the shedding of the endometrium during menstruation. Tuberculous endometritis, a rare cause of infertility in the UK, is due to spread from the Fallopian tubes and is, therefore, associated with menorrhagia owing to the tuberculous salpingo-oophoritis. If a tuberculous infection is suspected, the uterine curettings should be examined for the typical tubercles and the organism isolated by culture. Adenomyosis may also cause HMB. The causes of heavy menstrual bleeding are given in Box 1.

Box 1 Causes of heavy menstrual bleeding (HMB)

Unexplained or abnormal uterine bleeding (AUB)

Anovulatory HBM

- At puberty
- At maturity without obvious lesions
- In relation to the menopause, and in the years preceding

Underlying pathology

Ovulatory HMB

- Fibroids
- Chronic pelvic infection
- Endometriosis
- Adenomyosis
- Intrauterine contraceptive devices
- Bleeding disorders
- Thyroid disorders
- Tuberculous endometritis

Heavy menstrual bleeding with irregular cycles

During puberty, HMB can occur as a result of hypofunction of the anterior pituitary body, with consequent failure of ovulation, and therefore no corpus luteum is formed. The ovaries contain unruptured Graafian follicles; there is increased oestrogen production and a lack of the luteal hormone progesterone. Once the pituitary gradually assumes its normal cyclic activity, then the cycles often occur spontaneously. These are anovulatory cycles and are usually painless.

Perimenopausal women may experience heavy menstrual bleeding secondary to cessation of regular ovulatory cycles. When there is a complete absence of progesterone in the second half of the menstrual cycle, the cycle is referred to as *anovular*, drawing attention to failure of ovulation and formation of a corpus luteum. The endometrium may undergo polypoidal thickening with a characteristic microscopic appearance known as 'Swiss cheese' endometrium or 'complex hyperplasia'. Episodes of amenorrhoea of some weeks may be followed by prolonged irregular and heavy bleeding.

Heavy menstrual bleeding with pathology

Heavy menstrual bleeding can be associated with fibroids (benign leiomyomas), adenomyosis, pelvic infection, endometrial polyps, endometriosis, and the presence of an intrauterine contraceptive device. Of all the causes of pure HMB, leiomyoma (fibroids) of the uterus stands out as the only important growth associated with this symptom, and a simple bimanual examination most often suffices to show that such a tumour exists. The size and shape of the uterus is dependent on the number and size of the fibroids, as there may be more than one tumour in the uterus, whose shape may be exceedingly irregular. The uterus feels firm and, in most cases, is mobile.

The only difficulty in diagnosis, as a rule, lies in distinguishing a fibroid of the uterus from an ovarian cyst. This is sometimes difficult, for it is not always possible to say that a given tumour is actually the enlarged uterus. Ultrasound is the first-line diagnostic tool for identifying structural abnormalities. Fibroids may be submucosal, intramural, subserosal, or pedunculated. Distortion of the uterine cavity with an increase in the surface area from which menstruation occurs will lead to menorrhagia (Fig. 1).

Chronic pelvic infection (in the form of a pyosalpinx, a hydrosalpinx, a tubo-ovarian abscess, or chronic interstitial salpingitis) and ovarian endometriosis both give rise to HMB as a result of inflammation, but dysmenorrhoea, pelvic pain, dyspareunia, and backache are usually more prominent symptoms. In either case, a firm tender swelling in the pouch of Douglas is felt on bimanual palpation. Intermenstrual or irregular bleeding is also common in these cases.

Adenomyosis is a condition that can present with HMB and pain at the time of menstruation; on examination the uterus may be tender. The diagnosis can be confirmed only by histology, where endometrial tissue is found invading the myometrium (Fig. 2). In essence, there has been bleeding in the

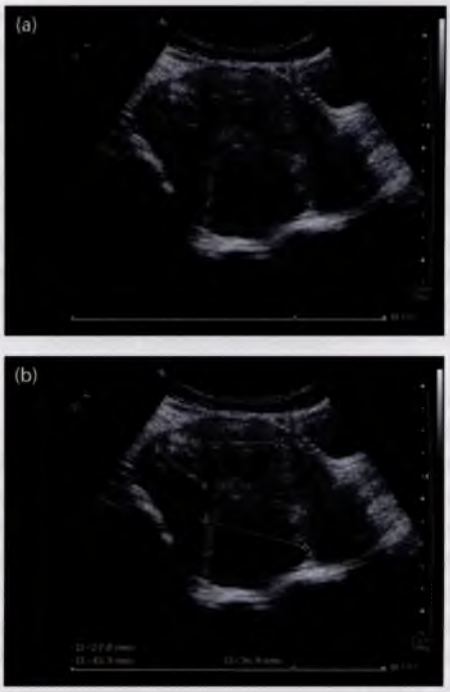

Figure 1 Ultrasound scan showing enlarged and distorted cavity due to fibroids.

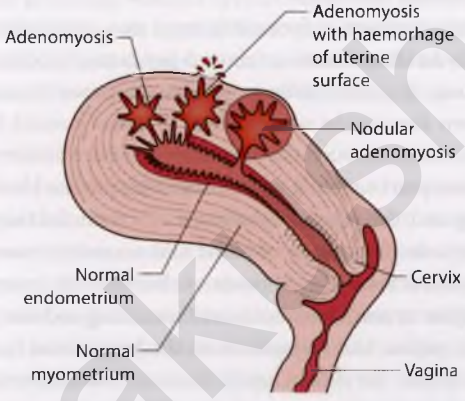

Figure 2 Diagram of adenomyosis, with endometrium extending into the myometrium.

myometrium that gives rise to the pain and tenderness. The condition is more common in parous women.

There is almost always some increase of the menstrual blood loss with the use of intrauterine contraceptive devices (IUCDs; copper devices) and, in some cases, the loss amounts to HMB. This results from the inflammatory reaction the coil sets up in the myometrium to prevent implantation of the fertilised egg. Changing the IUCD to a progestogen-releasing IUCD usually improves the situation.

Clotting defects

There are certain haemorrhagic disorders that can cause excessive menstrual loss. These include thrombocytopenic purpura, von Willebrand's disease and Christmas disease. Therefore any young woman presenting with anaemia secondary to menorrhagia should undergo a clotting screen. These women may suffer excessive menstrual loss and may require surgical intervention.

In thrombocytopenia, the blood loss relates to the platelet level and, in some cases, splenectomy for the underlying cause has improved the menstrual symptoms.

Anticoagulation in women who are on long-term anticoagulants for prosthetic heart valves, previous pulmonary embolism or, in some cases, antiphospholipid syndrome may develop significant period problems depending on the international normalised ratio level.

Thrombocytopenia can sometimes be complicated by HMB. As soon as the platelet level is back to normal, the blood loss usually becomes normal.

Medical disorders

The function of the thyroid and adrenal glands can influence the menstrual loss, although the mechanism is unknown. HMB tends to be more common in hypothyroidism than thyrotoxicosis, and is not uncommon with Cushing's disease.

Intermenstrual uterine bleeding

Intermenstrual uterine bleeding means loss of blood vaginally between the menstrual periods, and the term should be applied strictly only to irregular haemorrhages during the reproductive age range, that is, from puberty to the menopause. It may be used for losses of actual blood or for blood-stained discharges in which mucus is mixed with blood. For the purposes of discussion, irregular vaginal bleeding will be considered here under three headings:

- irregular bleeding during menstrual life;
- irregular bleeding before puberty and after the menopause;
- irregular bleeding during pregnancy.

It is important to emphasise that, if a woman has had regular periods and then starts to get irregular bleeding for no apparent reason, one must exclude pregnancy – and if not excluded, where that pregnancy is located, such as an ectopic pregnancy,

which is still a major cause of maternal death in the UK. Endometrial biopsy is recommended (NICE) if there is persistent intramenstrual bleeding.

Irregular bleeding during menstrual life

The causes of irregular bleeding during menstrual life are given in Box 2.

Box 2 Causes of irregular bleeding during menstrual life

Generative system
- Malignant growths
- Carcinoma of the cervix
- Carcinoma of the uterus
- Sarcoma
- Chorionic carcinoma
- Carcinoma of the Fallopian tube
- Carcinoma of the ovary

Benign growths
- Submucous fibroids
- Endometrial and endocervical polyps

Other
- Endometriosis
- Ectropion of the cervix
- Tuberculosis of the uterus

Endocrine
- Anovulatory heavy menstrual bleeding
- Breakthrough bleeding on the oral contraceptive pill and hormone therapy

Malignancy

Carcinoma of the cervix

Cervical cancer is an uncommon disease with an incidence that is becoming less common as a result of the cervical screening programme. It is estimated that a general practitioner in the UK will see one case of cervical cancer every 7–9 years. The cervix is replaced with a friable mass, which causes irregular bleeding as well as postcoital bleeding. The lesion can be diagnosed macroscopically, although many of these women will be seen in the colposcopy clinic so that a directed biopsy can be undertaken (see Cervical swellings).

Carcinoma of the uterine body

Endometrial carcinoma does occur during the reproductive age group, but it is much more common in postmenopausal women. It is the second most common genital tract tumour and presents with irregular bleeding. Risk factors include obesity (raised body mass index [BMI]), nulliparity, and history of polycystic ovarian disease. It is unusual to diagnose this condition before the age of 45 years, hence the NICE recommendations that women with menstrual irregularities before the age of 45 years should receive treatment for 3 months. If the irregularity persists, then a hysteroscopy and endometrial sampling should be undertaken. If the woman is over 45, this would be a first-line investigation (see Uterine swellings).

Sarcoma of the uterus

This is a very uncommon tumour and occurs in fibroids. It may present with irregular bleeding, but many of these women will be postmenopausal and present with a rapidly expanding pelvic mass. The risk of a fibroid becoming malignant is estimated at about 1 in 1000. This tumour may occur in an existing fibroid or appear de novo. The difficulty with this condition is the highly aggressive nature of the disease, which does not respond well to radiotherapy or chemotherapy as a rule (see Uterine swellings).

Chorionic carcinoma

This condition is fortunately very rare, and follows a hydatidiform mole in about 5 per cent of recorded cases. It always follows pregnancy, never having been seen in the uterus where pregnancy could be excluded, although the pregnancy may have occurred some years earlier. It is associated with profuse bleeding and the rapid development of a fetid discharge from decomposition of blood and necrosing tissues in utero. Secondary deposits of chorionic carcinoma appear as small, plum-coloured ulcerating nodules in the vagina, and secondaries in the lungs cause haemoptysis. The patient rapidly becomes ill with pyrexia and profound anaemia. A raised level of chorionic gonadotrophin is found in the urine. The diagnosis depends upon the finding of masses of trophoblastic cells in uterine curettings without any evidence of villous formation (see Bleeding during early pregnancy).

Other malignancies

Carcinoma of the Fallopian tube is a rare tumour and tends to present in the postmenopausal woman, but may present with irregular bleeding. Ovarian cancer is unlikely to cause bleeding unless it has invaded the uterus. Clear-cell carcinoma of the vagina is also rare and has been reported in teenage girls exposed to stilboestrol in utero.

Benign lesions that may cause irregular bleeding

Fibroids

Leiomyomas may cause a mixture of HMB and intermenstrual spotting. The irregular bleeding tends to occur when they are submucous. They may be in the process of extrusion when they may become infected and sloughing occurs. The reason for this is that, in these conditions, the tumours are partly strangulated by uterine contractions and consequently congested with venous blood. This results in bleeding, which is unpredictable in timing and amount.

Polyps

Polyps can occur within the cervix and endometrium. Cervical polyps are usually identified during a routine cervical smear test. If the tip becomes inflamed, it can give rise to vaginal bleeding or postcoital bleeding. Polyps within the endometrial cavity, whether fibroid or mucous, are common causes of intermenstrual bleeding, and are usually quite definitive growths. The mucous polyp is soft, strawberry-red, and pedunculated, and contains cystic spaces filled with glairy mucus. It rarely gives rise to a malignant growth. The fibroid polyp is hard and shows the glistening whorled appearance so well known in fibromyomas on section. These growths are liable to infection and sloughing, and are then apt to be mistaken for carcinoma or sarcoma macroscopically.

Endometriosis

This condition is defined as the finding of tissue outside the uterus that is histologically similar to that of endometrium, and is not strictly an inflammatory lesion. However, it is one of the commonest benign gynaecological conditions and may present with a myriad of symptoms, including painful bleeding and dyspareunia.

Ectropion of the cervix

This is a physiological condition in which there is eversion of the columnar epithelium from the endocervical canal towards the vagina. The columnar epithelium appears reddened because it is one cell thick and consequently translucent, allowing the blood supply below to be seen. The term erosion should be avoided, as it suggests something pathological. The epithelium can become inflamed and give rise to discharge, which sometimes results in contact bleeding, although intermenstrual bleeding is unusual. The columnar epithelium may undergo metaplastic change to squamous epithelium owing to pH changes within the vagina. This area is known as the transformation zone. It is in this area that pre-cancerous changes may occur. Pre-cancerous changes within the cervix are asymptomatic and usually only diagnosed by cytology and colposcopy.

Tuberculosis

Tuberculosis (TB) may affect the genital tract and give rise to irregular bleeding and infertility. It is an uncommon problem within the UK but is much more common in the developing world. Histology of the endometrial curettings may give the diagnosis, although a strong suspicion of TB suggests the need to involve a physician in the care of the woman.

Heavy menstrual bleeding without obvious pathology

Heavy menstrual bleeding without obvious pathology is also sometimes known as dysfunctional bleeding. It may occur at any age between puberty and the menopause, but 50 per cent occurs between the ages of 40 and 50 years, about 10 per cent at puberty, and the remainder between these ages. When it occurs in association with longer menstrual cycles, it is most likely the results of anovulation, and for this reason is more likely seen in adolescents, at the time of the perimenopause, and in women with polycystic ovarian syndrome. Usually when the bleeding is preceded by amenorrhoea for some weeks, the length of bleeding may be prolonged.

The histology of any curettings may prove to be essentially normal, although in women with an increased body mass index, or who have polycystic ovarian syndrome or are perimenopausal, endometrial hyperplasia may be present. Endometrial hyperplasia (Fig. 3) can occur as a result of excess oestrogen production. It is a premalignant condition that is rarely a cause of heavy menstrual bleeding but should be excluded in women who are overweight or are perimenopausal. These conditions have histological diagnoses, and how the woman is treated will depend on her age and fertility status. Women with complex hyperplasia with atypia are at risk of developing endometrial cancer, and thus hysterectomy is usually recommended.

Contraception and heavy menstrual bleeding

There are three main areas that can give rise to HMB:

- Copper-containing IUCDs. In some cases, the low-grade inflammatory response of the endometrium to the coil can result in irregular shedding. The initial treatment would be to remove the coil.

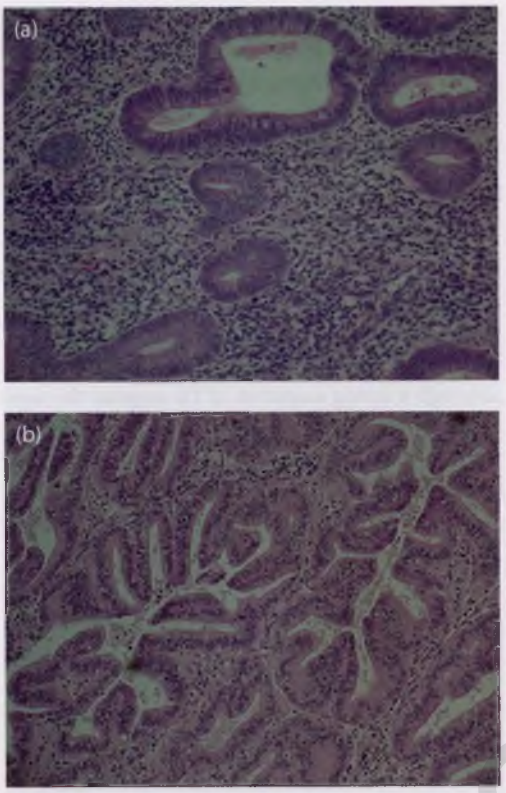

Figure 3 Histology of simple hyperplasia of the endometrium (a) and complex atypical hyperplasia (b).

- Progesterone contraception, whether as progesterone-only pills, the Mirena IUCD, or Depo-Provera, will usually result in the woman being amenorrhoeic. There are a number of women who develop irregular bleeding, which may be completely unpredictable, although it is usually not particularly heavy.
- The combined oral contraceptive pill usually gives good cycle control. However, breakthrough bleeding can occur owing to gastrointestinal upset, absorption and metabolism problems due to other medications (e.g. antibiotics and antiepileptic drugs), diet affecting the enterohepatic circulation, and a dosage too low for the individual.

Bleeding associated with ovulation

It is not uncommon for women to bleed very slightly about midway between the periods at the time of ovulation. When this is accompanied by lower abdominal pain (*mittelschmerz*), the diagnosis is straightforward.

Bleeding due to granulosa-cell tumour

When irregular bleeding occurs in the presence of an ovarian swelling, the possibility of a granulosa-cell tumour arises. Removal of the tumour and histology reveal its nature. The presence of an intrauterine lesion and a non-secreting ovarian tumour must not be overlooked.

Irregular bleeding before puberty and after the menopause

The bleeding that occurs from the vagina occasionally in newborn infants is usually due to a high concentration of oestrogen in the fetal circulation. It is usually trivial but a fatal case has been reported. Bleeding later in childhood may be due to sexual precocity, when secondary sexual characteristics will be in evidence, or due to a new growth, such as an embryonal rhabdomyosarcoma (sarcoma botryoides). Vaginoscopy under anaesthesia (and biopsy, if a lesion is found) is essential.

After the menopause, the identification of malignant growths, polyps, and senile endometritis can be established only by uterine curettage (see Bleeding, postmenopausal). Carcinoma of the body of the uterus (endometrial adenocarcinoma) is the commonest malignant growth after the menopause. In any doubtful case, routine dilatation and curettage of the uterus must never be omitted. Senile (atrophic) vaginitis must not be overlooked as a possible cause: the vaginal walls at the fornices become inflamed and may bleed if the surfaces rub together; the surfaces may be partly adherent, and the separation brought about by the examining finger may cause bleeding. Pyometra, or distension of the uterus with pus, may cause haemorrhage with a foul discharge. Although this is almost always due to malignant growth, it may be only the result of infection. The only growth of the ovary that produces uterine haemorrhage is the granulosa-cell tumour and may occur at almost any age (see Ovarian swellings).

In women with postmenopausal bleeding, ultrasound scanning to measure the endometrial thickness may be a useful way to triage these patients. If the endometrial thickness is 5 mm or less, then no further action is needed unless the bleeding continues. Otherwise hysteroscopy and endometrial sampling is recommended.

Useful website

National Institute for Health and Clinical Excellence. Heavy menstrual bleeding. NICE Clinical Guideline 44. London: NICE, 2007.

MENSTRUAL PERIODS, INFREQUENT (OLIGOMENORRHOEA)

Tony Hollingworth

Oligomenorrhoea is a term that defines menstrual periods that occur repeatedly at intervals between 6 weeks and 6 months. It is an arbitrary definition and may be misleading. It is considered that the normal menstrual cycle has an upper limit of 35 days. The proliferative phase, that is, the time during which the follicle (the egg) develops, is the variable part of the cycle. The secretory or luteal phase is the time from ovulation to menstruation, which is usually constant at 14 days. Cycles of 6 weeks' duration seem to show no difference from normal-length cycles in regards to follicular and hormone development.

There are several conditions that lead to oligomenorrhoea, and these range from normal conditions (for a particular woman) to the same conditions that cause amenorrhoea (see Menstrual periods, absent). Some common causes are:

- Polycystic ovarian syndrome, which accounts for about 90 per cent of cases of oligomenorrhoea compared with only 33 per cent of amenorrhoea. In this situation, the menstrual periods are usually light and the woman may not ovulate (anovulation).
- A prolonged proliferative phase, associated with ovulatory oligomenorrhoea. It often occurs in adolescent girls or at the time of menarche, and in older women in the perimenopausal phase.
- Prolactinomas and other endocrine problems.
- Weight related, either low or very high BMIs.

Clinically, oligomenorrhoea should be considered in the same way as amenorrhoea for the purpose of investigations and further management.

MENSTRUAL PERIODS, PAINFUL, (DYSMENORRHOEA)

Fredric Willmott and Tony Hollingworth

Painful periods are also known as *dysmenorrhoea*, which comes from the Greek meaning 'difficult monthly flow'; however, it is used now to mean 'painful menstruation'. It is a symptom complex which includes cramping lower abdominal pain radiating to the back and legs, and is often associated with gastrointestinal upset, malaise, and headaches. Dysmenorrhoea is one of the most common conditions to affect a woman's quality of life (between 20 and 90 per cent of women). This section should be read in conjunction with Menstrual periods, heavy and/or irregular. The condition can be divided into primary and secondary dysmenorrhoea.

Primary dysmenorrhoea occurs when the periods are painful and no organic or psychological cause can be found. It usually occurs at the beginning of reproductive life when the girl starts ovulating, approximately 6–12 months after menarche. The pain starts with the onset of menstruation and is generally associated with ovulatory cycles. There is an abnormally high production of endometrial prostaglandins, which causes excessive uterine contractions. Examination findings are usually normal, and further investigation may be necessary only if treatment fails to alleviate the symptoms. The options for treatment include the levonorgestrel-releasing intrauterine system (NICE recommendation, but this can be difficult to insert if nulliparous or virgo intacta), the combined oral contraceptive pill to inhibit ovulation, and non-steroidal anti-inflammatory (NSAID) agents, which act as prostaglandin synthetase inhibitors to decrease the concentration of local prostaglandins and thereby reduce pain and menstrual loss. NSAIDs are preferred over tranexamic acid in dysmenorrhoea (NICE 2007). In the rare cases that medical treatment fails, surgery is an option. This includes uterosacral nerve ablation and presacral neurectomy.

Secondary dysmenorrhoea occurs when the woman experiences painful periods where an organic or psychosexual cause can be found. Cyclical/menstrual pain starts after several years of normal periods. Pain is exacerbated by menstruation and may persist after menstruation finishes. The differential diagnosis includes:

- pelvic inflammatory disease;
- endometriosis or adenomyosis;
- submucosal fibroids;
- intrauterine polyps
- intrauterine contraceptive device;
- cervical stenosis following treatment for pre-cancer;
- ovarian tumour;
- previous pelvic or abdominal surgery;
- pelvic congestion syndrome;
- previous history of sexual abuse or other psychological problems.

Taking a detailed history is important in order to guide diagnostic tests. Pelvic examination should be performed and swabs taken, if indicated. A tender

uterus may indicate the possibility of adenomyosis; restricted mobility or a fixed retroverted uterus may suggest the presence of adhesions secondary to endometriosis, pelvic inflammatory disease, or previous surgery. A previous history of cone biopsy or other excision procedures for cervical intraepithelial neoplasia might suggest the possibility of cervical stenosis, which can require dilatation of the cervix.

Investigations will depend upon the history. An ultrasound scan may be useful, especially if vaginal examination is difficult or painful. Research evaluating the role and practicality of magnetic resonance imaging (MRI) is awaited. In many cases, laparoscopy may be indicated to exclude a particular pathology, especially endometriosis. If the findings are normal, then often reassurance in itself may be sufficient.

Treatment depends on the cause. If no pelvic pathology is found, the treatment can be as for primary dysmenorrhoea. If adhesions, endometriosis, or intrauterine pathology is found, hormonal preparations or surgery, or both, may be required.

Useful websites

Clinical knowledge library: www.cks.library.nhs.uk
Patient UK – painful periods: www.patient.co.uk/showdoc/23068726

MISCARRIAGE, RECURRENT

Mala Arora

Recurrent miscarriage is a term coined by Malpas of Liverpool to define women who have had three or more consecutive *miscarriages*. *Miscarriage* is defined as the loss of a pregnancy of less than 20 weeks' gestation or the loss of a fetus that weighs less than 500 g. This is so defined because fetuses below this weight and gestation will not survive.

Sporadic miscarriages occur in up to 25 per cent of pregnancies. A woman may have three sporadic miscarriages during her reproductive career, but these are usually interspersed with viable births and are not classified as recurrent miscarriages.

Primary aborters are women who have no previous term pregnancy and *secondary aborters* are women who have one or more pregnancies that have proceeded beyond 20 weeks' gestation.

The incidence of recurrent miscarriage is 1–2 per cent and the incidence of sporadic miscarriage is 10–11 per cent. By simple statistical extrapolation, the chance of a woman having three sporadic miscarriages in a row is 0.35 per cent. However, since the incidence of recurrent miscarriages is 1–2 per cent (i.e. 3–6 times higher), it points to the fact that a definitive pathology exists in these patients with recurrent miscarriages.

The causes of recurrent miscarriage are listed in Box 1.[1] The list is exhaustive, and more than one factor may operate in successive pregnancies, e.g., early miscarriages from any cause may be coupled with a late miscarriage resulting from cervical incompetence. On the other hand, early miscarriages may be coupled with a late fetal demise in patients with either congenital or acquired thrombophilia.

Box 1 Causes of recurrent miscarriage

Immunological
- Primary antiphospholipid syndrome
- Secondary antiphospholipid syndrome

Genetic
- Fetal trisomy, polyploidy, monosomy
- Parental balanced translocations, inversions, deletions, duplications

Hormonal
- Polycystic ovarian syndrome
- Luteal phase defects
- Hyperandrogenism
- Uncontrolled diabetes mellitus
- Hypothyroidism/hyperthyroidism
- Hyperprolactinaemia
- Premature ovarian failure
- Adrenal hyperplasia/Addison's disease

Anatomical
- Müllerian abnormalities, septate uterus
- Fibroids – submucous, intramural
- Uterine synechiae
- T-shaped uterus
- Cervical incompetence

Inherited thrombophilia
- Antithrombin III deficiency
- Deficiency of protein C and protein S
- Factor V Leiden mutation
- Methyl tetrahydrofolate gene homozygosity (hyperhomocysteinaemia)
- Prothrombin gene mutation

Infections
- Genital bacterial vaginosis, latent tuberculosis
- Systemic syphilis, Lyme's disease, toxoplasmosis, brucellosis

Systemic conditions
- Hypertension
- Chronic renal disease
- Chronic pulmonary disease
- Heart disease
- Severe rhesus sensitisation

Miscellaneous
- Obesity BMI >30
- Smoking, alcohol, drugs
- Exposure to irradiation
- Exposure to environmental toxins, pesticides
- Exposure to anaesthetic gases

Idiopathic
- Cytokine abnormalities
- Increased uterine natural killer cells
- Tumour necrosis factor
- Lack of pinopode formation (problem with endometrial formation)

BMI, body mass index.

Immunological causes

Antiphospholipid antibody syndrome (APS) is the commonest immunological cause of recurrent miscarriage. Antibodies are directed against negatively charged phospholipids, which are the major constituents of trophoblasts. These antibodies can cause placental thrombosis, infarction, impaired trophoblastic function, and abnormal placentation, leading to pregnancy-induced hypertension, intrauterine growth retardation (IUGR), intrauterine fetal death, and recurrent miscarriage.[2,3] Pregnancy loss usually occurs in the mid-trimester between 14 and 18 weeks; however, both early first-trimester losses and late third-trimester losses can occur. There is an ultrasound confirmation of a viable pregnancy prior to the pregnancy loss in most first trimester losses.

Diagnosis of APS

The diagnosis of APS is made by the presence of at least one clinical criterion and one laboratory criterion on two occasions 3 months apart.

Clinical criteria include the following:[4]

- one or more unexplained deaths of a morphologically normal fetus of more than 10 weeks' gestation documented by ultrasonography or direct examination;
- one or more preterm births at or before 34 weeks' gestation due to severe pre-eclampsia or placental insufficiency with evidence of IUGR;
- three or more miscarriages of less than 10 weeks' gestation when genetic, hormonal, anatomical and infective causes have been excluded.

Laboratory criteria include detection of either lupus anticoagulant or anticardiolipin antibodies or both.

Autoimmune disorders, such as systemic lupus erythematosus, systemic sclerosis, and autoimmune thrombocytopenia, are associated with recurrent miscarriage, and are often classified as secondary antiphospholipid syndrome (or SAPS). The mechanism of loss and the treatment are the same as those for APS.

Genetic causes

Genetic abnormalities in karyotypically normal parents

Various studies demonstrate that at least 50 per cent of clinically recognised pregnancy losses result from a cytogenetic abnormality,[5–8] of which 51 per cent show autosomal trisomies, 22 per cent show polyploidy, 19 per cent show monosomy, and 4 per cent show translocations, with the rest being unclassified genetic defects. The autosomal trisomies commonly encountered are those of chromosomes 3, 4, 9, 13–16, 19, 21, and 22.[9]

Genetic abnormalities in karyotypically abnormal parents

Women may have structural chromosomal abnormality in the following forms:

- Deletions and duplications produce large chromosomal defects, which may cause severe phenotypic anomalies; thus individuals with these anomalies rarely reproduce.
- Dicentric and ring chromosomes are mitotically unstable, so the chances of offspring acquiring these anomalies are very small.
- In men with balanced translocations, the reproductive potential is only slightly diminished.[10] In spite of their good reproductive performance, these individuals show a significant decrease in live births, and a significant increase in both fetal death and recurrent miscarriages.
- In unbalanced translocations in men, not only is the reproductive performance greatly decreased, but also the risk of abnormal offspring is increased.[10]

Hormonal disorders

A multitude of endocrinal disorders can cause recurrent miscarriage. *Polycystic ovarian syndrome* is one of the commonest endocrinal abnormalities affecting female reproductive performance. Besides infertility, it presents higher risks of first- and second-trimester miscarriages.[11,12]

Factors associated with a high miscarriage rate are *hyperandrogenism, hyperinsulinaemia* and *ovulatory dysfunction* that is associated with high levels of luteinising hormone and low levels of progesterone.

Women with poorly controlled *type 1 (insulin-dependent) diabetes mellitus* with glycosylated haemoglobin levels greater than eight standard deviations above the mean have a higher pregnancy loss rate.[13–15] Well-controlled diabetics have pregnancy loss rates similar to those of non-diabetics.[16] Apart from frank diabetes, syndrome X,[13] which is characterised by an impaired glucose tolerance test (GTT), hypertension, hypertriglyceridaemia, and a procoagulant state with increased coronary heart disease, is linked with recurrent miscarriages.

Abnormal maternal thyroid functions have been implicated as a cause of recurrent miscarriage.[17] However, mild or subclinical thyroid dysfunction with increased levels of thyroid antibodies has been associated with recurrent miscarriages.[18]

Hyperprolactinaemia usually causes infertility through luteolysis; however, in partially treated cases, the picture may change to miscarriages.

Although rare, the patient with an untreated *adrenal hyperplasia* may have an increased chance of recurrent miscarriage owing to hyperandrogenism. On the other hand, incipient *Addison's disease* will also cause recurrent miscarriages; the patient often has low blood pressure and hyperpigmentation.

Premature ovarian failure remains an important factor responsible for recurrent miscarriage, owing to declining ovarian function and poor quality oocytes. Women with follicle-stimulating hormone levels that fluctuate between 10 and 40 mIU/mL not only experience difficulty in conceiving but also have a higher rate of pregnancy loss.

Anatomic abnormalities

Anatomic abnormalities of the uterus and cervix are amenable to surgery. An estimated 15 per cent of couples (one in six) with recurrent miscarriage have an anatomic abnormality of their uterus as the primary cause. These abnormalities include:

- defects of Müllerian fusion, which include septate uterus, unicornuate uterus, and bicornuate uterus with unequal uterine horns;
- acquired anatomical defects, such as submucous or intramural fibroids, endometrial polyps, and Asherman's syndrome;
- small tubular uterine cavity: this may be secondary to diethyl stilboestrol exposure in utero or genital tuberculosis;
- cervical incompetence, which is diagnosed by shortening of the cervix on ultrasound scan.[19] It may be a congenital weakness or secondary to repeated cervical dilatation. It is also associated with unicornuate or bicornuate uteri.

Thrombophilias

These are rare inherited disorders that predispose an individual to venous and arterial thrombosis. They cause inadequate placental circulation owing to thrombosis in the placental vasculature, and lead to adverse pregnancy outcomes such as recurrent miscarriage, fetal death, and placental abruption.[20]

Congenital thrombophilias include:

- activated protein C resistance (APCR)[21] due to factor V Leiden mutation: a single missense (single point) mutation of the factor V gene can cause 90 per cent cases of APCR and is present in 5 per cent of the UK population;
- deficiency of antithrombin III: this occurs in 32–51 per cent of patients with thrombophilia;[22]
- deficiency of protein C and protein S: in patients with thrombophilia, 22–26 per cent have protein C deficiency, while 12–17 per cent have protein S deficiency;[22]
- prothrombin gene mutation G 20210A leads to elevated levels of prothrombin and is present in 2 per cent of the UK population;[22]
- homozygosity for the thermolabile mutation of methylene tetrahydrofolate reductase, causing hyperhomocysteinaemia.

The most common acquired thrombophilia is the antiphospholipid antibody syndrome.

Systemic conditions

Severe maternal illness, such as essential hypertension, cardiac disease, chronic pulmonary disease, and chronic nephritis, are important causes of recurrent miscarriages. Pregnancy in a rhesus-sensitised woman with a high titre of anti-D antibodies will also result in recurrent pregnancy losses.

Systemic infections such as syphilis, were an important cause of recurrent miscarriage in the past. Currently, Lyme's disease and toxoplasmosis

can result in repetitive losses. Bacterial infections such as *Brucella abortus* also cause recurrent miscarriage.

Genital infections

Genitourinary tuberculosis is classically associated with infertility but latent infection can also cause recurrent ectopic pregnancy as well as recurrent miscarriages. Bacterial vaginosis is now implicated in recurrent miscarriages, recurrent preterm labour, and preterm premature rupture of membranes.

Miscellaneous causes

Obesity is associated with increased risk of miscarriage after spontaneous conception, assisted reproduction and also in donor oocyte cycles. Hyperhomocysteinaemia is associated with thrombosis and can be genetic or dietary in origin. Administration of folic acid and vitamin B6 and B12 will help in decreasing homocysteine levels. Excessive smoking, alcohol intake, and the use of recreational drugs will cause recurrent miscarriage. Other factors include prolonged exposure to irradiation and anaesthetic gases, pesticides, and other environmental toxins.

Idiopathic

In 50 per cent of cases, the causes of recurrent miscarriages have yet to be clearly elucidated. Implantation is a complex process that involves synchronisation of endometrial maturity with fertilisation, expression of *HOX-A10* genes in the endometrium, and formation of pinopodes, as well as the presence of cytokines of the anti-inflammatory kind, such as interleukins 4, 6 and 10, leukaemia inhibiting factor (LIF), and transforming growth factor beta (TGF-β). A disturbance in any of the above processes will lead to early pregnancy losses. Absence of the cytokine leukaemia inhibitory factor in the endometrium is associated with recurrent miscarriages in the knockout mouse model, but its exact role in humans is yet to be elucidated. Other cytokine abnormalities in the endometrium are the subject of current research in recurrent miscarriages.

Hence recurrent miscarriages may occur due to a variety of causes, some well understood and others less so. Some are treatable, such as thrombophilia and those with an immunological, hormonal, or anatomical cause. Genetic causes are best investigated and treated through in-vitro fertilisation and pre-implantation genetic diagnosis. An abnormal cytokine environment may be responsible for some of the hitherto unexplained recurrent miscarriages.

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Useful websites

www.nice.org.uk/miscarriage
www.rcog.org.uk – Green-top Guideline 17, Nov 2011: Recurrent miscarriage, investigation and treatment of couples.
www.miscarriageassociation.org.uk

NOSEBLEEDS (EPISTAXIS) IN PREGNANCY

Mike Papesch and Eva Papesch

A nosebleed, or *epistaxis* (from the Greek *epi* meaning 'on' and *stazo* meaning 'to let fall in drops') is blood loss commonly from the front of the nose. Nosebleeds most frequently come from the anterior nasal septum called 'Little's area', first described by James L. Little (1836–1885), Professor of Surgery at the University of Vermont, USA.

Epidemiology

Nosebleeds are common in children, nearly always anterior in location and usually brief. In older patients, bleeding from the nose can be more severe, especially if the bleeding is from the back of the nose. They occur in about 15 per cent of the population, and peak in childhood and late adult life. They can also occur in pregnancy in association with increased blood pressure and the hypervascular state.

Anatomy

Anterior nosebleeds occur from Little's area, a watershed of arteries in front of the nasal septum. This is a confluence of blood vessels originating from both the internal and external carotid arteries (Fig. 1). Posterior nosebleeds are less common but much more severe, and originate from the sphenopalatine artery, a terminal branch of the maxillary artery (external carotid).

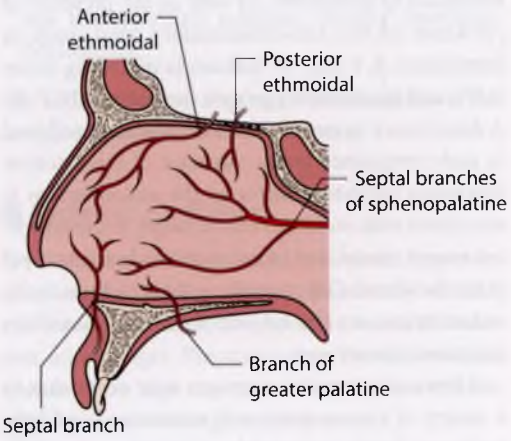

Figure 1 Arterial blood supply to the nose.

Aetiology of epistaxis

The aetiology of epistaxis is given in Box 1.

Box 1 Aetiology of epistaxis

- Trauma: nose picking, nasal spray, cocaine, surgery, foreign bodies, nasal septal perforation
- Nasal airflow/dry air: drying effect of septal deviation, airline travel
- Infective/inflammatory: acute viral/bacterial rhinitis/sinusitis, fungal infection,
- Pregnancy related: pyogenic granuloma gravidarum (nasal haemangioma of pregnancy), hypertension of pregnancy[1]
- Autoimmune: Wegener's granulomatosis
- Vascular malformations: haemangiomas, hereditary haemorrhagic telangiectasia[2]
- Neoplastic: inverted papilloma, adenocarcinoma
- Drugs: anticoagulants (warfarin, aspirin,[3] clopidogrel), non-steroidal anti-inflammatory drugs[4]
- Haemopoietic coagulopathies: blood dyscrasia, idiopathic thrombocytopenia purpura, haemophilia, etc.
- Cardiac: hypertension,[5] increased venous pressure[6]
- Metabolic: renal or liver disease, vitamin C and K deficiency, folic acid deficiency (and thrombocytopenia)[7]
- Vicarious menstruation and metastasis of endometrial tissue[8,9]

Pregnancy-related nosebleeds[10]

Pregnancy hormones affect the nasal mucosa, nasal cycle, and mucociliary nasal transport time, producing rhinorrhoea and nasal obstruction.[11,12] The increased vascularity of the nasal mucosa due to the effects of oestrogen makes bleeding secondary to minor trauma much more likely.

Pyogenic granuloma gravidarum (a form of lobular capillary haemangioma) occurs as oral (gingivitis gravidarum) or nasal lesions in less than 1 per cent of pregnant women.[13] These lesions range from a few millimetres to a centimetre in diameter, present as an elevated red or purple mass with a smooth, lobulated, ulcerative surface, and bleed easily with minimal trauma. Microscopically, the nodule consists of highly vascular granulation tissue displaying acute and chronic inflammation. They are hormone dependent, as they appear characteristically in the early months of pregnancy and, if not excised, usually regress following delivery.[14] They present with varying degrees of bleeding and nasal obstruction, and can occasionally be large and cause massive bleeding. Treatment is by excision.[15,16] If incompletely excised, they can recur and also develop satellite lesions.

The ulcerated surface of pyogenic granulomas often contains staphylococci or streptococci. One hypothesis has been that these organisms cause an overgrowth of granulation tissue because of delayed re-epithelialisation of a wound. Circulating angiogenic factors also play a role, particularly in pregnancy.[17]

Hypertension of pregnancy contributes to serious nosebleeds that may be difficult to control.

Clinical features

Anterior bleeds are usually unilateral, occur following minimal trauma, and are usually brief.

Posterior nosebleeds are often severe. They present with bilateral nasal bleeding, often with spitting up of blood. Severe nosebleeds[18] present as any acute blood loss episode with tachycardia, hypotension, sweating and pallor, features of hypovolaemic shock.[19] It is also important to be aware that women with heavy nosebleeds may present with antepartum fetal distress, even in the absence of maternal hypotension.

Management of small nosebleeds

The side and frequency of nosebleeds is important. History of trauma and nasal dryness is to be considered. Examination of the nose with a headlight may reveal a prominent anterior nasal septum vessel, with associated dry crusted blood. Minor anterior nosebleeds are managed with direct pressure over the soft part of the nose for 5 minutes by the clock (Fig. 2). The head is in the neutral position. Cotton wool and tissue nasal packs should be avoided, as these lead to re-bleeding when they are removed from the nose. Vaseline or other ointments (Naseptin – exclude peanut allergy as this contains arachis oil) are applied to the nose after the bleeding has stopped in order to aid healing and prevent scabbing and drying of the anterior nose. Ice is used to reduce nasal temperature and promote vasoconstriction of the nasal vessels. It is of more benefit to suck ice rather that apply ice to the forehead.[20–22] If nose bleeds are ongoing, and following application of cotton wool soaked with cophenylcaine or lignocaine and adrenaline to the anterior nose, bleeding vessels can be cauterised, commonly with silver nitrate. Naseptin cream is to be used on

the cauterised area for 3 weeks, three times a day, to aid healing. This cautery can be painful, requiring simple analgesics for symptom control. Sometimes cautery needs to be repeated. If bleeding is persistent, it is important to consider an underlying cause and to consider different treatments (see below). Ongoing use of simple moisturisers (E45 cream) or Vaseline can be useful to prevent dryness and bleeding from the anterior nasal septum.

Management of severe nosebleeds

History

On arrival, make sure you are wearing appropriate protective clothing, including gloves, glasses, and a mask. Postnasal bleeding leads to significant coughing and vomiting of blood, with resultant blood spray! Take note of the side of bleeding, the length and severity of the nose-bleed, and any precipitating or exacerbating factors. Control of severe nosebleeds can require volume replacement and resuscitation (the Airways, Breathing and Circulation response), as well as addressing the underlying cause. Drug history is important. Coexisting coagulopathies need to be considered, as well as ruling out specific underlying systemic illnesses, such as hereditary haemorrhagic telangiectasia.

Examination

Assessment of the haemodynamic state is paramount. Once the patient is stable, with an intravenous line in situ and appropriate investigations and fluid replacement achieved, the cause of the bleed should be addressed. A good headlight, nasal speculum, and suction make examination easier. The best position for examining the patient is on a bed with the head elevated about 70 degrees. Up to 90 per cent of nosebleeds can be seen originating from the anterior nasal septum (Little's area). Severe nosebleeds may be associated with bleeding from the mouth and haematemesis.

Removal of clot from the front of the nose (blowing of the nose or use of suction) allows a better view of the bleeding point and removes the fibrinolytic factors released in clot that prolong bleeding. Ribbon gauze, soaked with adrenaline and lignocaine, allows vasoconstriction of the mucosa and bleeding blood vessel. This provides a better view, may stop the bleeding, and provides anaesthesia to allow cautery of particular blood vessels. Simple pressure on the soft part of the nose for 5 min (Fig. 2) may again arrest the bleeding.

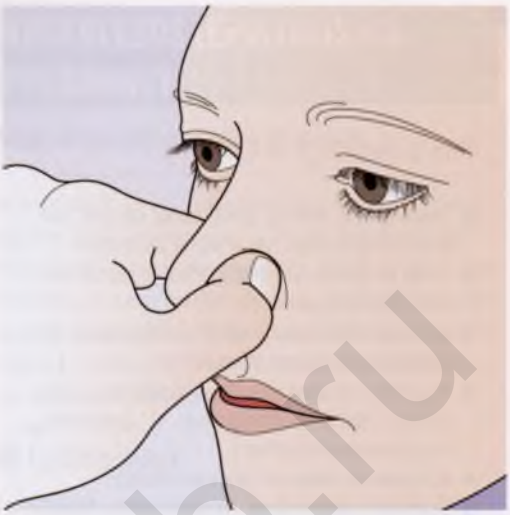

Figure 2 Treatment of minor nosebleeds.

Ongoing active bleeding not seen with this approach is usually further posterior. Rigid nasendoscopes allow a more detailed view of the nasal cavity, including the postnasal space.

Investigations

Full blood count, clotting profile, and cross-match may be necessary. Other tests are directed at potential or underling pathologies.

More severe nosebleeds are treated as for any acute blood loss. Coinciding with haemodynamic resuscitation, a full blood count, coagulation profile, and cross-match are to be done. Local control measures as above are important, and packing of the nose with adrenaline-soaked gauze (with constriction of the nasal mucosa) and suction may allow identification of the nosebleed, followed by cautery. More severe nosebleeds will require definite packing, and if bleeding is arrested, admission for observation for 24 hours. Nasal packs, such as Merocel packs (see Fig. 3; the larger pack has expanded after application of water), are easy to use and effective.

If bilateral nasal packs are used, monitoring of pO_2 is mandatory.[23] Prophylactic antibiotics are used to prevent toxic shock syndrome. Packs can remain in the nose for 1 day. On removal, the nose is again inspected for bleeding points and cauterised. If bleeding recurs or is continuous, early management in the operating theatre should be considered. Endoscopic (intranasal) ligation of the sphenopalatine artery, using a metal clip, at the back of the nose is required. One can also consider ligation of the anterior and posterior ethmoid arteries, although this is usually

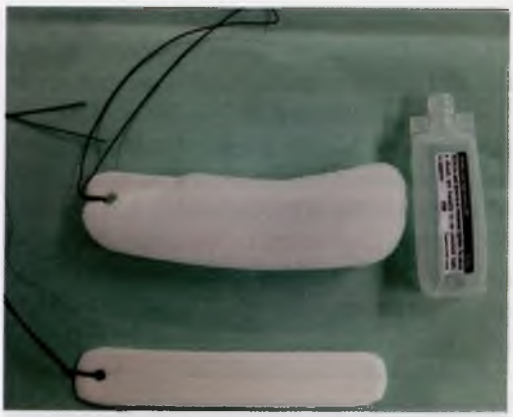

Figure 3 Saline soaking of a nasal pack showing expansion of the pack.

done via an external facial incision and is not first-line treatment. Arteriography and embolisation of the maxillary artery, in experienced hands, is an effective and safe technique, and should be considered, particularly if the epistaxis is severe and has been resistant to treatment as above. A distinct advantage is that it is performed under local anaesthesia and has been shown to be effective and safe in pregnancy.[24]

Extreme cases will require ligation of the external carotid artery (with little morbidity).[18]

Control of hypertension and any other underlying systemic condition is very important. Caesarean section or delivery may be required to allow control of hypertension and the arrest of bleeding.[18] Bed rest is important in severe nosebleeds, with appropriate deep venous thrombosis prophylaxis.

Tranexamic acid (an inhibitor of fibrinolysis) is sometimes used also to assist in controlling bleeding in pregnancy. It stabilises preformed clots and prolongs their dissolution. There is no increased risk of thromboembolism with this drug in this high-risk group of women.[25–27]

Prevention

Avoidance of nose picking is important. Vaseline or E45 cream applied to the anterior nose can help prevent drying of the nose and cracking and bleeding of blood vessels. Nasal saline washouts, such as NeilMed Sinus Rinse, saline nasal sprays, such as Sterimar, and moisturising gels, such as NasoGel, can be helpful.

Summary

Nosebleeds are common and occur in pregnancy. They are often trivial and occur on the anterior nasal septum. Simple measures, such as appropriately applied pressure and cautery, with use of nasal creams usually treat most bleeds. Pyogenic granulomas can occur in pregnancy and often require excision to control bleeding. Posterior nasal bleeds are rare, more severe and usually require packing. Endoscopic ligation of the sphenopalatine artery is often required to control these bleeds. Underlying systemic causes of bleeding must also be treated.

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OPHTHALMIC ISSUES AND THE MATERNAL EYE IN PREGNANCY

Rita Ohri

Ocular and ophthalmic problems in the healthy pregnant woman are relatively uncommon, and thus if there is symptomatic change, an ophthalmologist should be consulted.

Ophthalmology issues in the maternal eye in pregnancy occur as a result of:

- physiological changes primarily affecting the eye and periorbital tissues;
- systemic conditions that may arise de novo in pregnancy or pre-existing systemic conditions that are exacerbated by the pregnant state.

These may involve the eye and orbit (the cavity that holds the eye and its appendages), but intracranial conditions that involve the visual pathways or the cranial nerves may also present with an eye problem involving visual function or the visual field.

It is important that the obstetrician responsible for the care of the pregnant woman has a basic awareness of the possible physiological and pathological processes that may affect the eye and the visual pathways.

Some conditions may be symptomatic, while others may require screening to pick up problems in their early stages so that preventative action may be taken. In the latter the patient may not be aware of any symptoms and would be reliant on the clinician to refer her to an ophthalmologist if indicated.

The facies should be checked for such changes as lid and periorbital swelling, and any proptosis should be noted.

A basic eye examination would involve a check of the visual acuity – for distance and near vision.

Slit lamp examination allows a systematic examination of the conjunctiva, cornea, anterior eye chamber (for inflammation such as uveitis), the iris, lens, and vitreous for any haemorrhage or inflammatory cells.

Intra-ocular pressure and pupil reactions are checked and the retina and optic nerve are screened for any serous detachment, papilloedema or vascular anomalies.

Further tests such as visual fields and colour vision may give an indication of optic nerve dysfunction and retrobulbar (behind the eye) pathology. These examinations are best done by an ophthalmologist.

Dilatation of the pupil for proper examination of the fundus is safe using a short-acting mydriatic such as gutt. tropicamide 1% or gutt. cyclopentolate 0.5%.

A multi-system approach involving the obstetrician, ophthalmologist, neurologist, and radiologist may be required.

Non-pathological and physiological processes most commonly encountered

The cornea is the commonest tissue which may alter at any stage of pregnancy, and fluctuations in refraction may occur as a result. The patient may complain of non-tolerance of contact lenses, and spectacles that were previously satisfactory may not be so any longer. The cornea may undergo an increased sensitivity and thickness with microscopic changes in its fluid levels leading to a change in its curvature and refractive index. These usually settle down, in which case the patient can be reassured and advised to refrain from changing any correcting spectacles or contact lenses until things stabilise to a reasonably consistent level, when an appropriate change can be made.

Some changes may occur in the lens too, where there may be an alteration in accommodation and refractive index, leading to similar fluctuations in vision, as with the cornea.

Other tissues that may undergo a change are the lids and conjunctiva. These are easily examined by using a focal light source, and the patient may be quite symptomatic regarding these, as they may cause some discomfort of the eye. The lids may show some increased puffiness and chloasma, whereas the conjunctiva may become a little more hyperaemic, causing an increased redness. In some instances there is an increased dryness of the eye. Neither the redness, if mild, nor dry eye necessarily indicates a conjunctivitis or infection, and both may be relieved by simple lubricants with no other requirement for medication. However, these changes may indicate other conditions such as instability of the thyroid status, and once any local pathology has been ruled out, appropriate further investigations can be undertaken.

Pre-existing systemic conditions that are commonly present and may be exacerbated in pregnancy

Diabetes

Diabetic control may vary at any stage in pregnancy, and this makes the eye susceptible to an increased risk of diabetic retinopathy, especially if there is poor control. Coexisting hypertension, pre-eclampsia, and nephropathy greatly increase this risk. If gestational diabetes develops, the recommended guidelines are the same as for pre-existing diabetes.

It is recommended that all diabetic pregnant women undergo a baseline retinal check as a screening procedure in the early stages of pregnancy in the first trimester, with any follow-up tailored according to the findings. If there is no retinopathy at this examination, a three monthly check of the retina is recommended, which is usually adequate if the diabetes stays stable.

Any early retinopathy must be graded and treated according to the guidelines for treatment of diabetic retinopathy. The condition should be monitored by an ophthalmologist, as laser treatment may be required to stabilise any leakage into the retina. The frequency of the eye checks will then be appropriately adjusted (Figs 1–3).

Hypertension

Ophthalmologists are sometimes requested to do a routine check for hypertensive retinopathy. This is not required if blood pressure control is good and the

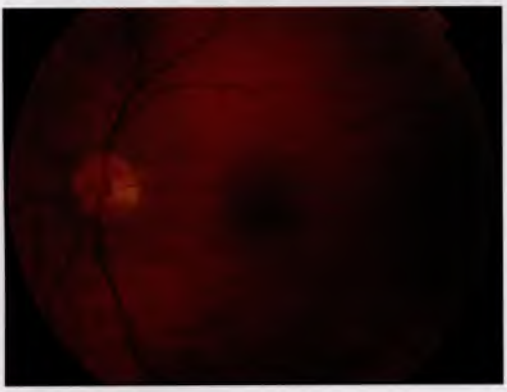

Figure 1 Normal fundus.

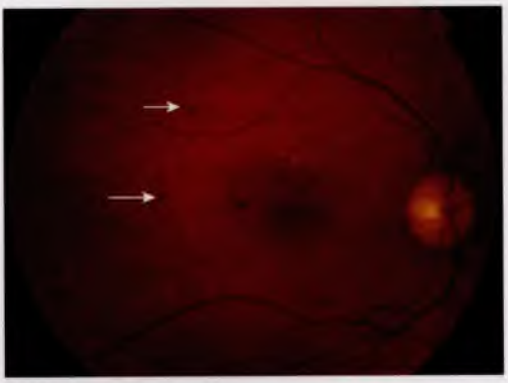

Figure 2 Diabetic microaneuryms (arrows).

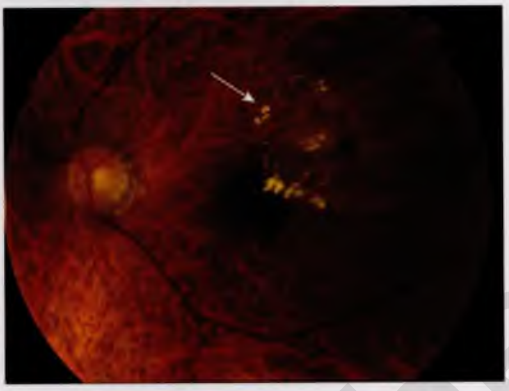

Figure 3 Diabetic microaneurysms and exudates (arrow).

patient is asymptomatic. Minimal changes in the retinal vasculature, with the increased vascularity that occurs in pregnancy, do not need any ophthalmic treatment but blood pressure monitoring and control by their obstetric clinician will clearly be regularly carried out.

Dysthyroid states

The eye is a target organ in thyroid conditions, and a previous dysthyroid state may be exacerbated in pregnancy.

The total T4 and T3 are elevated in pregnancy and Graves' disease accounts for 95 per cent of dysthyroid conditions in pregnancy. One in three patients with Graves' disease develop eye problems.

There may be puffiness of the lids with proptosis (forward displacement) of the eyes, conjunctival oedema, and dryness due to exposure. The intraocular pressure may be elevated, and, if there is a tense orbit due to oedema of the periorbital tissues, an optic neuropathy with optic disc swelling may occur. The extra ocular muscles may enlarge and lead to diplopia.

Treatment is aimed at stabilising the thyroid status and treating the eye signs, as indicated, by involving an ophthalmologist.

De novo conditions

Pre-eclampsia and eclampsia

The ophthalmologist does have a role to play when there is the development of pre-eclampsia if any eye symptoms and signs develop. Many of these women will show retinal vascular changes, mainly those of vasoconstriction.

Symptoms that patients with pre-eclampsia may present with are:

- blurring of vision or decreased vision;
- photopsia or light sensitivity and odd flashes of light;
- isolated field defects or scotomata;
- intermittent diplopia of a variable nature;
- severe visual loss and possibly even blindness in severe cases.

The pathology is due to:

- cardiovascular changes;
- haematologic changes;
- hepatic and renal impairment;
- neurological manifestations;
- cerebral changes.

Up to 25 per cent of patients with pre-eclampsia and 50 per cent of patients with eclampsia may be affected.

The obstetrician should refer patients with visual symptoms promptly, as severe eye signs associated with pre-eclampsia or eclampsia may require aggressive management both by the obstetrician and the ophthalmologist.

Visual loss in pregnancy

This can occur in 1–3 per cent of pregnancies. The causes include:

- cortical blindness;
- vascular occlusions;
- fronto-parietal infarcts and involvement of the lateral geniculate body in the visual pathway;
- retinal ischaemia associated with postpartum haemorrhage (not common);
- retinal detachment;
- ischaemic optic neuropathy;
- pituitary apoplexy (severe hypotension which affects the blood supply, as this is an end artery with no collateral circulation);
- amniotic fluid embolism.

There may be a retinopathy with retinal arteriolar constriction leading to oedema, haemorrhages, exudates, and cotton wool spots (indicative of localised ischaemia).

Exudative retinal detachment with serous fluid in the retina is present in less than 1% of women with pre-eclampsia but is found in up to 1 in 10 women with eclampsia.

Two conditions need special mention.

HELLP syndrome

The HELLP syndrome is a reversible leuco-encephalopathy syndrome: haemolysis, elevated liver enzymes, and a low platelet count are found. This occurs in 1–2 in 1000 pregnancies.

About 20 per cent of women with HELLP get disseminated intravascular coagulation leading to micro-angiopathic haemolytic anaemia. The patient may present with headache and visual blurring, and often the blood pressure is already elevated. It usually presents in the 3rd trimester and warrants prompt delivery of the child.

Postpartum the eye is at an increased risk of retinal detachment, which can be bilateral. This is due to choroidal ischaemia, which affects the retina, as the outer retina gets its nutrition from the choroid.

While the patient is treated with fresh frozen plasma for the disseminated coagulation and blood transfusion for the anaemia, the eye condition must be aggressively managed with systemic steroids as well as steroids applied topically to the eye and by sub-conjunctival injection. Acetazolamide (a carbonic anhydrase inhibitor) acts as a diuretic which may also play a part in reducing the swelling. With timely treatment the eye condition will resolve.

Purtscher's retinopathy

This occurs with pre-eclampsia and is rare. It is a risk in a poorly controlled pregnancy-induced hypertension coupled with a hypercoagulability state. In this, the woman presents with acute painless visual loss which is due to micro-vascular problems in the retina and optic nerve. Cortical infarcts may occur as there is occlusion of small arterioles by fibrin clots, platelet and leucocyte aggregation as well as fat or air embolism. Ocular blood flow can be examined with a Doppler examination. Neuroretinitis or malignant hypertension may be considered in the differential diagnosis. There is no known treatment for Purtscher's retinopathy, although intravenous steroids have been administered in some cases, though without much success in restoring vision. Symptoms disappear at about 6 weeks postpartum but may leave the woman severely visually compromised (Fig. 4).

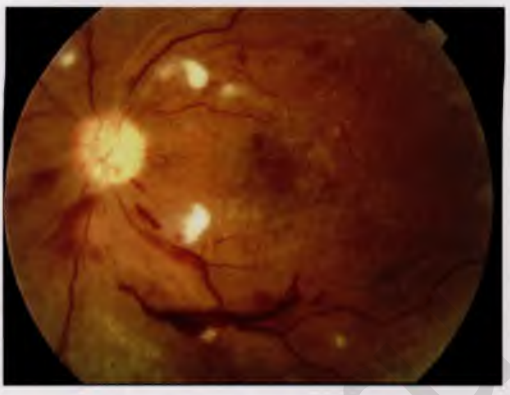

Figure 4 Retinal ischaemic changes in Purtscher's retinopathy.

Embolism

This can lead to intermittent visual obscurations or even sudden loss of vision due to a retinal or intracranial embolus. Risk factors include:

- Purtscher's retinopathy;
- pre-existing cardiovascular conditions, e.g. valve disorders;
- amniotic fluid emboli;
- hypercoagulability: cotton wool spots and retinal haemorrhages.

Cortical blindness

This may occur in 15 per cent of patients with severe pre-eclampsia or eclampsia. Visual recovery may take only hours or up to 8 days. Magnetic resonance imaging (MRI) may show focal occipital lobe oedema. Reversible posterior leucoencephalopathy syndrome may be the cause, as may occipital anomalies.

Neuro-ophthalmic issues

Pituitary conditions

The optic chiasm straddles the pituitary gland, and since there is a physiological enlargement of the pituitary gland in a normal pregnancy, any other pituitary pathology over and above that may cause visual problems such as field loss and, if advanced, loss of visual acuity and colour vision (Fig. 5).

Prolactinoma is the commonest pituitary adenoma in pregnancy. Eosinophil adenoma, which can cause acromegaly, is the next commonest adenoma. A basophil adenoma, which can cause Cushing's disease, is rare in pregnancy but is important to diagnose, as the effects on hypertension and renal function can exacerbate pre-existing changes.

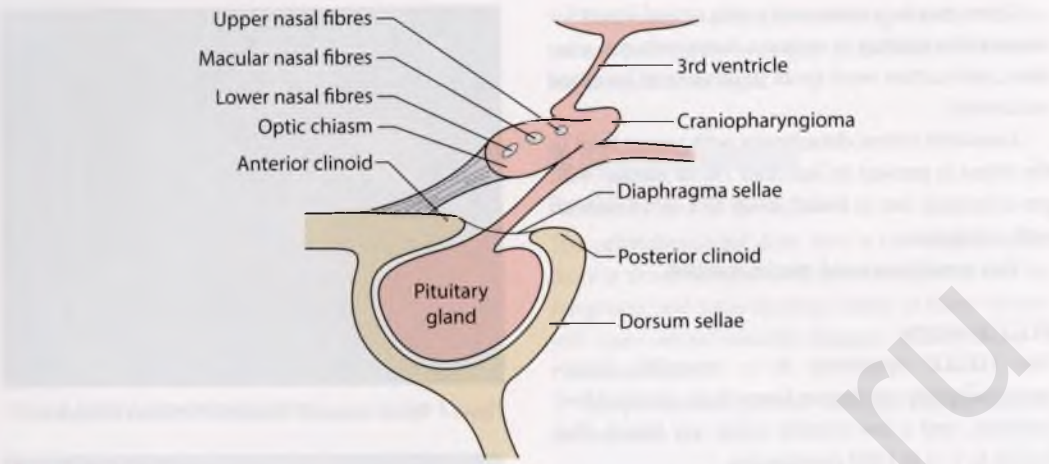

Figure 5 Optic chiasm.

Sheehan's syndrome

This is rare condition that is caused by a necrosis of the pituitary gland and the resulting hypopituitarism and optic nerve compression. About 90 per cent of patients get headache and vomiting and may also develop a reduced consciousness. It is a result of haemorrhage or infarction of the pituitary gland, and pregnancy is one of the precipitating factors. There may have been a pre-existing macroadenoma. Severe hypotension or massive haemorrhage may result in the necrosis.

Visual impairment occurs because of compression of the optic chiasm, leading to a superior quadrant field defect. Cavernous sinus compression results in involvement of the third, fourth, and sixth cranial nerves as well, leading to diplopia. An upper lid ptosis may be present.

Treatment should involve the endocrine and neurosurgical teams as well as the ophthalmologist. Management involves resuscitation, hydrocortisone, and assessment of endocrine function.

As soon as the patient is stabilised, the visual field should be accurately recorded if possible, and daily visual acuity and visual field testing can be used as an indicator of a worsening condition which would precipitate a referral to the neurosurgeons to undertake surgical decompression. If surgery is required, it should be undertaken within the first 7 days of onset of the condition.

Pseudotumour cerebri

This is the condition of idiopathically raised intracranial hypertension. Pregnancy is one of the associated conditions. Symptoms consist of:

- headache, nausea, and giddiness;
- ringing of the ears;
- blurred vision (fleeting episodes) or visual obscurations;
- diplopia;
- photopsia.

An eye examination of the fundus after dilating the pupil shows optic nerve swelling, and there may be peripheral field loss. An MRI would rule out an intracranial tumour or thrombosis, and a stenosis in the ventricles is often seen. The cerebrospinal fluid (CSF) pressure is raised. Treatment is to prescribe acetazolamide sometimes combined with another diuretic. Anti-migraine medication is helpful for symptomatic analgesia. In prolonged or resistant cases, a shunt or optic nerve sheath fenestration may be required to prevent a secondary optic atrophy.

Ocular infections pertinent to pregnancy and the maternal eye

Infections in pregnancy such as rubella and toxoplasmosis are a major threat to the developing fetal eye but not to the maternal eye. A new toxoplasmosis infection acquired during pregnancy may well cause a chorioretinitis in the fetus, but the risk to the adult eye is very small.

If a woman already has congenital ocular toxoplasmosis scarring, which may have been quiescent in the retina, and a flare-up of acute chorioretinitis occurs in pregnancy, the threat to the fetal eye is minimal. An early ophthalmic examination is advisable. Symptoms would be a visual disturbance with a possible red eye if a uveitis has developed with the chorioretinitis. This is treated with either spiramicin or pyrimethamine if it

threatens the macular region, but may not need treatment if it involves only the peripheral retina.

Other ocular infections such as gonorrhoea and chlamydia that are commonly encountered may cause ophthalmic problems and are a threat to the newborn eye, causing ophthalmia neonatorum, so it is important to screen the mother and treat all contacts.

With gonorrhoea, the woman may develop a mucopurulent discharge of the eye. She can be treated with local eye drops once a conjunctival swab for gram stain, culture, and sensitivity has been taken.

Chlamydia causes a red eye with a lot of follicles and lid swelling. Discharge is not very marked. Again it is important to treat this to prevent a conjunctivitis and corneal involvement in the newborn. Oral erythromycin is effective in this situation.

Syphilis and HIV infection should be screened for, as they too have serious implications for the newborn.

Viral infections

Herpes simplex causes a keratitis (inflammation of the cornea) and may be a recurrent problem in the maternal eye, as once the virus has entered the cornea it can cause relapses of keratitis, which can lead to corneal opacity and scarring. Antiviral agents such as Zovirax are effective but should be used with caution in the first trimester.

Some commonly asked questions

Q. Shall I change my spectacles or contact lenses?

If the refraction has stabilised then it is appropriate to change any spectacles.

Q. Shall I continue contact lens wear?

If contact lenses are tolerated, there is no contraindication to their usage and further comfort can be increased with the addition of a bland lubricant that is suitable to use with contact lens wear.

Q. Does a patient with previous history of retinal surgery need to have delivery by caesarean section or is it safe to try delivery by a normal labour?

There is no ophthalmic indication to undertake a caesarean section in a patient that has had successful previous retinal surgery for a retinal detachment.

Q. Do diabetic patients with gestational diabetes need screening for retinopathy?

A woman with gestational diabetes must have screening for diabetic retinopathy as recommended for any other diabetic patient.

Q. Does a patient with a previous retinal detachment need an examination prior to labour?

There is no risk to the retina if there are no new symptoms, but it may be advisable for the woman to have a fundus check mainly for reassurance.

Q. Should a patient with consistent and prolonged headaches in pregnancy have an eye examination?

Yes, it is worth looking at the optic nerve for papilloedema and also at the visual field if indicated.

Q. Should any pregnant woman with conjunctivitis be screened for infections such as gonorrhoea and chlamydia?

Yes, as although the maternal eye can be treated, the new-born eye is susceptible to these infections and may get corneal scarring and reduced vision for life as a result.

The pregnant woman is usually a healthy individual, but the marked physiological changes associated with pregnancy can be accompanied by serious pathological changes in the eye that can cause severe morbidity, and an awareness of the more serious of these conditions that warrant prompt action is essential.

It is also important to be aware of the risks of treatment, especially in the first trimester. Treating ocular conditions with local eye medication is the safer option than using systemic drugs that may have implications for the developing fetus.

ORAL AND DENTAL CONSIDERATIONS IN PREGNANCY

Sarah Viggor and Shahid I. Chaudhry

The effects of pregnancy on the oral cavity are essentially confined to the oral soft tissues, with the hard tissues being largely unaffected.

Dental caries

There is no evidence that teeth are weakened by calcium depletion during pregnancy.[1] However, changes in salivary composition, a cariogenic diet, and gastric reflux may increase the risk of developing dental caries (Fig. 1).[2] This is important, as the stress of dental pain and the timing of any subsequent treatment needs to be considered. Individuals at risk of caries and gingivitis should be identified at the pre-conception

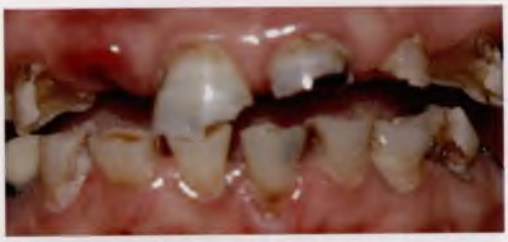

Figure 1 Dental caries.

stage so that they can be motivated to improve their oral hygiene and maintain it throughout their pregnancy. If treatment is necessary, the second trimester is considered to be the safest period. When treating patients in the supine position in the third trimester, a reduction in blood pressure and cardiac output can result from compression of the inferior vena cava by the uterus, causing dizziness and syncope. Prolonged treatment sessions and advanced restorative care should therefore be avoided. Furthermore, there is no evidence to support any adverse effects of maternal dental amalgam on fetal neurodevelopment, although the placement of new amalgam restorations during pregnancy is generally avoided.[3]

Behçet's syndrome

Behçet's syndrome (Fig. 2) is an auto-inflammatory multisystem disorder of relapsing oro-genital ulceration with ocular inflammation. In the majority of individuals with active Behçet's syndrome at the time of conception, pregnancy positively influences their symptoms with, remission continuing postpartum. A minority may experience worsening of their oral disease during pregnancy, necessitating systemic immunosuppression. Overall, Behçet's syndrome appears not to be associated with an increased rate of pregnancy-related complications.[4]

Dental radiography

Dental radiography should not adversely affect the fetus as the primary beam is unlikely to irradiate the pelvic area. When considering radiographic examination, however, the benefits and potential risks should be discussed with the patient and an informed decision made appropriate to the clinical need.

Local anaesthetic

It is important to manage pain and anxiety appropriately when carrying out dental treatment during pregnancy to reduce stress on the mother, which otherwise could adversely affect the fetus. The use of lignocaine with adrenaline for local anaesthesia is safe. Mepivacaine and bupivacaine can cause fetal bradycardia and should be avoided.[5]

Pemphigus vulgaris

Pemphigus vulgaris is an autoimmune vesiculobullous condition characterised by widespread, fragile blisters affecting the mucosa and skin (Fig. 3). Oral involvement may precede skin involvement and, although rare, may present or increase in severity during pregnancy. This is important as it can

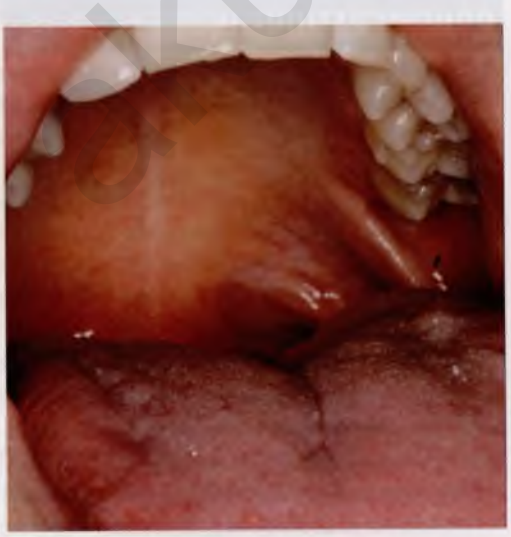

Figure 2 Oro-pharyngeal scarring secondary to Behçet's syndrome.

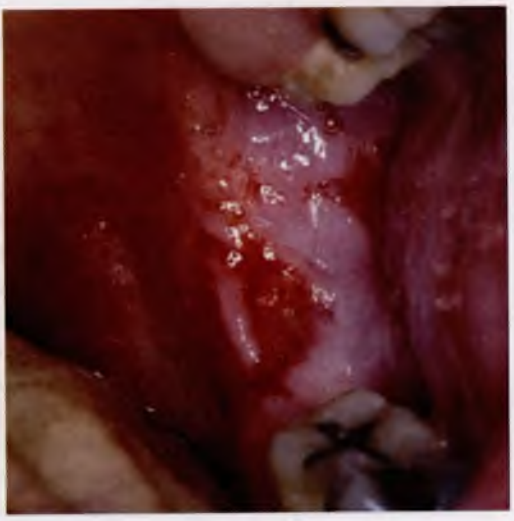

Figure 3 Superficial erosion of left retromolar region.

adversely affect pregnancy outcome and has been associated with fetal demise. Transplacental transmission of pemphigus vulgaris can occur as the result of transfer of IgG antibodies.[6] In the majority of cases this will present as localised skin involvement which improves within a few weeks of birth and rarely progresses to adult pemphigus.

Periodontal disease and adverse pregnancy outcomes

Studies have demonstrated an association between periodontal disease and adverse pregnancy outcomes such as premature birth, pre-eclampsia, and low birth weight.[7] This highlights the importance of preventative dental care before, during, and after pregnancy. Pregnant women are exempt from dental treatment costs throughout their pregnancy in the UK and for 1 year after the birth of their baby. Regular visits to the dentist should be encouraged.

Pregnancy epulis

A localised gingival swelling may occur in pregnancy, often in response to chronic irritation, resulting in a pregnancy epulis (a pyogenic granuloma occurring in a pregnant female). Clinically epulides appear as sessile or pedunculated, erythematous swellings characteristically arising from the interdental papillae (Fig. 4). They are often painless, can bleed easily, and histologically are composed of immature vascular granulation tissue. Treatment should focus on maintaining excellent oral hygiene to limit reactive inflammation as they commonly regress postpartum. If the epulis is large and causing a functional problem, then surgical removal should be considered, although the lesion is likely to recur.

Pregnancy gingivitis

Gingival inflammation (gingivitis) is common in pregnancy. It is caused by dental plaque and exacerbated by circulating levels of oestrogen, progesterone, and their metabolites. This exaggerated response is thought to be immune mediated and reflective of an increase in vascular permeability of the gingival tissues. Pregnancy gingivitis (Fig. 5) predominantly affects the anterior segments of the oral cavity and is characterised by generalised, marginal inflammation of the gingivae with bleeding and varying degrees of hyperplasia. It appears during the second and third trimesters and is self-limiting, with resolution occurring during the postpartum period. It is not associated with an overall increased risk of developing chronic periodontal disease. Treatment is essentially preventative with oral hygiene instruction and removal of plaque and calculus deposits.[8]

Recurrent aphthous stomatitis (RAS)

Recurrent aphthous stomatitis (RAS) affects approximately 20 per cent of the population and refers to otherwise healthy individuals who develop regular crops of mouth ulcers (Fig. 6). The aetiology is multifactorial and not easily defined. There has been some suggestion that flares of oral aphthae become less frequent during pregnancy but this has not been supported by large studies.[9] Aphthous ulcers during pregnancy can be managed using topical corticosteroid preparations and analgesic oral rinses such as benzydamine hydrochloride (0.15 per cent). Haematinic deficiencies (iron, vitamin B12, and folate) may exacerbate the condition and should be excluded.

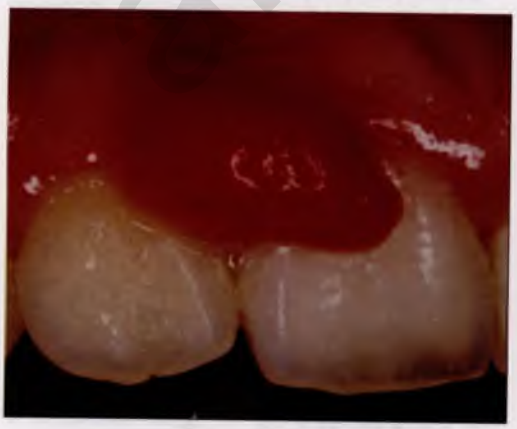

Figure 4 Pregnancy epulis.

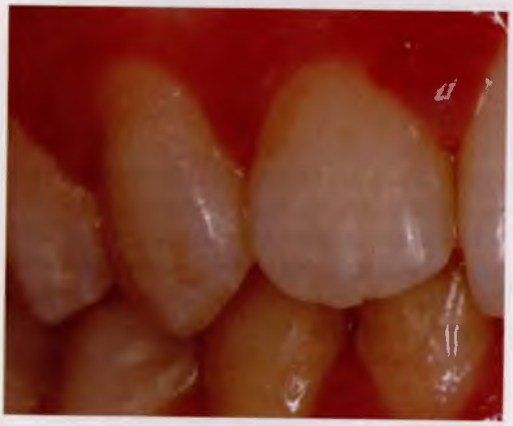

Figure 5 Pregnancy gingivitis.

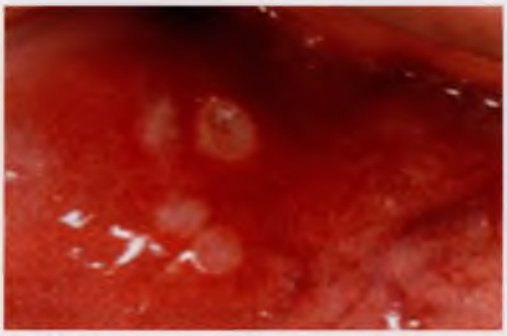

Figure 6 Recurrent aphthous stomatitis (minor).

Treatment of inflammatory mucosal disease

Extensive inflammatory disease of the oral mucosa may cause significant morbidity and adversely impact nutrition. No medication should be considered completely risk free, and therefore careful consideration must be given with regards to the overall impact of therapy on both mother and fetus.

Mild to moderately potent topical steroids may be used as first-line treatment for inflammatory disorders of the oral mucosa such as RAS, pemphigus vulgaris, mucous membrane pemphigoid, lichen planus, and lupus erythematosus. Super-potent topical steroids may be used as second-line therapy for short periods and appropriate obstetric advice sought in view of the potential for fetal growth restriction.[10]

Systemic corticosteroids increase the risk of gestational diabetes and should be instituted at their lowest effective dose with patients being counselled about the low risk of oral clefts with first trimester exposure. Low levels of prednisolone are transmitted in breast milk, so it is recommended that breastfeeding occurs three hours after dose administration. Other systemic agents may be used in pregnancy depending on the clinical need. Azathioprine crosses the placenta but is generally considered safe in pregnancy, and no adverse effects have been reported in breastfed infants from mothers taking azathioprine. Dapsone, which is used more frequently in patients with mucous membrane pemphigoid, has not been shown to be associated with adverse outcomes and is considered safe during breastfeeding. Colchicine, methotrexate, and mycophenolate mofetil are contraindicated in pregnancy. The safety profile of biologics in pregnancy has not been fully established, and so they should be prescribed on a risk-benefit ratio, and discontinued before 30 weeks' gestation.[11]

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OVARIAN SWELLINGS

Karina Reynolds and Nicola Fattizzi, revised by Rashna Chenoy

The ovary is essentially made up of three types of cell:

- those that produce the eggs and are, therefore, totipotential;
- those that produce the hormones;
- those that wrap it all up together.

Swellings can occur involving any of these types of cells.

Overall, ovarian swellings still represent one of the most difficult diagnostic problems for a gynaecologist owing to the lack of specific symptoms. Most ovarian masses cause no specific symptoms or signs because the abdomen represents a very large cavity that can cope with bulky masses without symptomatology until they become large (Figs 1 and 2). A small number of patients present with acute symptoms, such as in severe pelvic infection or torsion or rupture of an ovarian cyst, but for many the onset of symptoms is very gradual. Indeed, in a significant proportion of cases, large masses are an incidental finding at a routine gynaecological examination or a pelvic ultrasound scan for other reasons. The symptoms can include:

- generalised abdominal discomfort;
- dull pelvic pain and dyspareunia;
- increasing abdominal girth;
- pressure symptoms;
- urinary symptoms, frequency and urgency;
- weight loss and general debility;
- flatulence and dyspepsia.

The management of a patient presenting with an ovarian lump depends on a combination of several predictive factors, which include the following.

- *Age*: one of the most important predictive characteristics for an ovarian mass.
- *Menopausal status*: in the pre-pubertal and post-menopausal age groups, an ovarian swelling must be considered to be abnormal. Consequently, further investigations are indicated and a surgical approach to treatment may be required. In the reproductive age group, the differential diagnosis of an ovarian mass may be more complex, and surgery is indicated after careful evaluation.
- *Size of the mass*: an adnexal mass >5 cm in diameter that persists longer than 6–8 weeks is an indication for surgery. Functional ovarian cysts generally measure less than 7 cm and disappear within 4–6 weeks. In postmenopausal women, cysts >5 cm in diameter are more likely to be malignant, whereas the smaller unilocular cysts are almost invariably benign.
- *Ultrasound features*: including shape, size, capsular characteristics, internal septae, vegetations and solid components, and the appearance of the fluid (Figs 3 and 4). This investigation may be combined with an assessment of blood flow by means of colour/power Doppler. In fact, irregular masses with uneven capsules adherent to adjacent structures, irregular and thickened

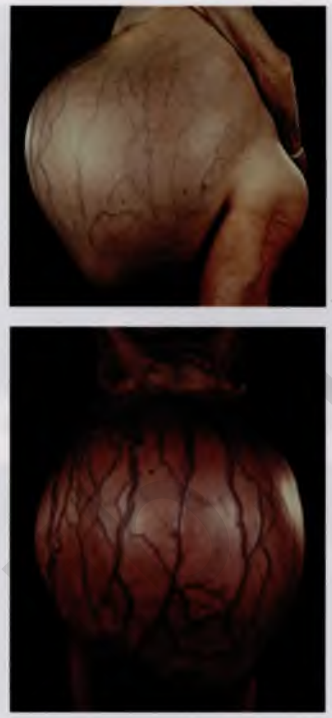

Figure 1 Woman presenting with gradually increasing abdominal girth.

Figure 2 Fluid removed from the same woman's ovarian cyst.

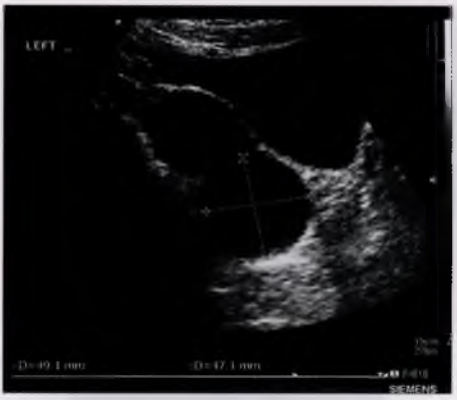

Figure 3 Ultrasound scan appearance of a simple ovarian cyst.

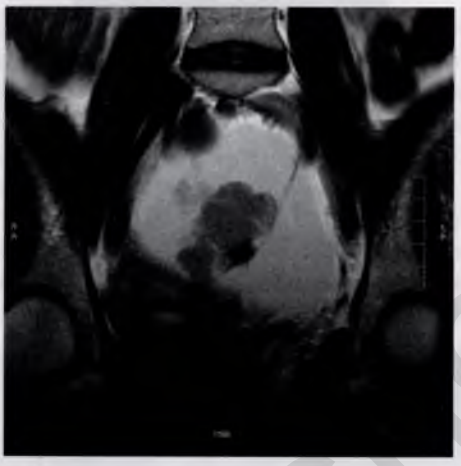

Figure 4 T2-weighted coronal scans showing a large predominantly cystic mass in the pelvis containing septations and solid components typical of an ovarian carcinoma. The uterus and cervix can be seen inferior to the mass and are separate from it.

septae, vegetations, solid areas, and low-resistance blood flow are all in keeping with a likely diagnosis of malignancy. Further imaging, if needed, would be by computerised tomography scanning.

- *Bilaterality*: bilaterality of an ovarian swelling, the presence of ascites and rapid growth are highly suspicious of malignancy.
- *Symptoms*: the only specific symptomatology is that secondary to the nature of the mass. These are endocrinological if the lump is hormone-secreting or chronic anovulation-dependant; pain in the case of endometriotic cysts; and septic in the event of acute or subacute pelvic inflammation.
- *Tumour marker serum levels* (CA125, carcino-embryonic antigen [CEA], CA19-9, β-human chorionic gonadotrophin, and alpha fetoprotein [AFP]): CA125 can be of some help in distinguishing benign and malignant tumours given that, in the majority of epithelial ovarian cancers, CA125 levels are raised (usually over 100 UI/mL). However, 50 per cent of stage 1 epithelial ovarian cancers present with normal CA125 levels. Furthermore, this is not a specific test, and levels may be elevated with endometriosis, uterine fibroids, dermoid cysts, or anything that causes peritoneal irritation (see Appendix).

It is recommended that a 'risk of malignancy index' (RMI) should be used for postmenopausal women presenting with an ovarian mass to select out those women requiring surgery in a Cancer Centre (i.e. those at >75 per cent risk of having an ovarian cancer). The RCOG have produced a guideline outlining the use and interpretation of the RMI:

$$\text{RMI} = U \times M \times \text{CA125 level}$$

where U is ultrasound findings (0 = no features, 1 = one feature, 3 = 2–5 features), the features being:

- multilocular cyst;
- evidence of solid areas;
- evidence of metastases;
- presence of ascites;
- bilateral lesions;

and M is menopausal status (premenopausal = 1, postmenopausal = 3). Values <25 indicate low risk, 25–250 moderate risk, and >250 high risk of malignancy.

In general terms, ovarian swellings can be divided into three main groups: functional, non-neoplastic, and neoplastic.

Functional

Epidemiologically, during the reproductive age, functional ovarian masses (follicular and corpus luteal cysts) are the most common, followed by endometriotic cysts and dermoid cysts.

A corpus luteum is formed following the release of the ovum (egg), and this will maintain a pregnancy up to 63 days' gestation (on a 28-day cycle). In most cases, the size of this 'cyst' will reach 20–25 mm in diameter. In general, most ovarian cysts of 5 cm diameter or less will regress without any need to intervene, although it may be useful to repeat an ultrasound scan after 2–3 cycles. Clinically, it may be difficult to palpate an ovarian cyst until it is greater than 5 cm. If the cyst is larger, it may require removal to avoid the complications of torsion, rupture, and haemorrhage.

In postmenopausal patients, the functional genesis of the ovarian lump is less probable since it may occur within 2 years of the last menstrual period.[1]

Functional cysts, related to the absence of the ovulation, are filled with fluid and can be up to 5–6 cm in diameter. They can be found occasionally in healthy women and in patients with endocrine diseases. They usually regress spontaneously within a couple of weeks, when the subsequent menstrual period occurs. If they do not disappear, either a follicular or corpus luteal cyst can be formed.

The presenting symptoms may be acute due to torsion, rupture, or haemorrhage, or they may present with a spectrum of menstrual problems, as in endometriotic cysts. They may also be an incidental finding on pelvic ultrasound scan.

Non-neoplastic

Non-neoplastic benign ovarian cysts include the following:

- *Theca lutein cyst*: the formation of a theca lutein cyst is due to a process of luteinisation of an unruptured follicle and is secondary to an abnormal ovarian exposure to exogenous (ovarian hyperstimulation syndrome) or endogenous (gestational trophoblastic tumours) hormones. It may be associated with hyperemesis and pressure symptoms and can lead to pre-eclampsia-type symptoms later in pregnancy.
- *Corpus luteal cyst associated with pregnancy*: this solid, quite often voluminous, non-neoplastic, pregnancy- related mass may be an incidental finding during caesarean section and usually regresses spontaneously after pregnancy.
- *Haemorrhagic corpus luteal cyst*: this can arise after ovulation owing to heavy bleeding from the shallow follicular microvessels. It may result in haematoma within the corpus luteum (vague or no symptoms) or can present with haemoperitoneum if the cyst ruptures (pain leading to an acute abdomen with peritoneal signs). The differential diagnosis in this situation would also include ectopic pregnancy and acute appendicitis (if on the right side).

Follicular, corpus luteal, and theca lutein cysts should not be treated surgically unless complications (rupture with haemoperitoneum, twisted cyst) occur that require such intervention.

- *Endometriotic cysts*: these often contain brown or altered blood (chocolate cysts) and can range from a few millimetres to 10 cm in diameter. They may be bilateral and may be difficult to distinguish from other benign ovarian masses. The definitive diagnosis is confirmed histologically. However, a patient's history (acute pelvic pain during the second phase of the menses, pain in intercourse, or persistent pelvic pain, mainly if drug-resistant, along with the finding of some nodularity involving uterosacral ligaments and cul-de-sac) may be helpful in anticipating the diagnosis.
- *Simple cysts in postmenopausal women*: these are often found on imaging and do not require intervention unless >5 cm and symptomatic. Most are small (<1 cm) and are thought to represent inclusion cysts that are the remnants of ovulation during the reproductive era.
- *Tubo-ovarian abscess* is a common cause of adnexal swelling. These usually occur bilaterally and are sequelae of acute salpingitis/pelvic inflammatory disease. Frequently, they can be palpated on bimanual examination as very firm, exquisitely tender, bilateral fixed masses, possibly located in the pelvic cul-de-sac. The symptoms and signs are similar to those of acute salpingitis, although pain and fever have often been present for longer. A ruptured tubo-ovarian abscess is a life-threatening surgical emergency, as septic shock may develop rapidly.

Neoplastic/malignant

In the UK, ovarian malignancy kills more women than all other genital tract cancers taken together. However, it is an uncommon disease and it is estimated that a general practitioner will see one case of ovarian cancer every 5 years. According to a simplified World Health Organisation classification, ovarian tumours can be classified as follows:

- *Epithelial*: benign (cystadenoma; Fig. 5), borderline, and malignant (Fig. 6). Most epithelial ovarian cancers present late when the disease has already spread beyond the ovary. In these cases, the ovarian mass is usually associated with clear evidence of extraovarian disease, ascites, and possibly pleural effusions.
- *Germ cell*: the dermoid cyst represents a very particular benign type of germ cell tumour (Fig. 7). These cysts contain sebaceous material, hair, and sometimes teeth owing to the totipotential nature of the cells. These cysts do have a markedly high risk of torsion, perhaps because of the high fat content of most dermoid cysts, allowing them to float within the abdominal and pelvic cavity. Torsion causes

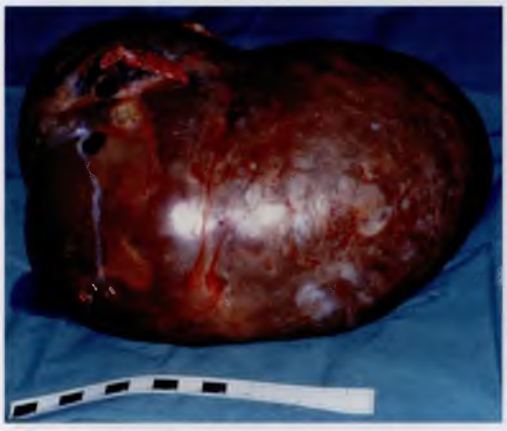

Figure 5 Cystadenoma of the ovary.

Figure 6 Malignant ovary.

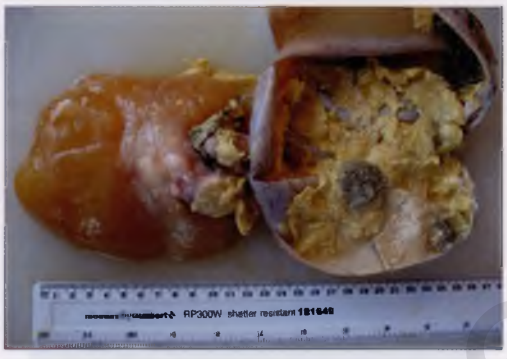

Figure 7 Dermoid cyst showing hair and sebaceous material.

severe constant pain that radiates down the medial aspect of the leg and is often associated with vomiting. If the torsion is partial, the pain may be intermittent.

- *Sex-cord stromal*: hormonal production from granulosa and thecal cell tumours can lead to precocious puberty in a child, menstrual problems during the reproductive age, and postmenopausal bleeding in the older woman owing to endometrial hyperplasia. The androgen-secreting tumours (Sertoli–Leydig tumours) are likely to cause hirsutism, acne, alopecia, and behavioural alterations. Struma ovarii may present with hyperthyroidism.
- *Uncommon*: including lymphomas, melanomas, sarcomas. A very interesting association of symptoms can be found in Meigs' syndrome, classically characterised by a fibroma associated with ascites and a right pleural effusion. Removal of the tumour cures the effusion and ascites.
- *Metastatic*: up to 10 per cent of ovarian masses are secondary to metastases from some other organ and, in many cases, the ovarian metastases are detected before the primary tumour. The most common metastatic cancers are those arising from the colon, stomach, breast and, of course, the female genital tract. Bilaterally enlarged ovaries, which contain signet-ring cells on microscopic assessment, have been named after Krukenberg, who described these ovarian tumours in patients with metastatic gastric or (less commonly) colonic cancer.

Reference

1. Green-top Guideline 34: Ovarian cysts in postmenopausal women. (www.rcog.org.uk).

Useful websites

www.nice.org.uk – Ovarian cancer and initial management CG122. April 2011.
www.pathways.nice.org.uk – for ovarian cancer.
www.rcog.org.uk – Green-top Guideline 62: Ovarian masses in premenopausal women. 2011.

PAIN DURING INTERCOURSE

Hugo M Fernandes

Painful intercourse, also known as *dyspareunia*, is a common form of sexual dysfunction regularly seen by the gynaecologist. Its prevalence is thought to range from 8 to 22 percent in women. It may be classified as:

- *Superficial*: pain arises at the vaginal introitus.
- *Deep*: pain is felt within the pelvis.

The pain may be continuous or intermittent in nature, and continue after intercourse has finished. These symptoms can be further divided:

- *Primary dyspareunia*: pain has always been present from the time of first intercourse, use of tampon, or speculum examination. Often there is a psychological component needing expert counselling.
- *Secondary dyspareunia*: symptoms occur after previously having had painless sex (or examinations) and may be secondary to underlying pathology.

Dyspareunia may lead to vaginismus, which is the involuntary spasm of the pubococcygeus muscle, such that penetration becomes difficult or impossible. This may follow a single episode of pain but usually occurs when a pattern of dyspareunia has become established. While vaginismus is a multidimensional condition, it may have predisposing factors common to anxiety disorders. Anticipation of the pain leads to contraction of the muscles, which decreases lubrication, further making sexual activity painful.

Superficial dyspareunia

Superficial dyspareunia can be classified according to the local anatomical conditions.

Vulval causes

- Infections: relevant swabs and antifungal/antibiotic agents are needed. Candidal infections may require long-term (3–6 month) antifungal treatment in persistent cases, and *C. glabrata* may require addition treatment (boric acid). Once weekly treatments are not sufficient.
- Bartholinitis: poorly treated local infection of the Bartholin's gland can lead to chronic irritation. Marsupialisation has always been the standard treatment to drain the cyst and create a new duct for the gland. If the cyst is not infected, then NICE guidelines recommend treatment with a catheter (see Vulval swellings).
- Skin conditions: lichen planus or lichen sclerosus (see Vulval itching), may lead to pain secondary to development of cracks and fissuring of the vulval skin.
- Neoplasms: malignant and premalignant conditions need appropriate diagnosis and treatment.

Urethral causes

These are usually rare and quite specific anatomical problems.

- Urethritis and cystitis: may be chronic in nature and lead to constant pelvic discomfort. Similar innervation to the vulva may lead to chronic sensitivity. Midstream urine specimen for culture plus a cystoscopy can assist diagnosis. Appropriate antibiotic therapy and some tricyclic antidepressants (amitriptyline) may assist.
- Caruncle: easily seen on inspection and usually found in postmenopausal women. This may become inflamed and tender, but responds well to topical oestrogen.
- Urethral diverticulum: uncommon condition presenting with a midline mass that requires surgical excision.

Vaginal causes

- Vaginismus: previously described. Requires multimodal treatment which can include physiotherapy, pelvic retraining, counselling, desensitisation, and medications (benzodiazepines, amitriptyline).
- Poor lubrication: may be physiological (oestrogen deficiency) or secondary to psychosexual causes including poor sexual technique. Treat the underlying cause, and increase the length of foreplay or use water-based lubricants.
- Atrophic vaginitis: secondary to oestrogen deficiency. Treatment is as above for the atrophic vulva.
- Infective vaginitis: may also be associated with vulval pain. Candida, *Trichomonas*, herpes, and gonorrhoea are common causes. Routine local swabs need to be undertaken with appropriate treatment instituted. Poor management can lead to chronic sensitisation of vaginal tissue to pain (allodynia).
- Anatomical problems: vaginal atresia or imperforate hymen may be found on examination and may require an ultrasound or evaluation under anaesthetic to assess for associated anatomical problems.
- Scarring: postoperative scarring or contractures (episiotomy or perineal tear repairs) may lead to narrowing and tightening of the entrance to the vagina. A firm mass in the area may represent a neuroma. Surgery to remove scarring is an effective treatment, though can lead to more scarring.
- Post-radiotherapy: radiation-induced scarring and fibrosis is a common side effect that can be largely prevented by the use of vaginal dilators at the time of initial treatment.

The common pathways of innervation within the pelvis means that pain during intercourse may be referred to the vagina, vulva, or perineum from a non-associated area. An anal fissure, thrombosed and inflamed piles, arthritis of the hips, or lumbar spine may lead to a poorly localised pain. Disproportion in size is rarely of importance, as the vagina is very distensile.

Deep dyspareunia

Deep dyspareunia is caused by deep stretching of the involved pelvic tissues during coitus. It may occur on each occasion or be sporadic, cyclical, or result from only deeper penetration. The pain may be acute or lead to a dull aching in the pelvis after intercourse. Clinically the symptoms can often be reproduced with bimanual vaginal examination. Common causes include:

- Endometriosis (Fig. 1): ectopic deposits of endometrium throughout the pelvis lead to adhesions, scarring, and dense firm nodules in particular on the ovaries, uterosacral ligaments and pouch of Douglas. Diagnosis is by laparoscopy. The amount of endometriosis often does not correlate with the degree of symptoms, however. Treatment options

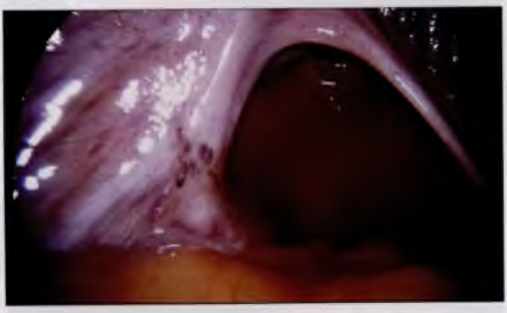

Figure 1 Laparoscopic view of an endometriotic nodule affecting the uterosacral ligaments.

depend on the amount and location of disease but laparoscopic excision remains the gold standard. Medical therapy (gonadotrophin releasing hormone [GnRH] analogues; progestogen-containing intrauterine devices [IUDs]) may decrease the symptoms of milder disease.

- Pelvic inflammatory disease (PID) (Fig. 2): both acute and chronic infections can cause deep pain through inflammation. Chronic infection can lead to scarring and adhesion formation which fixes the pelvic organs in place. Appropriate antibiotics should be used at all stages to treat infection; however, ongoing pain from a chronic pelvic infection may require pelvic clearance. Laparoscopy may reveal perihepatic adhesions (Fitz-Hugh–Curtis syndrome), which is usually pathognomonic of *Chlamydia* infection.
- Retroverted uterus: while this is a normal variation, the uterus may become trapped against the bony pelvis during intercourse. The problem may be complicated by endometriosis or adhesions from PID. Positional change during coitus is often sufficient; however, surgery to 're-suspend' the uterus may be needed.
- Pelvic congestion: while prominent vasculature of the pelvis (Fig. 3) may be diagnosed at laparoscopy, this is a controversial cause of pelvic pain. Pelvic exercises to drain the pelvis and progestogens may be effective.
- Ovarian cysts: larger cysts may twist intermittently, have internal bleeding, or rupture. Endometriomas may be fixed to the pelvic side walls or other organs and stretch with intercourse. Surgical removal is required.
- Pelvic hypertonicity: increased pelvic muscle tension is made worse by spasm and activation of sensitive trigger points with intercourse. The origin may go back as far as childhood and usually requires a multimodal approach with physiotherapists, counselling, and medications.

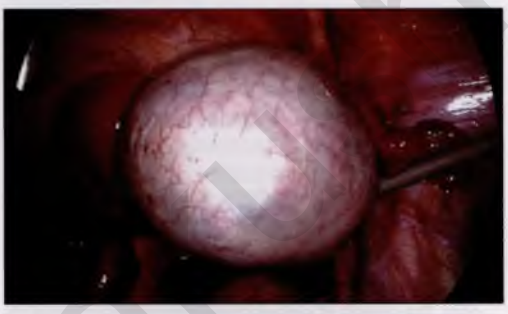

Figure 2 Laparoscopic view of a large ovarian cyst.

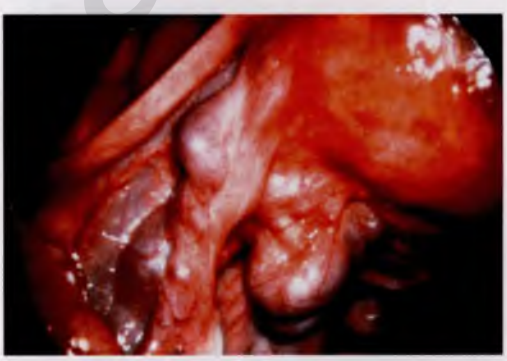

Figure 3 Laparoscopic view of prominent vasculature of the pelvis.

While diagnostic laparoscopy is a very useful tool in determining a gynaecological cause, the lack of any findings can also serve to reassure the woman that there is no pathology, and thus help break the cycle of expecting pain and then experiencing it.

Suggested reading

Fischer G, Bradford J. *The Vulva: A Clinician's Practical Handbook*. Family Planning NSW, 2010.

SOGC Female Sexual Health Consensus Clinical Guidelines. SOGC Clinical Practice Guideline No. 279, 2012.

PALPITATIONS IN PREGNANCY

Abhishek Joshi and Sandy Gupta

This section examines some of the issues regarding assessment and management of palpitations in pregnancy.

Gender differences

Palpitation is an unpleasant awareness of an abnormal beating of the heart. The symptoms may be brought about by a number of cardiac disorders, including cardiomyopathy, valvular heart disease and coronary heart disease, or as a consequence of congenital heart disease, although most palpitations are benign. There are a number of predisposing factors in women for arrhythmia that may be exacerbated during pregnancy. Women in general have a longer QT interval and also a higher incidence of atrioventricular nodal re-entrant tachycardias. Intrinsically women have higher heart rates, and sinus nodal recovery times are reduced. Women have a lower incidence of atrial fibrillation (AF); however, once in AF, they have a higher mortality.

Other factors that occur specifically in pregnancy lead to arrhythmogenesis (see Fig. 1). The increase

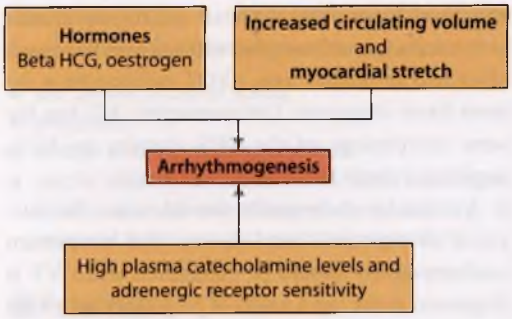

Figure 1 Factors in pregnancy that predispose to arrhythmogenesis. Beta HCG, beta human chorionic gonadotrophin.

in cardiac output in pregnancy causes an increase in myocardial stretch, leading to arrhythmias. Hormonal factors such as the increase in oestrogen and beta human chorionic gonadotrophin also predispose to the development of arrhythmias. Finally, increases in sympathetic tone and adrenergic receptor sensitivity related to high plasma catecholamine levels, which occur in pregnancy, increase the tendency for arrhythmia.[1]

Investigation of palpitations

The investigation of palpitations in pregnancy is similar to non-pregnant patients, and includes baseline electrocardiograms (ECGs), echocardiogram, and 24-hour Holter monitoring. Caution is advised with exercise treadmill testing, as peak exercise can be associated with fetal bradycardia, so fetal monitoring and a low workload protocol are advised.

Generally, benign arrhythmias can be treated with avoidance of stimulants (e.g. caffeine and alcohol) and reassurance for the patient. However, more serious arrhythmias may need further treatment. The choice of agent used is related primarily to established safety in pregnancy. The following section will address these issues.

Supraventricular tachycardias

The effect of pregnancy on the incidence of supraventricular tachycardia (SVT) is unclear, but low oestrogen states may be arrythmogenic.[1] SVTs include atrio-ventricular nodal re-entrant tachycardias (AVNRT), atrio-ventricular re-entrant tachycardia (AVRT), AF, and atrial flutter. Presentation is usually with palpitations.

Management of AVNRT and AVRT is the same as for non-pregnant women. If vagal manoeuvres such as carotid massage or breath-holding fail, then adenosine may be used, and has been shown to be safe in the second and third trimesters.[2] If first-line measures fail, intravenous beta-blockade, such as propranolol or metoprolol, can be used.[3] There are reservations about using verapamil because of the risk of prolonged hypotension. Electrical cardioversion is indicated if chemical cardioversion fails or the mother becomes unstable. There is evidence to show that DC defibrillation is safe in all stages of pregnancy, the amount of current reaching the fetus being insignificant.

An underlying cause, such as thyroid disease, should be excluded. There are certain indications for considering curative ablation therapy, such as drug-refractory SVT, poorly tolerated SVT, and when pregnancy is planned in a woman known to have troublesome SVT. If ablation has to be carried out during pregnancy, then this should ideally wait till the second trimester. Abdominal lead shields can be used to minimise the radiation risk to the fetus.

Atrial fibrillation (AF) and flutter

Atrial fibrillation (AF) and flutter are rare in pregnancy and may indicate underlying structural heart disease, such as congenital heart disease or rheumatic valvular disease, or endocrine dysfunction, such as thyroid disease. Patients presenting with atrial fibrillation for the first time should have an ECG, echocardiogram, and routine blood tests, including thyroid function tests performed regardless of pregnancy status. AF and atrial flutter carry a risk of embolic stroke from stasis on blood in the left atrial appendage.

The first episode of AF may revert spontaneously; however, if this does not occur, chemical (with flecainide or ibutilide[4]) or electrical cardioversion should be considered in the first 48 hours to reduce the need for anticoagulation to prevent stroke in AF.[5] If the duration of AF is greater than 48 hours, or is unknown, then patients should be anticoagulated for at least 3 weeks prior to and 4 weeks after attempted DC cardioversion. Pharmacological maintenance of sinus rhythm with medication should be reserved for those with recurrent haemodynamically significant episodes of AF.

If sinus rhythm is not achieved, then ventricular rate control can be achieved with oral beta-blockers, calcium channel antagonists or digoxin.

Anticoagulation depends on the risk of stroke. It is mandatory when planning cardioversion, and

in the post-cardioversion phase if there has been a period of AF or flutter greater than 48 hours. All patients should be assessed for stroke risk, regardless of whether they return to sinus rhythm, using the CHADSVA2SC2 score.[6] This scoring system looks at the patients background of **C**ongestive heart failure (1 point), **H**ypertension, **A**ge (>75 years, 2 points; >65 years, 1 point), **D**iabetes (1 point), **S**troke history (2 points), **V**ascular disease (1 point), and **S**ex (1 point if female). Those with a score of 2 or more should be offered systemic anticoagulation. However, there is no validated scoring system specifically for pregnancy, and so a pragmatic approach is probably best in a hypercoagulable condition. Low-molecular-weight heparin (LMWH) is generally considered safe, as it does not cross the placenta and is the drug of choice for anticoagulation. Warfarin is safe in the second trimester, but is contraindicated in the first. Atrial flutter is managed in much the same way, but is more amenable to ablation.

Ventricular tachycardias

Ventricular tachycardias are rare in women of childbearing age with structurally normal hearts, and so inherited conditions should be considered.[7]

Inherited long QT syndrome is a recognised cause of ventricular arrhythmia. A retrospective analysis of the over 400 pregnancies with QT abnormalities[8] suggests the postpartum period of pregnancy is associated with the highest risk of serious cardiac events, resulting in death, aborted cardiac arrest, or syncope. Beta-blockade seems to reduce this risk; therefore, in terms of risk and benefit to baby and mother, continued therapy during and after pregnancy is recommended.[9] There are many common medications that cause the QT interval on ECG to become prolonged, such as amiodarone, sotalol, cisapride, clarithromycin, and chloroquine. Prolongation of the QT interval on ECG can lead to a particular type of ventricular tachycardia (VT) with a characteristic oscillating baseline called 'torsade de pointes'. Obviously those agents that prolong the QT interval of ECG and lead to torsade de pointes should be stopped during pregnancy. Idiopathic ventricular tachycardia may arise from the right ventricular outflow tract or the inferior left-sided ventricular septum. It should be noted that right ventricular outflow tract (RVOT) tachyarrhythmia is generally benign and can occur in people with structurally normal hearts. If there is no structural abnormality detected and the ventricular tachycardia is monomorphic with left bundle branch block and an inferior axis, RVOT tachycardia is the most likely diagnosis. (Monomorphic VT has the same morphology of the QRS complex on ECG, implying a single focus in the ventricle.)

Ventricular tachycardia should raise the suspicion of structural heart disease, and peripartum cardiomyopathy should be considered when VT is diagnosed in the last 6 weeks of pregnancy, or within 4 weeks of delivery. When VT is detected, immediate DC cardioversion is safe at any point in pregnancy.

Adenosine, verapamil, or beta-blockade may be used to terminate idiopathic ventricular tachycardias. Radiofrequency ablation may be an option prior to a planned pregnancy. Structural heart disease puts the mother at increased risk of sudden death, and thus anti-arrhythmics should be given and an implantable cardioverter defibrillator considered.[10]

Other VTs may be terminated with lignocaine, and beta-blockade may be used to avoid recurrence. Procainamide may be used as a second line to terminate tachyarrhythmia. Quinidine has also been used for termination and prophylaxis. Sotalol has been used for prophylaxis. Amiodarone should be avoided because of the range of side effects to both mother and fetus. As always, haemodynamically compromising ventricular arrhythmia should be treated with electrical cardioversion.

Implantable cardioverter defibrillators and pacemakers

Implantable cardioverter defibrillators (ICDs) are increasing in use as indications broaden, and they are safe in pregnancy.[10] An ICD should not deter women from pregnancy, and the underlying structural heart disease is a more important factor. During delivery, the ICD should be activated. The only circumstance where the ICD may be deactivated is when caesarean section and electrocautery may be considered, to avoid inappropriate shocks.

Congenital heart disease

Congenital heart disease and repair of complex abnormalities has led to an increase in the number of female patients with congenital heart disease reaching childbearing age and having successful pregnancies. SVT and VT as well as high-grade atrioventricular block can lead to significant comprise

during pregnancy in these patients. Factors that appear to predict arrhythmia in this group are:

- poor cardiac functional status;
- polysplenia;
- residual atrioventricular regurgitation;
- specific anatomy and haemodynamic scars from surgery, which may cause arrhythmogenic focus, and may be uncovered by the increased preload of pregnancy.[11]

Fetal risk

There has been an attempt to classify fetal risk by the US Food and Drug Administration. Table 1 summarises the recommendations.

Pregnancy may promote arrhythmogenesis by virtue of hormonal and haemodynamic changes within the body. In the structurally normal heart, SVTs are more common than AF and VT, though infrequent overall. Congenital heart disease and pregnancy is a growing field with new challenges for electro-physiologists, cardiologists, and obstetricians as survival and assisted-reproductive technologies continue to improve the conception rate in this group of women. ICDs and radiofrequency ablation are helping in treating the more serious arrhythmia. Figure 2 summarises some of the features of arrhythmias in pregnancy.

Table 1 US Food and Drug Administration (FDA) risk class

FDA risk class	Description
Class A	Controlled studies show no risk
Class B	No evidence of risk in pregnant women, but either animal studies do show risk, or no adequate human studies have been conducted
Class C	Studies in pregnant women are lacking, and animal studies are positive for fetal risk, or lacking
Class D	Positive evidence of risk – can be used if potential benefit outweighs risk
Class X	Contraindicated – do not use, regardless of potential benefit

Drug class	Drug	FDA risk class	Fetal side effects
IA	Quinidine	C	Thrombocytopenia, 8th nerve toxicity
IA	Procainamide	C	None known
IA	Disopyramide	C	Uterine contractions
IB	Lignocaine	B	Central nervous system depression at toxic levels
IB	Mexiletine	C	Little data available
IC	Flecainide	C	None known
IC	Propafenone	C	None known
II	Propranolol	C	Intrauterine growth retardation
II	Metoprolol	C	Intrauterine growth retardation
II	Atenolol	D	Intrauterine growth retardation, preterm delivery
III	Sotalol	B	None known
III	Amiodarone	D	Congenital malformations, thyroid toxicity
III	Ibutilide	C	No data available
III	Dofetilide	C	No data available
IV	Verapamil	C	Hypotension with intravenous use
IV	Diltiazem	C	Little data available
	Digoxin	C	Monitor for digoxin toxicity
	Adenosine	A	None known

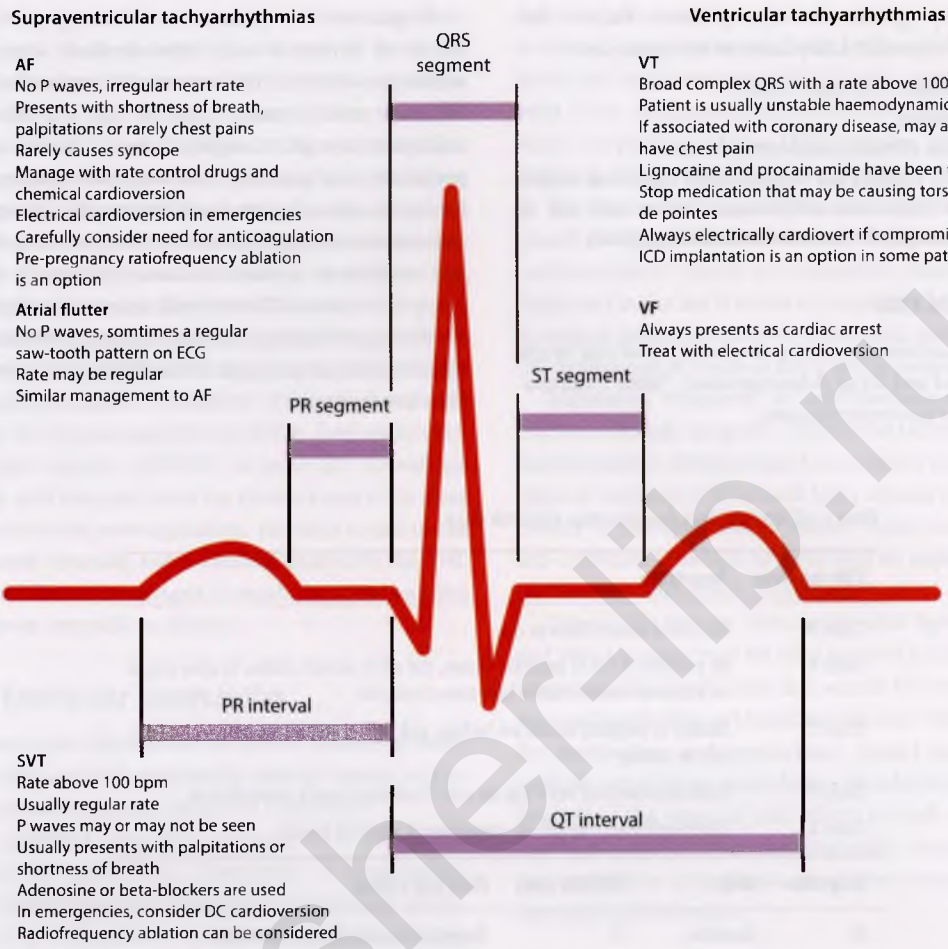

Figure 2 A summary of the different types of arrhythmias found during pregnancy and their treatment. AF, atrial fibrillation; bpm, beats per minute; DC, direct current; ECG, electrocardiogram; ICD, implantable cardioverter defibrillator; SVT, supraventricular tachycardia; VF, ventricular fibrillation; VT, ventricular tachycardia.

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PELVIC PAIN

Hugo M Fernandes

All women will at some time experience pelvic pain associated with events such as menstruation, ovulation, or sexual intercourse. While only a few women seek medical advice for such pain, it is the principal reason for over 40 per cent of gynaecological laparoscopies performed. Pelvic pain may be either visceral or somatic in origin. Visceral pain is transmitted by the autonomic nervous system and presents as a vague, deep, dull sensation that is difficult to localise and may even present as referred pain. Somatic pain on the other hand is usually constant with sharp periods of exacerbation and is well localised over the affected area. Stimuli that produce pain may include:

- distension and/or contraction of a hollow organ;
- rapid stretching of the capsule of a solid organ;
- irritation of the parietal peritoneum, e.g. blood, pus, cyst contents;
- ischaemia or necrosis of tissue, e.g. torsion of an ovary, cyst or mass;
- neuritis secondary to any inflammatory, neoplastic or fibrotic processes in adjacent organs.

The differential diagnosis of pain in the pelvis can be subdivided as follows:

- *Acute*: patient is ill and requires resuscitation with intravenous fluids or other products for hypovolaemia, sepsis, or dehydration. Urgent surgery may be required.
- *Subacute*: the onset of pain is sudden but does not cause the patient to be severely ill. While a diagnosis is established, the patient may require 24–48 hours of observation or analgesia. If the pain does not improve or the diagnosis is in doubt, a laparoscopy may be warranted.
- *Chronic*: intermittent or constant pain of at least 6 months duration. Often the result of long- standing and sometimes uncertain pathology. Symptoms and clinical and laparoscopic findings are often poorly correlated, with up to 50 per cent of patients who undergo laparoscopy showing no abnormality.

Acute and subacute pain

When assessing this type of pain, it is important that one is efficient but diligent. It is imperative that life-threatening conditions are considered and managed early. One should always consider a possible pregnancy-related condition in any woman during her reproductive years, and a positive pregnancy test should be considered an ectopic until otherwise proven. It is also important, however, to consider physiological and less emergent causes. The differential diagnosis for this type of pain can be classified in the following way:

- *Physiological*: this is often associated with menstruation or ovulation. Pain (dysmenorrhoea) is not an unusual feature of menstruation, with two thirds of women reporting some level of discomfort. It is the result of an increase in local prostaglandins within the uterus and often has a familial predisposition. Some women routinely experience some dull pain in the midline or either iliac fossa at the time of ovulation. This pain usually occurs 14 days before the next period (mittelschmerz) and may be accompanied by slight vaginal bleeding. Usually the timing of either of these diagnoses and the absence of any abnormal pelvic findings make the diagnosis clear.

- *Pregnancy related*: it is always important to consider or test for pregnancy in any woman during her reproductive years. The severity of pain and presentation will dictate the management. Miscarriage may present with bleeding and pain, which often reflects the inevitable nature of the miscarriage. On examination the cervical os will be open. Management is usually conservative unless there is excessive or prolonged bleeding. Ectopic pregnancy is still a major cause of maternal mortality and may present with anything from vague abdominal discomfort to an acute abdomen, depending on the gestation. While this problem can be treated conservatively with methotrexate, the vast majority of cases still require some form of operative intervention. Other problems in pregnancy include fibroid degeneration, which may be very acute, require hospital admission, and can cause the pregnant uterus to become very irritable.
- *Ovarian*: this acute pain usually reflects a cyst accident in the form of torsion, rupture, or haemorrhage (Fig. 1). The degree of peritonism will dictate the management.
- *Infection*: pelvic inflammatory disease (PID) is most common in young women. It is often but not always sexually transmitted, with *C. trachomatis* and *N. gonorrhoea* the most common organisms. Pain is usually bilateral and may be associated with a low-grade pyrexia, vaginal discharge, and discomfort with internal examination. Left untreated, PID may result in tubo-ovarian abscesses (Fig. 2) and adhesions and lead to a chronic pelvic pain syndrome.

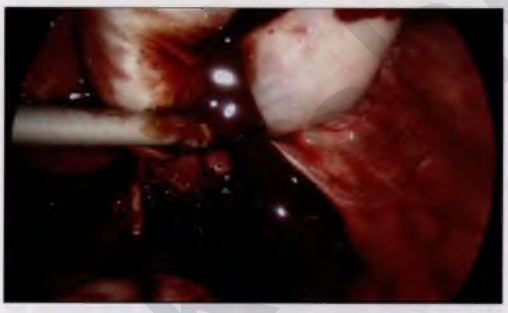

Figure 1 Laparoscopic view of ruptured endometrial cyst.

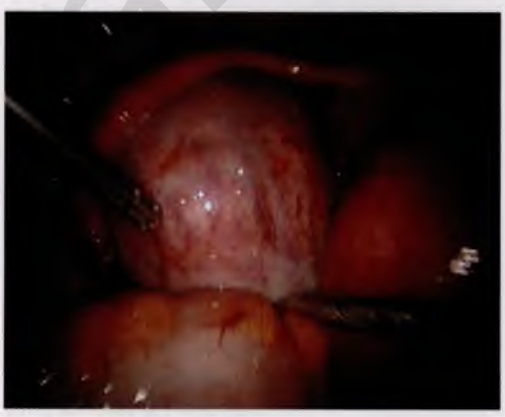

Figure 2 Tubo-ovarian mass.

- *Endometriosis*: this condition may cause both acute and chronic pelvic pain and is present in 10 per cent of women. This acute pain is usually cyclical and deep, is often site specific, and can be accompanied by painful intercourse, voiding, or bowel opening. Pain with a central heavy sensation and heavy periods may suggest the uterine form of the disease (adenomyosis). Diagnosis is usually confirmed by laparoscopy.
- *Pelvic tumours*: it is unusual for malignancies to present in the first instance with acute pain. Fibroids, ovarian cysts, and other masses may cause pain, however, if blood supply is compromised.

It is important to think laterally and consider all causes of pelvic pain, including the non-gynaecological:

- *Urinary tract*: including urinary tract infection, retention, and renal stones. A simple urine dipstick will often assist in this diagnosis.
- *Gastrointestinal*: diagnoses include appendicitis, gastroenteritis, constipation, diverticular disease, inflammatory bowel disease, acute hernial accidents, mesenteric infarction, and malignancy. Several causes (e.g. appendicitis) are life-threatening and require expedited management. Often the degree of acuteness and patient age will suggest the pathology.

Routine investigations

These will vary between presentations, but a full blood count and pregnancy test should be performed. If infection is considered, then swabs of the vaginal vault and endocervix to exclude chlamydia or gonorrhoea should be performed. A mid-stream specimen of urine may exclude a urinary infection. The mainstay of gynaecological investigation is the ultrasound scan, which may be very useful in diagnosing many of the possible causes. Similarly, a plain abdominal X-ray may be useful if bowel problem is suspected. An intravenous pyelogram may exclude a calculus. When in doubt, a diagnostic laparoscopy may be necessary.

Chronic pelvic pain

Any acute cause of pain, even with appropriate initial management, may lead on to a chronic condition. It is important to remember that chronic pelvic pain is not a diagnosis, but rather a symptom and that there is often more than one contributing factor. It accounts for 10 per cent of all gynaecological visits and up to a third of laparoscopies performed and is a significant burden to patients. A history of episodes of acute pelvic pain, increased number of sexual partners, and a higher incidence of psychosexual trauma as a child

may be present. A good history will often point to the appropriate initial investigations, which should include a quality pelvic ultrasound and vaginal swabs. While laparoscopy has been considered the 'gold standard' for diagnosis, it should be considered only after less interventional tests. Management of pain may be difficult and require multimodal intervention, including analgesia and hormones as well as psychological and physiotherapy input. Common causes include:

- *Adhesions*: while these may be found to some degree in 20–50 per cent of patients with chronic pain (Fig. 3), their role as a cause of pain is controversial. Evidence exists only for division of dense vascular adhesions which may cause pain on organ movement or stretching.
- *Residual/entrapped ovary syndrome*: this occurs when adhesions are significant enough to envelope an ovary or when ovarian tissue is left behind following hysterectomy. Typically this is associated with dyspareunia and a fixed, tender ovary at the vaginal vault. Medical suppression or removal of the ovary both have reasonably good outcomes.
- *Endometriosis*: this involves the abnormal implantation of endometrium outside the uterine cavity and can lead to scaring, adhesions, and a 'fixed' pelvis (Fig. 4). It may present with dysmenorrhoea, dyspareunia, infertility, and pelvic, rectal or bladder pain; however, there is poor correlation between symptoms and disease volume. Adenomyosis may cause a similar pain and is also associated with heavy periods. Diagnosis and definitive management of both is usually by laparoscopy. Hormonal suppression may also be used as primary or adjuvant treatment. Hysterectomy is the most definitive management but has the best outcomes only when ovaries are also removed.
- *Irritable bowel syndrome*: this condition may be a primary cause of lower abdominal pain and is often confused with a gynaecological cause.
- *Pelvic congestion*: this is associated with dilated veins in the broad ligament and uterus and presents with dull, aching pain and occasional sharp exacerbations. Its association with chronic pain is controversial, though treatment with progestogens seem to be effective.
- *Psychological*: there is a complex relationship between chronic pelvic pain and psychosexual abuse as a child. Depression, anxiety, or somatisation may predispose or contribute to pain as an adult. This should be explored with patients, as management of issues such as depression and sleep disturbance may improve the ability to cope with chronic pain.

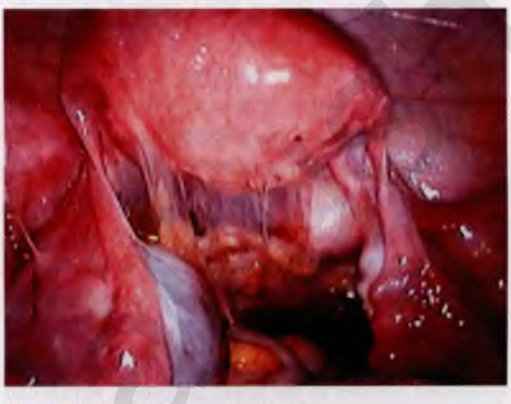

Figure 3 Laparoscopic view of adhesions.

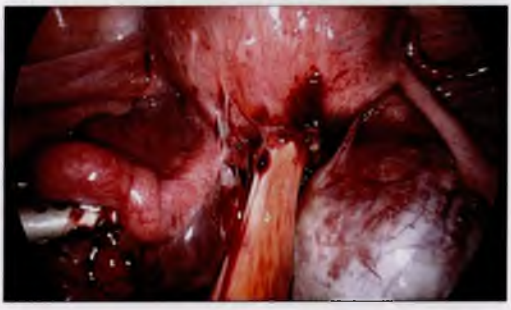

Figure 4 Laparoscopic view of severe chronic endometriosis.

Suggested reading

RCOG Green-top Guideline 41: Chronic pelvic pain: initial management. 2012.

SOGC Clinical Practice Guideline 164: Consensus guidelines for the management of chronic pelvic pain – Parts 1 & 2. 2005.

RCOG Green-top Guideline 24: The investigation and management of endometriosis. 2008.

PELVIC SWELLINGS

Anupama Shahid and Tony Hollingworth

Swellings that arise from the pelvis can be considered under their anatomical site of origin. A number of structures may appear to be pelvic when their true site of origin is really abdominal. Ultrasound scanning has improved the detection of lesions that are not necessarily palpable without a vaginal or rectal examination. The background to the swellings can be simply described by the 'five Fs':

- fat
- fluid
- faeces
- flatus
- fetus

Careful history-taking, clinical examination, and appropriate imaging should be able to establish the diagnosis. Many of these swellings will be

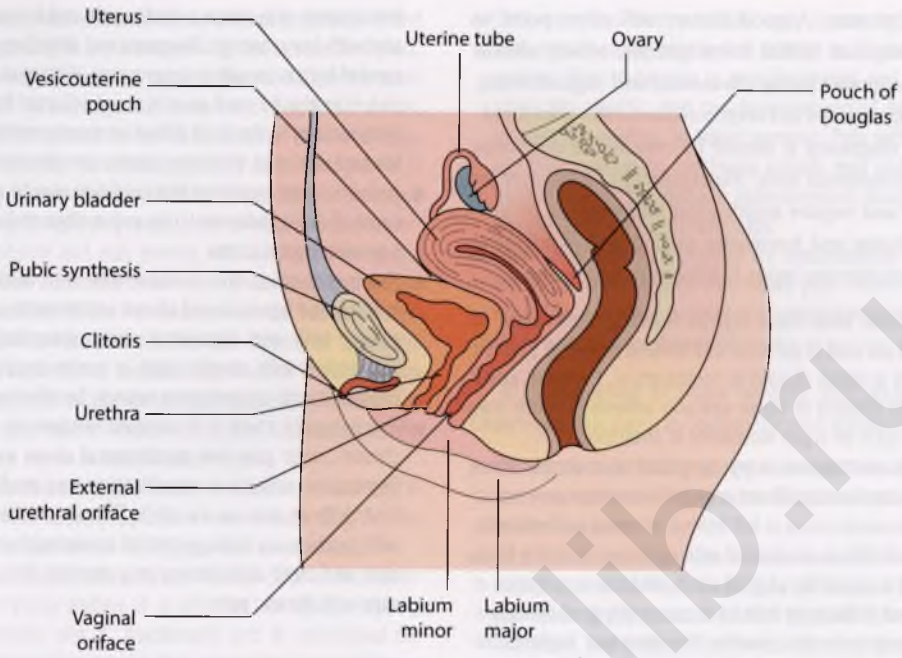

Figure 1 Sagittal section diagram of the female pelvis.

dealt with under individual organ sites. Therefore, this section will provide an overview and reference should be made to those sections in this book. These swellings will be considered anatomically from anterior to posterior, finally dealing with the bony surround of the pelvis (Fig. 1).

Bladder

- Simple distension or retention.
- Transitional cell carcinoma (see Haematuria).

The commonest difficulty which arises in the diagnosis of pelvic swellings is to distinguish between the distended bladder, pregnant uterus, ovarian cyst, and uterine fibromyoma; and the commonest mistakes are made in identifying these swellings. The distended bladder is the easiest to dispose of, with the passage of a catheter settling the question; yet neglect of this simple procedure has led to the abdomen being opened.

Vagina

- Haematocolpos.
- Hydrocolpos.

Distension of the vagina by menstrual fluid is not likely to be mistaken for anything else, if only on account of the absolute closure of the atretic membrane, which gives rise to it. This condition is often referred to as 'imperforate hymen' (see Menstrual periods, absent, Fig. 3); this is not correct because the atresia is at a higher level in the vagina than the hymen, which is always perforate.

Haematocolpos (blood-filled vagina) is practically the only central tumour occurring between the rectum and the bladder reaching from the level of the hymen to the pelvic brim (see Menstrual periods, absent). It presents in girls about the age of 16–17 years, who frequently present with acute retention of urine owing to the fact that the swelling fills the pelvis, and the distended bladder in front is forced upward into the abdomen. Primary amenorrhoea (absent periods) is present, although monthly symptoms without loss of blood may have taken place for some time. Two swellings are present: the tender distended bladder in the lower abdomen, which can reach as high as the umbilicus, and the distended vagina filled with menstrual fluid in the pelvis. The uterus can usually be felt like a cork movable upon its upper extremity. The lower pole of the haematocolpos presents a blue-coloured swelling at the vulva.

A similar swelling may be found on rare occasions in newborn girl babies, with the vagina is filled with a milky fluid (hydrocolpos).

Uterus

- *Pregnancy related*, either normal or abnormal, with or without associated tumours of the uterus or ovary.

- *Non-pregnancy related*:
  - *benign*: the most common of which are fibroids (leiomyoma). Others causes include haematometra and pyometra (blood or pus in the uterine cavity, respectively), many of which will prove to be benign, but malignancy should be considered and excluded.
  - *malignant*: the most common being endometrial carcinoma, but rarer tumours would include mixed Müllerian tumours, uterine sarcomas, and choriocarcinomas.

A comprehensive history is always important and, in the reproductive age group, one should always consider the possibility of pregnancy with uterine swellings. Pregnancy and fibroids are the two most common causes of uterine swelling and, together with other causes, are dealt with more fully in Uterine swellings.

Cervix

The cervix is an integral part of the uterus (womb), and its size will vary depending on the age of the woman. It increases in size with puberty and may continue to do so with pregnancy or the development of cervical fibroids. It will eventually reduce in size with the onset of the menopause. If the woman develops a prolapse, it can become oedematous, especially if it appears outside the vagina (procidentia). The swellings can be divided into benign and malignant. These will be covered in Cervical swellings.

Ovary

The ovary can be considered a reproductive organ made up three basic types of cells:

- those that produce the eggs or ova (totipotential cells);
- those that produce secretions (sex-hormone secreting cells);
- the remaining cells that wrap these cells together (epithelial cells).

Each of these types of cells can produce ovarian swellings. The totipotential cells can produce dermoid/germ-cell swellings. The hormone-secreting sex-cord cells may produce excess amounts of hormone, which can lead to irregular shedding of the endometrium in the case of oestrogen, and to hirsutism and virilism through an excessive testosterone production. The epithelial cells account for the majority of ovarian swellings. These can be classified thus:

- *Benign*: including cysts and fibromas;
- *Malignant*: primary origin in the form of epithelial tumours (85 per cent), sex-cord tumours (6 per cent), germ-cell tumours (2 per cent) and, uncommonly, sarcomas or lymphomas. Secondaries (6 per cent) originate from the gut, breast, lung, and thyroid.

The differential diagnosis of ovarian swellings will be considered elsewhere (see Ovarian swellings). Ovarian cancer is the most frequently occurring genital tract cancer in the UK, although overall is much less common than breast cancer by a factor of 6 to 1. It is estimated that a general practitioner will see one new case of ovarian cancer every five years.

The ovary produces a cyst every month in the form of an ovarian follicle, which will in turn release an egg (ovum). These follicles may reach up to 25 mm in diameter. As a rule of thumb, an ovarian cyst up to 5 cm in diameter should resolve on its own: an ultrasound scan should be repeated after two to three menstrual periods to ensure that it has resolved. If the cyst grows larger than 5 cm, it is likely to require removal. The main complications of an ovarian cyst include torsion, rupture, and haemorrhage. The largest cyst removed in the UK weighed 63 kg; the world's largest was removed in 1905 in the USA and weighed a staggering 145 kg. If the cyst increases to a very large size, it is likely to be benign, or possibly of borderline malignancy. The ovary is not usually palpable on vaginal examination until it is at least 5 cm in diameter. It is usually not palpable in a postmenopausal woman, as the incidence of ovarian cysts is much less compared to that in the premenopausal women, and any ovarian cyst in these women should be considered with a high index of suspicion until proven otherwise.

Fallopian tubes

- *Pregnancy related*: tubal gestation or progressive extrauterine pregnancy (ectopic).
- *Inflammatory*: salpingitis, which may lead to a hydrosalpinx or pyosalpinx.
- *Malignant*: carcinoma of the Fallopian tube being very uncommon.

With small tumours confined to the pelvis, or rising only a little above the brim, diagnosis is often difficult. In practice, however, extrauterine gestation and its resulting blood tumour standout pre-eminently as a swelling, which must be recognised at once if treatment is to be successful (Fig. 2).

Before rupture or abortion has occurred, a tubal gestation is essentially a small tumour in one posterolateral corner of the pelvis, attached to the uterus, indefinite in consistency, remarkably tender, and perhaps – although not always – associated with amenorrhoea of short duration and acute attacks of pain in the pelvis. Definite signs of pregnancy may be

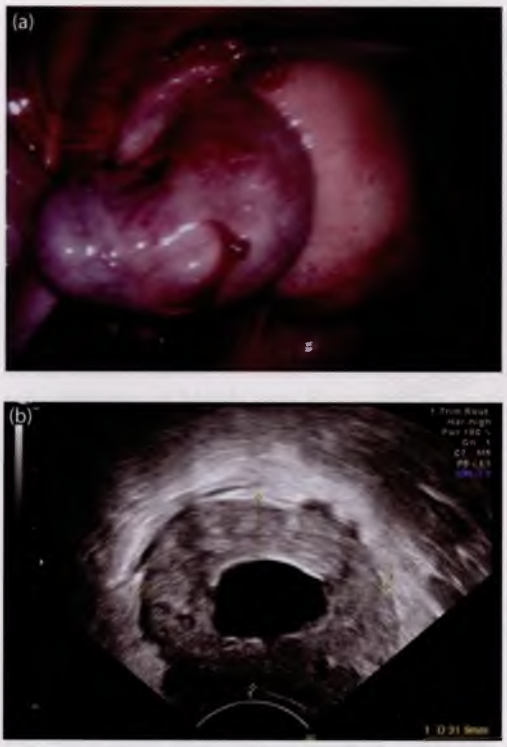

Figure 2 Laparoscopic picture of an ectopic pregnancy (a) and an abdominal ectopic pregnancy on ultrasound (b).

entirely wanting, but a pregnancy test will be positive. It may be mistaken for a chronic salpingo-oophoritis, a small cystic ovary, a small pedunculated fibroid, or a small ovarian dermoid.

The differential diagnosis may be difficult, and attacks of pain unassociated with menstruation are not likely to occur in any of the above conditions; the pains are usually the result of overdistension and stretching of the tube from haemorrhage into its wall or lumen around the fertilised ovum. Unless the swelling is tender (often very tender), it is not likely to be due to a tubal pregnancy. When tubal abortion has occurred, or tubal rupture, the signs of internal bleeding accompanied by sudden pain and collapse, with haemorrhage from the uterus or the passage of a decidual cast, usually make the diagnosis obvious. Intraperitoneal haemorrhage is more commonly severe and copious with tubal rupture than with tubal abortion. If the patient recovers from the initial bleeding, the clinical picture may be that of a retro-uterine or peritubal haematocele. The uterus is pushed forwards and upwards against the symphysis pubis, and the mass of blood clot can be felt posteriorly causing the posterior fornix and also the anterior wall of the rectum to bulge. Vaginal examination is very tender. Tubal miscarriage is most likely to be mistaken for an ordinary intrauterine miscarriage; but the presence of a tender mass on one side of the uterus, with a closed cervix and a negative ultrasound scan, and the absence of uterine contractions or extrusion of any products of conception, should make the diagnosis clear. Pain is much more severe and external bleeding is much less in extrauterine pregnancy.

The essential point in diagnosing an ectopic pregnancy is to approach every woman of childbearing age who complains of irregular bleeding and abdominal pain with the possibility of pregnancy, and then determine where that pregnancy is. No two cases are alike, and there are more exceptions to the rule in the symptomatology of this condition than in any other. Risk factors for ectopic pregnancy include history of pelvic inflammatory disease, tubal surgery including sterilisation, progesterone-only contraception, intrauterine contraceptive devices, and a history of infertility. The development of ultrasound has a major advance in the early diagnoses of ectopic pregnancy. A transvaginal scan can diagnose an intrauterine pregnancy as early as 4 weeks and 3 days in a woman with regular 28-day menstrual cycles. It must be emphasised that, while maternal death is not common in the UK, ectopic pregnancy remains a major cause.

Progressive extrauterine gestation is a rare occurrence, and is the result of continued growth of an embryo after a partial separation from the tube as a result of rupture or extrusion from the fimbriated end (abortion). The continued enlargement of a mass beside the uterus, and amenorrhoea and progressive signs of pregnancy are the most characteristic points. Abdominal pain in late pregnancy is a characteristic feature. The uterus may be felt in the pelvis separate

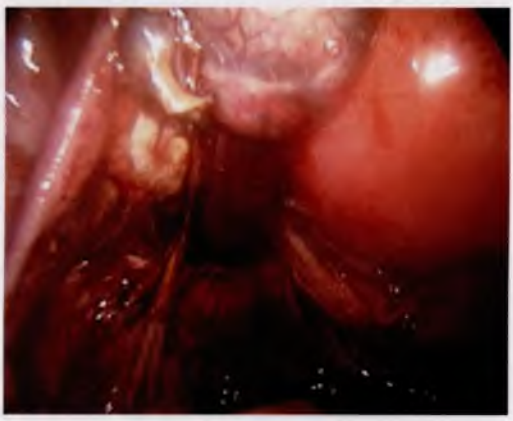

Figure 3 Laparoscopic picture of pelvic inflammatory disease.

from the fetal sac. The diagnosis, however, is difficult, because there is always some effused blood, which obscures the outlines of the uterus, and makes it appear to be a part of the pelvic mass. The fetus is often situated high above the pelvis and it tends to lie transversely facing downward. A radiograph reveals the fetus adopting a position that is characteristically odd, the spine hyperextended or acutely flexed, and the head and limbs at unusual angles to the trunk.

If, on a lateral view, radiography shows fetal parts overlapping the maternal spine, the pregnancy must be extrauterine. Ultrasonography will establish the absence of an intrauterine gestation and also the size of the uterus, which never exceeds that of 5 months' gestation even in the presence of a full-term extrauterine pregnancy, and the cervix does not soften to the same degree. In those cases where the fetus lies in the front of the false sac, it will feel very superficial owing to the absence of uterine wall in front of it, and between it and the examining hand. The fetus is, however, often difficult to palpate, owing, perhaps, to the placenta in front, which may give rise to a loud vascular soufflé just medial to the anterior superior iliac spine on the side from which it derives its main blood supply (via the ovarian vessels).

The swellings due to salpingo-oophoritis are usually easy to distinguish. They form fixed tender masses in the pelvis, seldom of any definite shape, but occasionally present with the characteristic retort shape, with its narrow end near the uterus, which the tube assumes when distended with fluid (Fig. 3). The history is usually that of an acute illness at some period, with usually bilateral pain in the pelvis, rise of temperature, and peritoneal irritation. These patients have been sexually active. It is preceded, as a rule, by uterine discharge and heavy vaginal bleeding. This inflammatory disturbance in women can be associated with long periods of infertility, owing to occlusion of the fimbrial ends of the tubes. In the chronic state, pelvic pain, congestive dysmenorrhoea, dyspareunia, vaginal discharge, menorrhagia, and infertility occur. The signs of suppuration, pyrexia and leucocytosis, wasting, and daily sweating are usually absent, and the pus in the tubes is sterile. Swabs should be taken including from the endocervix for *Chlamydia*, and the patient should be referred to the local genitourinary medicine clinic for ongoing/contact tracing management.

A large pelvic abscess may accompany salpingo-oophoritis, or may occur alone without infection of the tubes, as is seen occasionally in puerperal septic infections. When it does occur, it is of course peritoneal. It fixes the uterus in a central position, bulges into the posterior fornix and rectum, and tends to rupture into the rectum, before which occurrence there may be copious mucoid discharge from the anus. It is usually acute in onset and accompanied by signs of local peritonitis. A swinging temperature, leucocytosis, sweats, and the symptoms of fever are present, all suddenly improving when the abscess discharges itself. It is likely to be confounded with pelvic cellulitis, in which the uterus is fixed in a laterally displaced position. This swelling causes one lateral fornix to bulge and extends right out to the lateral pelvic wall, tends to burrow along the round ligament to the groin, and may point there like a psoas abscess. It can be slow in onset, chronic, and not accompanied by signs of local peritonitis. It always follows labour, or abortion, whereas pelvic abscess of peritoneal origin may occur with salpingo-oophoritis or appendicitis, quite apart from pregnancy. Pelvic cellulitis never bears any relation to salpingo-oophoritis. It may take many weeks to resolve, which it usually does without pointing.

Malignancy within the Fallopian tube is extremely uncommon and, as a consequence, has no obvious localising signs. It may well behave like an ovarian cancer, and the diagnosis may only be confirmed histologically after surgery.

Pelvic peritoneum, retroperitoneal swellings and connective tissue

Encysted peritoneal fluid, hydatid cysts, and retroperitoneal lipomas are generally diagnosed as ovarian cysts, and their true nature is discovered only at operation. There are no definitive signs by which these conditions may be diagnosed and, as they all require operative treatment, postoperative diagnosis meets their requirements. Encysted peritoneal fluid due to tuberculosis may be suspected, if tuberculous lesions are present elsewhere in the body. They lack the definite outline of an ovarian cyst and are often semi-resonant on percussion.

Urachal cysts occur in front of the uterus and in close relation to the bladder; but in spite of this, they are usually mistaken for ovarian cysts. It is to be remembered, however, that ovarian cysts are likely to occur only in front of the uterus when they are large, but dermoid cysts of the ovary of small size occasionally do so. Urachal cysts are embryological remnants and rarely attain a large size (see Fig. 4).

The omentum should also be included in this group, which can form a 'cake' as a result of secondary transcoelomic spread from a primary ovarian

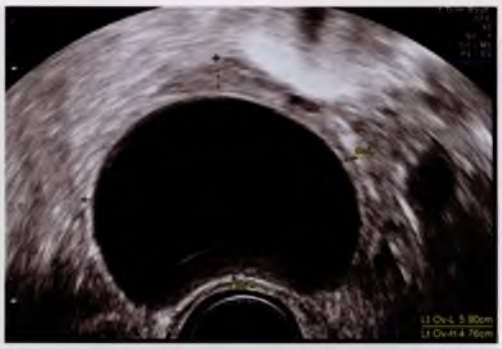

Figure 4 Ultrasound image of a benign uniloculated ovarian cyst <5 cm in size.

tumour. Usually they tend to be palpable abdominally and, as the omentum originates from the transverse colon, it is really an abdominal swelling, although it can become involved with the tumour pelvically.

Bowel

Appendicitis with pregnancy occurs occasionally and may be mistaken for torsion of an ovarian pedicle. The swelling due to appendix inflammation is, however, in close relation to the anterior superior spine of the ilium and the right iliac fossa. The lump is ill defined and rarely fluctuates unless there is a large abscess. The acute onset may be similar to that of torsion of an ovarian pedicle. There is usually a definite fluctuating tumour when an ovarian cyst is present, and some interval between it and the iliac crest can usually be felt. Bowel cancer is more common than the common gynaecological tumours, as is diverticulitis. These patients tend to present with a history of altered bowel problems, with or without rectal bleeding.

Bone

Abnormal growth of the pelvic bones is very rare, although any tumours may be either cartilaginous or sarcomatous. Any tumours will be found to be continuous with the bones in the pelvis from which they arise. If it is growing from the sacrum, then it will have the rectum in front of it, unlike all gynaecological swellings in the pelvis, which have the rectum posterior to them. In most cases, the uterus and adnexae can be palpated bimanually, and shown to be free from disease and unconnected with the mass. The only possible gynaecological problem for which it may be mistaken is adherent inflammatory reaction from infection of the tubes and ovaries (salpingo-oophoritis). When complicated by the presence of a pregnant uterus, their true nature may be difficult to determine unless examination reveals that they are absolutely fixed and continuous with the bones of the pelvis.

Radiological imaging followed by biopsy may determine the diagnosis. These are rare problems and unlikely to present to the gynaecologist.

Other structures

Many of these lesions are not primarily pelvic, but they are included in the list because they are liable to be mistaken for pelvic tumours. Thus, renal, splenic, and pancreatic tumours may reach the pelvic brim, but the history ought to show that they have grown down from above, not up from below. Renal swellings may be associated with urinary changes, or absence of urinary secretion on the affected side, as detected by the cystoscope or an intravenous pyelogram.

Malformations of the genital tract are associated with developmental abnormalities of the renal tract. It is not uncommon to find a solitary pelvic kidney in patients with congenital absence of the vagina and uterus.

Splenic enlargements may be associated with changes in the blood picture. Pancreatic cysts are the least likely to be mistaken for pelvic swellings, but they have been difficult to distinguish from ovarian tumours with long pedicles. Diagnosis will be dependent on appropriate imaging.

PREMENSTRUAL SYNDROME

Harry Gibson and Tony Hollingworth

Premenstrual syndrome (PMS) can be defined as the cyclical recurrence during the luteal phase of the menstrual cycle of distressing psychological, behavioural, and physical symptoms not attributable to underlying organic or psychiatric illness. Symptoms essentially occur in the 2 weeks prior to menstruation and resolve by the end of menstruation. The woman should then be free of symptoms between the end of menstruation and subsequent ovulation.

Psychological and somatic disturbances are part of the normal physiology of the menstrual cycle: the majority of women (95 per cent) will experience some mild premenstrual symptoms, with only a small percentage (5 per cent) being totally symptom free. However, when exaggerated, they may lead to severe psychological disturbance and behavioural

abnormalities. In a small group of women (5 per cent), these symptoms have a major impact on their lives and have led to suicide and acts of aggression, and have even been cited as defence in murder trials!

Physical symptoms may include bloating, muscle cramping, joint pain, pain and tenderness in the breasts, headaches, temporary gain in weight, and some swelling of the hands and feet. Psychological manifestations include mood swings, emotional tension, bad temper, nervousness, irritability, lack of concentration, sense of loss of control, depression, and insomnia, sufficient to interfere with the normal enjoyment of life. Previous diagnostic criteria have been criticised as too restrictive, such as those from the American Psychiatric Association for premenstrual dysphoric disorder. Therefore, the International Society for Premenstrual Disorders (ISPMD) recently defined looser criteria for the diagnosis of core PMS, which takes into account the wide variety of symptoms experienced by patients. These criteria are listed in Box 1.

The aetiology of this condition remains obscure and as a result presents therapeutic difficulties. The underlying cause may be a combination of imbalances/abnormalities of the ovarian steroid production and central nervous transmitters. It has been shown that women with PMS have lowered levels of whole blood serotonin concentrations and platelet serotonin in the premenstrual phase. Several selective serotonin reuptake inhibitors (SSRIs) have now been shown to improve PMS symptoms. Elimination of the cyclical ovarian function can result in the complete suppression of symptoms, and this is supported by the absence of symptoms after menopause or during pregnancy. Despite cyclical ovarian steroid function being the trigger for PMS, there is no definitive diagnostic test to distinguish it from other disorders. The nature of the symptoms is less important than the timing, and keeping a diary of symptoms is necessary for supporting the diagnosis and is useful in distinguishing primary PMS from secondary. The latter are a group of patients who have true PMS with underlying psychopathology. If the symptoms do not follow the pattern described, then an alternative diagnosis needs to be considered and appropriately managed in primary care or by a psychologist.

Treatment depends on the severity of symptoms and begins for patients with mild problems with general advice, simple analgesia, counselling, education, exercise, and reassurance. There is

Box 1 ISPMD Criteria for diagnosing the core premenstrual disorder

- Symptoms occur in ovulatory cycles
- Symptoms are not specified: they may be somatic and/or psychological
- The number of symptoms is not specified
- Symptoms are absent after menstruation and before ovulation
- They must recur in the luteal phase
- Symptoms must be prospectively rated and recorded over a minimum of two cycles (for example by use of a symptom diary)
- Symptoms must cause significant distress or significant impairment to normal daily activity and relationships

reasonable evidence for the use of cognitive behavioural therapy, especially as it seems the effects are more prolonged compared to SSRIs. Complementary therapies may be beneficial, but the data is limited. Calcium and pyridoxine (vitamin B6) are supported by weak evidence, and trials support luteal phase spironolactone to reduce mood symptoms and swelling or bloating. Symptom diaries should be maintained in order for the clinician to assess the outcome of treatment. If simple therapies are not effective, or the symptoms are severe, it is recommended that referral to secondary care be considered. Ideally, this should comprise a multidisciplinary team that includes a gynaecologist, psychiatrist, counsellor, and dietician. Figure 1 shows the RCOG-recommended hierarchy of therapies for managing severe PMS.

Selective serotonin reuptake inhibitors (SSRIs) have proven value in the treatment of PMS, although they are not licensed for this indication. Dosing can be continuous, or restricted to the luteal phase of the cycle. Another approach is ovulation suppression; this may start with continuous use of the combined oral contraceptive pill (OCP), providing there are no contraindications to its use. Second-generation OCPs can exacerbate PMS symptoms, so it is recommended to select an OCP containing anti-androgenic/anti-diuretic progestogens, such as drospirenone (Yasmin®). Alternatively, percutaneous estradiol (either patch or implant) has shown favourable evidence of efficacy. If using unopposed oestrogen, it is necessary to include cyclical low-dose oral progestogen, or use the Mirena intrauterine

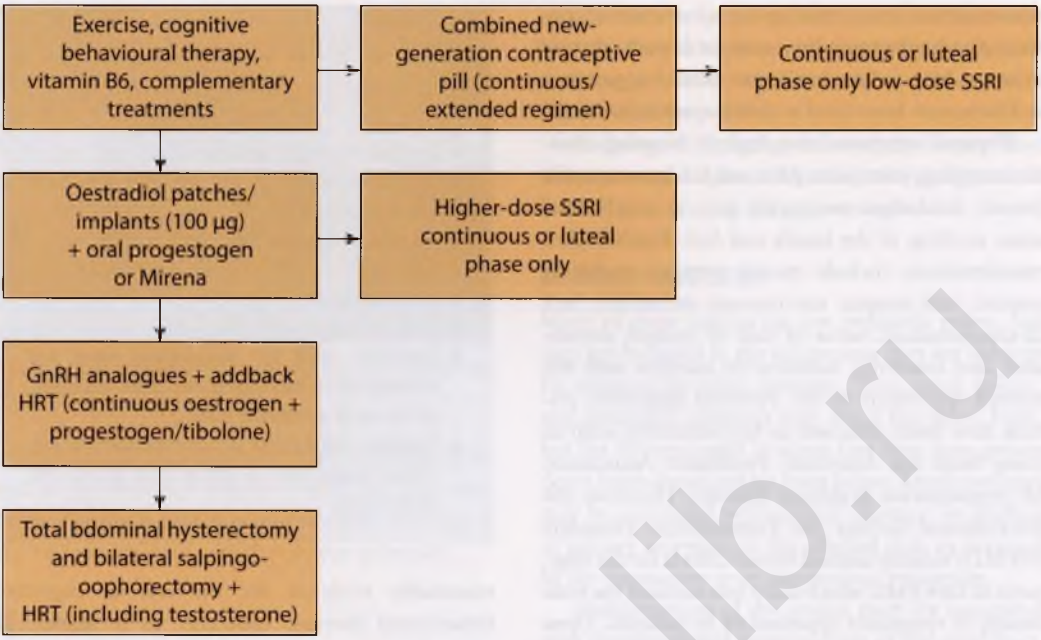

Figure 1 RCOG-recommended hierarchy of therapies for managing severe premenstrual syndrome. GnRH, gonadotrophin releasing hormone; HRT, hormone replacement therapy; SSRI, selective serotonin reuptake inhibitor.

system, to reduce the risk of endometrial hyperplasia. Progesterone-only regimes are the only licensed hormonal therapy in the UK; however, in meta-analysis they have been shown to be ineffective.

Danazol will also suppress the ovulation cycle, but may cause hirsutism, acne, and occasionally irreversible deepening of the voice. Gonadotrophin-releasing hormone analogues should be used only in severe cases and are preferable to total abdominal hysterectomy with bilateral salpingo-oophorectomy. In both cases, add-back hormone replacement therapy in the form of continuous oestrogen combined with progestogen or tibolone is required to maintain bone mineral density and avoid menopausal symptoms.

Useful resources

Clinical Knowledge Summaries: cks.nice.org.uk/premenstrual-syndrome

O'Brien S et al. Diagnosis and management of premenstrual disorders. *BMJ* 2011; **342**: d2994

Patient Forums and Support: www.pms.org.uk

RCOG Green-top Guideline 48: www.rcog.org.uk/guidelines

PROLAPSE OF UTERUS AND VAGINA

Jai B Sharma

A prolapse is the protrusion of an organ or structure beyond its normal anatomical position. Pelvic organ prolapse, as defined by the International Continence Society, is the descent of one or more vaginal segments: the anterior, posterior, and apex of the vagina or, after hysterectomy, the vaginal vault.

Aetiology

Pelvic organs are supported by the pelvic floor. The anatomy of the pelvic floor is shown in Figure 1 in Birth injuries, maternal.

The vaginal supports have been divided into three levels by De Lancey. Level 1 is provided by the transverse cervical (Mackenrodt's or cardinal) and uterosacral ligaments as the superior attachment; level 2 by the anterior vaginal wall and recto-vaginal fascia as the lateral attachment; and level 3 by the perineal body and perineal membrane as the distal attachment. The supports of the uterus are shown in Figure 1 and the ligamentous supports of the uterus in Figure 2.

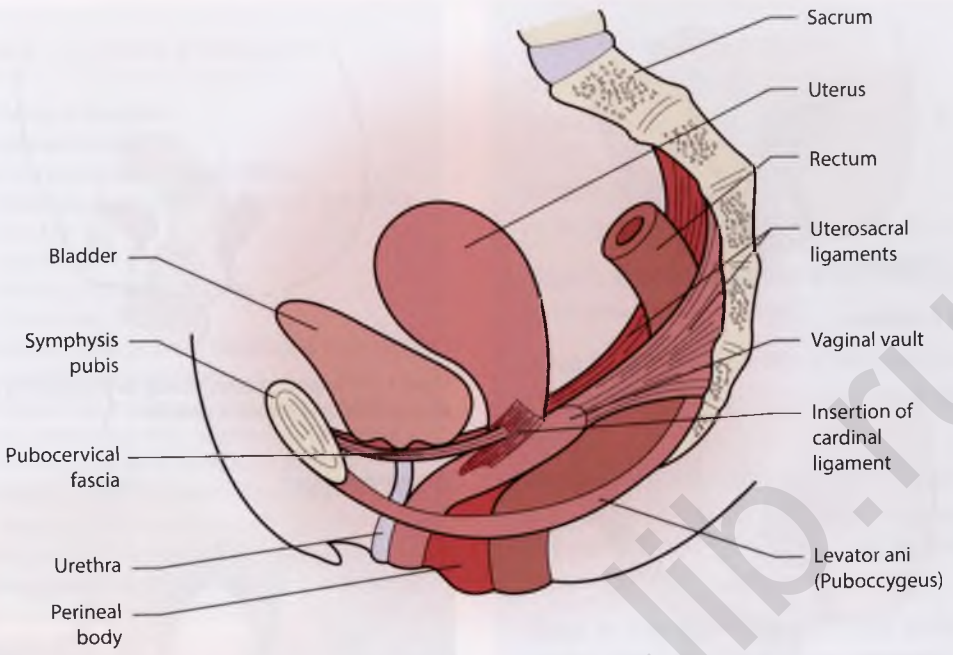

Figure 1 Supports of the uterus.

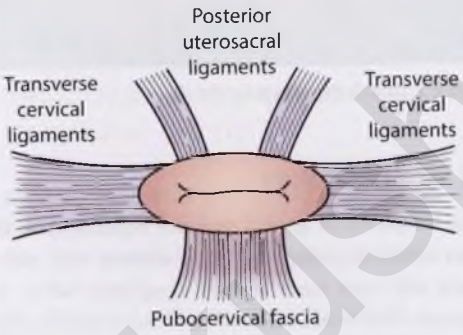

Figure 2 Ligamentous supports of the uterus.

Uterovaginal prolapse may be caused by breaks in the integrity of the uterosacral ligaments, weakness of pelvic floor muscles or changes in the normal vaginal axis. It usually results from child birth trauma, further compounded by urogenital atrophy in elderly women owing to lack of oestrogens. It is more common in elderly multiparous women and is more common in Caucasians than in Afro-Caribbeans. Prolapse in nulliparous women is rare. The various predisposing factors of prolapse are shown in Box 1.

Box 1 Causes of prolapse

- Pregnancy and childbirth trauma
- Ageing and oestrogen withdrawal
- Smoking
- Constipation
- Obesity
- Strenuous exercise
- Excessive and strenuous work in wrong postures
- Pelvic tumours
- Raised intra-abdominal pressure
- Previous surgery:
  - pelvic surgery
  - bladder neck suspension
  - Burch's colposuspension
- Chronic cough

Classification

The pelvic organ prolapse is divided into the following categories according to which part is involved:

- Cystocoele: prolapse of deeper part of the anterior vaginal wall, including the bladder (Fig. 3).
- Urethrocoele: prolapse of the upper part of the anterior vaginal wall carrying the urethra with it.
- Cysto-urethrocoele: the combination of prolapse of both upper and lower part of anterior vaginal wall including the bladder and urethra.
- Rectocoele: prolapse of the lower part of the vagina including the rectum (Fig. 4).

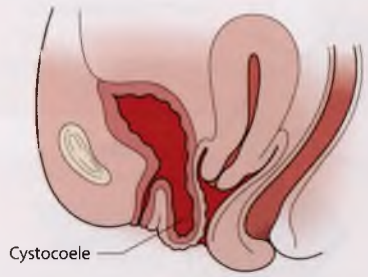

Figure 3 Cystocoele.

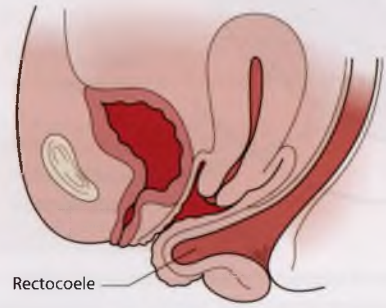

Figure 4 Rectocoele.

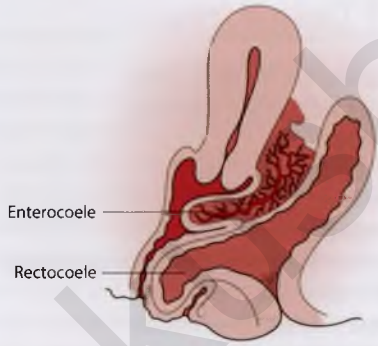

Figure 5 Enterocoele and rectocoele.

- Enterocoele: prolapse of the posterior fornix with the upper part of vagina; this is related to the pouch of Douglas and may contain loops of small intestines (Fig. 5).
- Uterine prolapse: descent of the cervix with the uterus through the introitus. This is classified into the following (Fig. 6):
  - first degree – the cervix descends to the vulva but does not come out through the introitus;
  - second degree – the cervix protrudes through the vulva;
  - third degree – the cervix is below the vulva (Fig. 7);
  - fourth degree – the whole of the uterus is outside the vulva (procidentia).
- Vault prolapse: prolapse of the vaginal vault after hysterectomy.

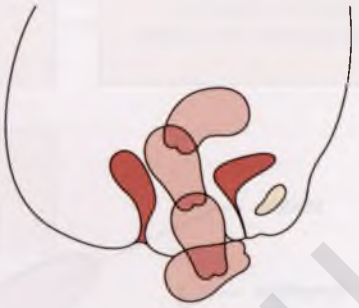

Figure 6 Uterovaginal prolapse, showing the position of the normal uterus and the three degrees of prolapse.

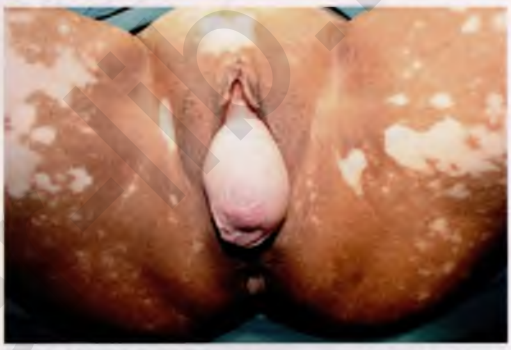

Figure 7 Third-degree prolapse of the uterus.

Symptomatology

The symptoms of genital prolapse depend upon the part which is prolapsing. Thus women with cystocoele will have more urinary symptoms, while the patients with rectocoele will have more bowel symptoms. However, patients with genital prolapse may not have any symptoms other than prolapse. The various symptoms are shown in Box 2.

POPQ (pelvic organ prolapse quantification) classification of genital prolapse

This objective, site-specific system for describing, quantifying, and staging pelvic support was introduced by Bump et al. in 1996.[1] It has been approved by the International Continence Society and the American Urogynecologic Society for the description of female pelvic organ prolapse. It measures positions at nine sites on the vagina and perineal body in relation to the hymen. The details are given in Boxes 3 and 4, and in Figure 8.

Box 2 Symptoms of prolapse

- Feeling of discomfort
- Heaviness in pelvis
- Lump coming down through introitus
- Worsening of symptoms on standing and at the end of the day
- Dyspareunia
- Difficulty in inserting tampons
- Chronic lower backache
- Vaginal discharge and/or bleeding due to mucosal ulceration and lichenification
- Urgency and frequency of urine (in cystocoele)
- Recurrent urinary tract infections (in cystocoele)
- Incomplete emptying of bowel (in rectocoele)
- Difficulty in moving bowels (in rectocoele)
- Tenesmus (in rectocoele)
- Digital defaecation (in rectocoele)
- Rarely, ureteric obstruction and chronic renal failure

Box 3 Measurements of positions on the vagina and perineal body in relation to the hymen for POPQ (pelvic organ prolapse quantification) classification (see Fig. 8)

Aa 3 cm proximal to urethral meatus on anterior vaginal wall
Ap 3 cm proximal to urethral meatus on posterior vaginal wall
Ba Most distal portion on anterior vaginal wall
Bp Most distal portion on posterior vaginal wall
C Most distal edge of cervix or vaginal cuff
D Post vaginal fornix
Gh Genital hiatus – middle of external urethral meatus to post midline hymen
Pb Perineal body – post margin of genital hiatus to mid-anal opening
Tvl Total vaginal length – greatest depth of vagina when points C and D are reduced to normal position

Differential diagnosis

Differential diagnosis of a lump at the vulva and pelvic organ prolapse is shown in Box 5. It requires proper history-taking, examination, and investigations to establish a clear diagnosis.

Box 4 Pelvic organ prolapse staging: POPQ (pelvic organ prolapse quantification) classification (see Fig. 8)

Stage 0: No prolapse
Aa, Ba, Ap, Bp are –3 cm and C or D ≤ –(tvl – 2) cm

Stage 1: Most distal portion of the prolapse
–1 cm (above the level of hymen)

Stage 2: Most distal portion of the prolapse
≥ –1 cm but ≤ +1 cm (≤1 cm above or below the hymen)

Stage 3: Most distal portion of the prolapse
> +1 cm but < +(tvl – 2) cm (beyond the hymen; protrudes no further than 2 cm less than the total vaginal length)

Stage 4: Complete eversion; most distal portion of the prolapse
≥ + (tvl – 2) cm

tvl, total vaginal length.

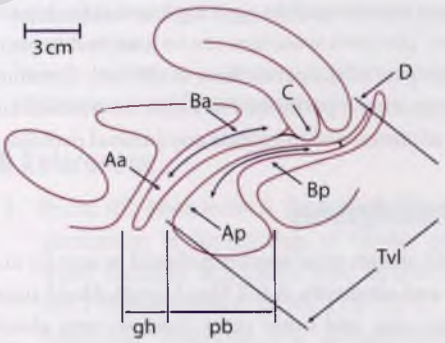

Figure 8 POPQ (pelvic organ prolapse quantification) classification of genital prolapse. Six sites (points Aa, Ba, C, D, Bp, Ap), genital hiatus (gh), perineal body (pb) and total vaginal length (Tvl) used for pelvic organ support quantification. (Reproduced from Bump et al., *Am J Obstet Gynecol* 1996; 175: 10 with permission from Elsevier.)

Examination of the patient

After taking a complete history and detailed general physical examination, including heart and chest examination, the abdomen and inguinal regions are examined for any lumps or hernias. Local perineal examination for the prolapse is performed in detail to know which part of the genital

Box 5 Differential diagnosis of lump at introitus

- Uterine prolapse
- Vaginal prolapse
- Cystocoele
- Urethrocoele
- Rectocoele
- Enterocoele
- Vault prolapse
- Vaginal cyst (Gartner's cyst and others)
- Imperforate hymen with haematocolpos
- Hypertrophy of cervix
- Urethral diverticulum
- Cervical polyp and endometrial polyp
- Chronic inversion of uterus
- Tumours of vulva, vagina, and cervix

tract is affected. Any stress urinary incontinence is checked. The perineum is also examined for its length and integrity of perineal body. Any concomitant rectal prolapse and anal pathology, such as haemorrhoids, are identified. Speculum examination using Sim's speculum can be done in the Sim's lateral position (left lateral position with the left leg being extended and the right leg flexed at the hip and knee). The Sim's speculum can be used to determine which part of the pelvic floor is affected. Bimanual examination is performed to assess the position and size of uterus, and to exclude any adnexal pathology.

Investigations

A mid-stream urine specimen should be sent for culture and sensitivity. A full blood count, blood sugar, blood urea, and other renal function tests should be performed if considered necessary. Urodynamic studies may be required in the presence of a severe degree of prolapse (procidentia) and urinary stress incontinence. In cases of severe prolapse with ureteric obstruction, renal tract ultrasound or an intravenous urogram should be performed. Cystoscopy is indicated only when bladder stones or other bladder pathologies are suspected.

Management

The treatment for genital prolapse can be either conservative or surgical, depending upon the severity of symptoms and prolapse, the patient's age, her willingness for the treatment, and her suitability and fitness for surgery.

Conservative treatment

Patients with first- or second-degree uterine prolapse, or with a small cystocoele or rectocoele, may not need any surgical treatment. They should be counselled and could be followed up as outpatients. They can be advised about perineal floor exercises in consultation with a physiotherapist, who will teach them to contract the correct muscles. Vaginal cones may be used for the same purpose.

Pessary treatment

This is also a type of conservative treatment in which a suitably sized (depending upon the size of introitus) ring pessary (52–102 mm) is put in the vaginal vault to keep the cervix high up in the vagina. It is used when the patient is awaiting surgery or for women who present a high surgical risk. Appropriate counselling is important. The pessary should be changed every 4–6 months. Follow-up is important as the pessary can cause ulcerations in the vagina or can get embedded in the vagina, and it is important to avoid these complications. The use of ring pessaries has not become popular in developing countries owing to unreliable follow-up. There have been reports of vaginal cancer due to a forgotten pessary, which has become embedded and caused ulceration eventually leading to malignancy. Pessaries can also be used during pregnancy as a temporary measure for prolapse.

Surgical treatment

This is usually the mainstay of treatment for genital prolapse. The type of surgery depends upon the age of the patient, her fertility status, and the severity and type of prolapse. A complete procidentia may need to be reduced by packing the vagina and using local oestrogen cream prior to surgery. This will decrease any local swelling and also help to heal any decubitus ulcer, which is best treated before surgical treatment.

The following procedures are available.

Manchester repair (Fothergill's suture)

This is rarely performed these days. The approach is vaginal and there is conservation of the uterus. The elongated cervix is partially amputated. Cervical amputation is followed by approximating and shortening of the Mackenrodt's ligaments anterior to the cervical stump and elevating the cervix. Any repair of an associated cystocoele or rectocoele is undertaken if necessary at the same time.

Vaginal hysterectomy and repair

This is the mainstay in the treatment of prolapse, especially in women who have completed their family and in elderly fit women. In this operation, the uterus is removed by the vaginal route after dividing and ligating the uterosacral and the cardinal ligaments, followed by the uterine arteries and finally the broad ligament. The uterosacral ligaments should be tied posteriorly to obliterate the potential enterocoele space. An anterior repair (cystocoele repair) is performed for cystocoele and urethrocoele, which are usually present with uterine prolapse. Kelly's repair is performed in cases of stress urinary incontinence. For severe stress urinary incontinence, tension-free vaginal tape should be used with prolapse surgery. Enterocoele and rectocoele repairs are usually performed at the same time.

Vaginal vault prolapse

This is the prolapse of the vault of vagina, usually after an abdominal or vaginal hysterectomy. Small vault prolapse may be dealt with conservatively by perineal floor exercises. A shelf pessary may be used if surgery is not considered an option. However, large vault prolapses usually require surgical treatment. Vaginal sacrospinous ligament fixation is done by the vaginal route by tying the vaginal vault with the sacrospinous ligament. For more severe vault prolapse, an abdominal sacrocolpopexy (open or laparoscopic) is a better choice of procedure. In this case, a Mersilene tape strip is attached to the vault and the vault is attached to the sacral promontory.

The surgery could be performed under a spinal block and, very occasionally, with local anaesthetic, if the patient is not suitable for a general anaesthetic.

RCOG recommendations for management of vault prolapse[2]:

- Assessment of the woman should be comprehensive and objective, addressing quality of life and identifying all pelvic floor defects, and should be based on standard tools.
- McCall culdoplasty at the time of vaginal hysterectomy is a recommended measure to prevent enterocoele formation.
- Suturing the cardinal and uterosacral ligaments to the vaginal cuff at the time of hysterectomy is a recommended measure to avoid vault prolapse.
- Sacrospinous fixation at the time of vaginal hysterectomy is recommended when the vault descends to the introitus during closure.
- Anterior and posterior repair along with obliteration of the enterocoele sac are inadequate for post-hysterectomy vaginal vault prolapse.
- Abdominal sacrocolpopexy is an effective operation for post-hysterectomy vaginal vault prolapse. In comparison, sacrospinous fixation may have a higher failure rate but has lower postoperative morbidity.
- Vaginal sacrospinous fixation is more suitable for physically frail women, because of the morbidity associated with abdominal surgery.
- Abdominal sacrocolpopexy is more suitable for sexually active women, as sacrospinous fixation is associated with exaggerated retroversion of the vagina, leading to a less physiological axis than that following sacrocolpopexy.
- It is not clear whether prophylactic continence surgery is beneficial in women who are urodynamically continent, and it should not be routinely recommended.
- Iliococcygeus fixation does not reduce the incidence of anterior vaginal wall prolapse associated with vaginal sacrospinous fixation and should not be routinely recommended.
- Caution is advised with vaginal uterosacral ligament suspension: although it is effective for post-hysterectomy vaginal vault prolapse, there is a risk of ureteric injury.
- Clinicians should be aware that laparoscopic procedures involve a high level of expertise and longer operation times. Laparoscopic sacrocolpopexy appears to be as effective as open sacrocolpopexy.
- The ureters are particularly at risk during laparoscopic uterosacral ligament suspension.
- There is insufficient evidence to judge the value of other laparoscopic techniques.
- Colpocleisis is a safe and effective procedure that can be considered for those women who do not wish to retain sexual function.
- There is insufficient evidence to judge the safety and effectiveness of total mesh reconstruction.

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PROLONGED PREGNANCY

Dhammike Silva, Dilip Visvanathan and Sujatha Thamban

There are many terms that have been used to describe this condition, which include 'post date' and 'postterm'. A term *pregnancy* is defined as a pregnancy from 37 to 41 completed weeks of gestation. Therefore, a prolonged pregnancy has been defined by WHO and

FIGO as a 'pregnancy that lasts for more than 294 days' or 42 weeks. The incidence of post-term pregnancy varies from 5 to 10 per cent, regardless of ethnicity.

The terms *postmaturity* and *postmaturity syndrome* is used to describe a fetus born postterm with a poorly functioning placenta. The infant appears long and thin with dry scaly skin and long fingernails and in some cases with meconium staining of the skin and membranes. It has been suggested that the postmaturity syndrome is a growth restriction in postterm fetuses.

Prolonged pregnancy may be associated with the following:

- *Uteroplacental insufficiency*, which may lead to a higher rate of emergency caesarean section during labour, intrapartum death, and stillbirth. The increased rates of stillbirth with increasing gestation from term are illustrated in Table 1.
- *Macrosomia*: the intrauterine growth continues, leading to an increase in fetal weight. As a result, in a prolonged pregnancy, there is an increased incidence of macrosomia. This leads to problems at the time of delivery, including shoulder dystocia, bone fractures, and Erb's palsy in the baby, and cervical and perineal trauma in the mother.
- *Poor neonatal outcome*: epidemiological studies have also shown an increase in neonatal and infant mortality after a prolonged pregnancy. In a prolonged pregnancy, there is an increase in meconium-stained liquor due to development/maturation of the vagus nerve, which results in reflex anal tone changes. Even though there is a theoretical increased risk of meconium aspiration syndrome, this has not been borne out by any of these studies.

The causes of prolonged pregnancy include incorrect dates, fetoplacental factors, and true prolonged pregnancy (Box 1).

Table 1 The increase in rates of stillbirth and infant mortality with advancing gestation from term

	37 weeks	43 weeks
Stillbirth	0.35/1000	2.12/1000 (×6)
Stillbirth + infant mortality	0.7/1000	5.8/1000 (×8)

Box 1 The causes of prolonged pregnancy

- Incorrect dates
- Fetoplacental causes, e.g. anencephaly
- Maternal causes – previous prolonged pregnancy

Incorrect dates

Pregnancy is dated from the first day of the last regular menstrual period (LMP) using Naegle's rule of adding seven to the date and subtracting three from the month number. This results in an average pregnancy of 280 days. If the date of conception is certain, then it will be approximately 2 weeks less if the menstrual cycle is 28 days. If the pregnancy occurs after in-vitro fertilisation, then 16 days must be subtracted from the date of embryo transfer to obtain the LMP.

Dating scans in the first trimester of pregnancy have been shown to reduce the incidence of prolonged pregnancy caused by the unreliability of just using the LMP date alone. It is estimated that 10–45 per cent of women do not remember the date of their LMP. Furthermore, the length of gestation is assumed to be 266 days, which may have genetic, racial, and geographical variation, however.

If the periods have a 28-day regular cyclicity and the woman has not used any hormonal contraception for 3 months prior to conception and has not had bleeding after the LMP, the accuracy of the LMP to date pregnancy increases.

Ultrasonography is now routinely used to confirm pregnancy. Pregnant women should be offered an early ultrasound scan between 10 weeks 0 days and 13 weeks 6 days to determine gestational age. This will ensure consistency of gestational age assessment and reduce the incidence of induction of labour for prolonged pregnancy.

Crown–rump length (CRL) should be used to determine gestational age. If the CRL is above 84 mm or if the pregnancy is beyond 14 weeks of gestation, then the gestational age is estimated using head circumference or biparietal diameter. The sex of the fetus or racial characteristics do not seem to influence this accuracy.

Crown–rump length is measured with the fetus in the longitudinal axis, the callipers being placed on the outer margin of the head and the rump. Later on in pregnancy, it becomes more difficult as the fetus curls up. If measured correctly (Fig. 1), it is the most accurate dating measurement, with an error margin of ±5 days. The problems with CRL measurement are that, if there is any degree of fetal flexion, the CRL will be underestimated (Fig. 2). In very early pregnancy, it is important not to include the fetal limbs or the yolk sac, as this will overestimate the CRL. When dating a twin pregnancy, the CRL of the larger twin is used.

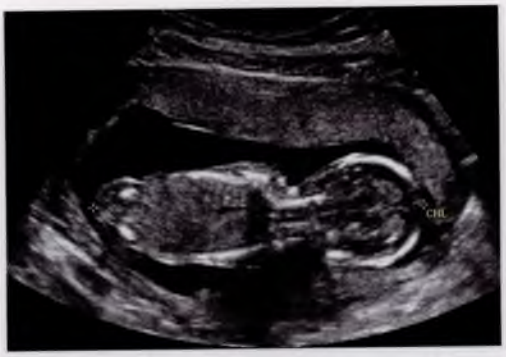

Figure 1 The proper fetal attitude for accurate measurement of crown–rump length.

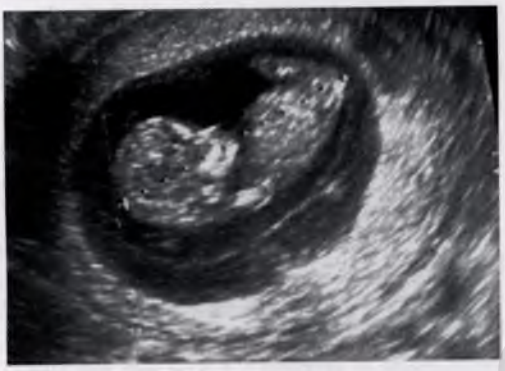

Figure 2 Measurement of crown–rump length (CRL). In this image, there is a certain amount of fetal flexion, which would underestimate the CRL.

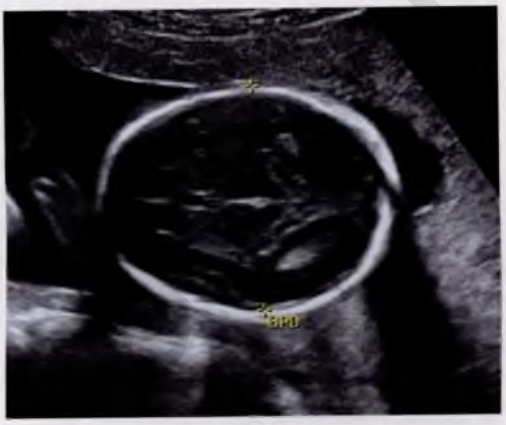

Figure 3 Ultrasound image showing biparietal diameter measurement taken at the optimum section.

After 12 completed weeks, the fetus tends to curl up even further and it becomes more difficult to measure the CRL accurately. The biparietal diameter (BPD) of the fetal skull or the head circumference then becomes the standard measurement to estimate gestational age. From the 12th week to the 22nd week the relationship of BPD to gestational age is linear.

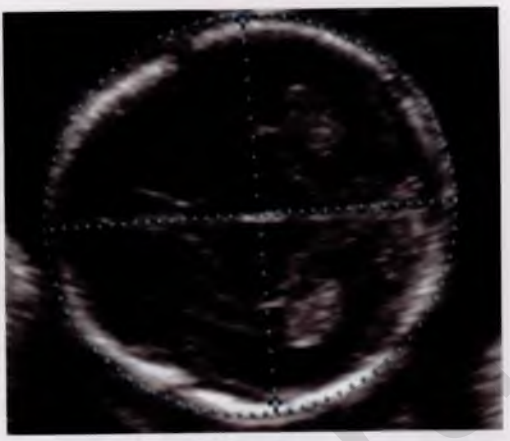

Figure 4 Ultrasound image showing head circumference measurement taken at the optimum section.

The BPD is the maximum diameter of a transverse section of the fetal skull at the level of the biparietal eminences (Figs 3 and 4). An accurate measurement of the BPD has the following characteristics: the section must be ovoid, there must be a midline echo (falx), the cavum septum pellucidum must be visualised at one-third the distance of the fronto-occipital, and the thalami must be symmetrically positioned on either side of the midline echo.

If the correct section is not taken for the BPD measurement, the potential margin of error can be high. The BPD is difficult to measure if the head is in an occipito-anterior or posterior position. Tilting the patient or filling the bladder may help in achieving the optimal fetal position. The head can sometimes appear flattened, and consequently the BPD is underestimated. This usually occurs when the fetus is in the breech or the transverse position. In these situations, the head circumference is a more accurate measurement. Composite measures for pregnancy dating include the femur length (Fig. 5) and abdominal circumference as well.

After 24 weeks' gestation, dating becomes less accurate as genetic, racial, and individual pregnancy factors may influence the linearity of the measurements. The predicted date may vary from the actual one by 2–3 weeks.

Table 2 summarises the ultrasound measurements taken to estimate gestational age and the accuracy of these for re-dating a pregnancy.

Fetoplacental causes

In other mammals, the onset of labour is determined by the fetal hypothalamo–pituitary–adrenal axis.

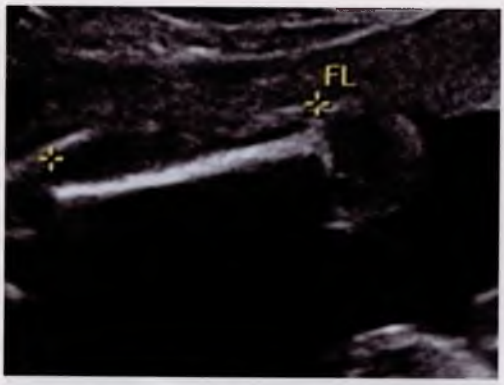

Figure 5 Ultrasound image showing measurement of femur length.

Table 2 The parameters used for gestational age assessment. If the LMP is uncertain, re-dating may be carried out. If the LMP is certain, a repeat scan is suggested in 2 weeks to exclude growth restriction and aneuploidy as a cause

Parameter	Gestational age	Accuracy
CRL	6½ to 12 weeks	±5 days
BPD	13–27 weeks	±7 days
BPD/HC	>28 weeks	14–21 days

BPD, biparietal diameter; CRL, crown–rump length; HC, head circumference; LMP, last menstrual period.

There is a drop in serum progesterone levels associated with a rise in serum oestrogen levels and increased steroid production by the adrenal gland. However, in humans, studies have failed to show a drop in progesterone or change in oestrogen level in maternal plasma before and after the onset of labour. An increase in oestrone levels in the umbilical vein following spontaneous onset of labour has been shown, indicating that these changes may be occurring in the fetoplacental unit. Prolonged pregnancy may be rarely associated with low oestrogen levels, which occurs in the following conditions.

Anencephaly

This occurs when there is a failure of closure of the cranial end of the neural tube at the end of the third to fourth week of gestation. Consequently, there is an absence of the forebrain (cerebrum and cerebellum), the skull vault and almost always the covering scalp, and the brainstem is poorly developed. The condition is incompatible with extrauterine life.

Anencephaly can now be diagnosed from 11 weeks. In the early stage, there is acrania. Here the vault of the skull is missing but the forebrain is intact. This may progress to exencephaly, which is herniation

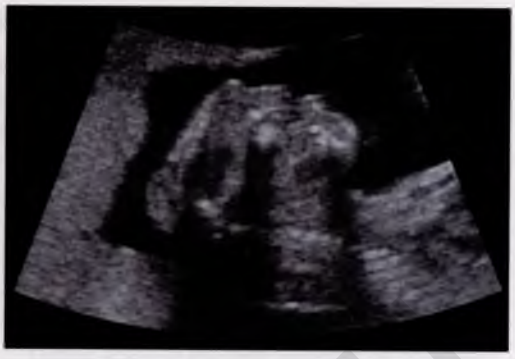

Figure 6 A fetus with anencephaly at ultrasound.

of the forebrain. Amniotic fluid erodes the forebrain, leading to anencephaly. At scan, it will not be possible to obtain a BPD measurement, as the cranial vault is symmetrically absent (Fig. 6). The orbits are more pronounced, giving a frog's eye appearance. There is a 50 per cent risk of associated lower spinal cord defect. An omphalocoele may also be present. The liquor volume may be increased and fetal movements may be marked.

In the past, maternal serum alphafetoprotein levels were used to screen for neural tube defects. At 16–18 weeks of pregnancy, a level that was greater than 2.5 multiples of the mean detected 88 per cent of all anencephalic infants.

Absence of a fetal pituitary gland

Absence of a fetal pituitary gland, usually in anencephaly, leads to fetal adrenal cortex atrophy with a consequent reduction in dehydroepiandrosterone sulphate (DHEAS) production. DHEAS is a precursor of serum oestradiol, which, therefore, is reduced. This is thought to be the reason for prolonged labour.

Fetal adrenal hypoplasia

This is a rare inherited disorder where there is atrophy of the adrenal cortex. Consequently, there is deficiency in both mineralocorticoid and glucocorticoid activity. In pregnancy, serum oestriol levels are low, and there is a tendency towards prolonged labour. The significance of this condition is that neonates can present with salt wasting and hyperpigmentation.

Placental sulphatase deficiency

This is a rare condition in which there is a deficiency in one of the enzyme systems required for the synthesis of oestrogen in the human placenta. Most case reports describe prolonged pregnancy with failure of induction of labour. Most such male babies presented

with salt wasting and hyperpigmentation during the neonatal period.

Management of post-term pregnancy

Interventions in a woman with a prolonged pregnancy include induction of labour and, less frequently, elective caesarean section in an attempt to reduce these potential complications. Induction of labour has been shown to reduce the perinatal mortality rate without increasing the rate of caesarean section, especially if the induction is after 41 completed weeks of gestation. It is now routine practice in most units to offer induction of labour after 41 weeks of gestation, and this has been supported by RCOG guidelines.

NICE recommends that, prior to formal induction of labour, women should be offered a vaginal examination for membrane sweeping. All women with uncomplicated pregnancies should be offered induction of labour beyond 41 weeks. From 42 weeks, if women decline induction of labour they should be offered increased antenatal monitoring consisting of at least twice weekly cardiotocography and ultrasound estimation of maximum amniotic pool depth.

Despite this practice, there is a considerable amount of controversy surrounding the routine induction of labour for prolonged pregnancy. Most of the meta-analyses rely on a single study, which has the largest number of recruits. Repeat analysis of these results indicates that the risks of prolonged pregnancy may not be as high as previously indicated and that the risks of emergency caesarean section have likewise been overestimated. A recent study further confuses the issues, as it suggests that the length of pregnancy may vary between racial groups. Stillbirth rates in certain groups occur earlier in the pregnancy than previous studies have suggested. If the results of this study are confirmed, then it may mean that the timing of induction of labour should be earlier than 41 weeks in these racial groups.

Close intrapartum fetal surveillance should be offered, irrespective of whether labour was induced or not.

Previous prolonged pregnancy

A previous history of prolonged pregnancy increases the risk in a subsequent pregnancy being prolonged to 20 per cent. This was thought to be due to the influence of parental genes. Initially only maternal genes were thought to be implicated; however, a more recent study has shown that if a woman changes her partner between pregnancies, her risk of a prolonged pregnancy is significantly reduced. Other factors that also contribute are advancing maternal age and a body mass index (BMI) of >25. Increases in BMI result in excess fat in the ischiorectal fossae, preventing descent of the presenting part of the fetus.

Further reading

Antenatal care – NICE Guideline 62, Guidance: nice.org.uk/cg62/2010.

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PROTEINURIA IN PREGNANCY

Peter Muller, revised by Rachel Wooldridge

Proteinuria is defined as excessive protein excretion in the urine. There are generally four primary reasons for its development:[1]

- glomerular filtration abnormalities, e.g. pre-eclampsia or glomerulonephritis;
- tubular reabsorption abnormalities, e.g. acute tubular necrosis;
- overload, e.g. multiple myeloma or rhabdomyosis;
- acute physical stressors, e.g. acute illness or exercise.

In pregnancy, 300 mg per 24 hours is considered the upper limit of normal. Above this level is defined as *significant proteinuria*, and *severe proteinuria* is >5 g per 24 hours.

Measurement of proteinuria

Urine dipstick

The urine should be obtained as a mid-stream specimen and urinalysis performed within an hour of sample collection. The dipstick urine protein level may be recorded at none, 1+, 2+, 3+, or 4+. Generally, 1+, 2+, 3+, and 4+ equate to 30 mg, 100 mg, 300 mg, and 2000 mg of protein per dL, respectively (Multistix 10 SG, Bayer Diagnostics Manufacturing, Bridgend, UK).

The advantage of dipstick testing is the ease of performance with an immediate result. Unfortunately, the dipstick urine protein has been shown to correlate poorly with the quantitative 24-hour urine total protein[2–4] and spot urine protein/creatinine ratio.[5] This is due to the variation of the urine protein levels during a 24-hour period,[6] which in turn may be secondary to changes in water intake, rate of diuresis, exercise, diet, and recumbency,[7] as well as inter-observer variation from the semi-quantitative measurement.[2]

A systematic review investigating the accuracy of visual reading of dipsticks in pregnant women found that +1 proteinuria gave a sensitivity and specificity of 55 per cent and 84 per cent when predicting significant proteinuria on 24-hour urine collection.[4]

The same systematic review also looked at a study using automated reading of urine dipsticks and found a sensitivity of 82 per cent and specificity of 81 per cent.[4] NICE recommends that an automated reagent-strip reading device be used for urine dipsticks in secondary care settings.[8]

Urinary protein is increased in urinary tract infections, and this should be excluded in all cases. In pregnant women, both nitrites and leucocyte esterase on the urine dipstick have a low sensitivity but high specificity for urinary tract infection. Therefore, if both are negative, infection can be ruled out.[9] A positive nitrite test needs further investigation with microscopy, culture, and sensitivity of a midstream urine specimen.

24-hour urine protein

The 24-hour urinary protein excretion is considered the 'gold standard' for quantification of urinary protein,[7] with significant proteinuria being defined as >300 mg/24 h.[8] It is usually collected starting in the morning after complete emptying of the bladder. The 24-hour urine demands measurement of the full urine output over a 24-hour period up to and including the first void of the following morning. The advantage of this method is that it is the standard for which disease state and progression is measured. The disadvantage is that the test can be cumbersome as well as time-consuming. Results often take a few days to return so immediate management decisions may be delayed. Patients' privacy may be compromised in the outpatient setting which may in turn affect compliance. One way to estimate the compliance of the 24-hour urine protein is to review the total urine volume and to calculate the creatinine excretion.

Spot urine protein/creatinine ratio (PCR)

When the glomerular filtration rate is relatively constant, the protein and creatinine excretion rates will also be constant. The protein/creatinine ratio will then correct for the normal variation in water excretion over 24 hours. PCR has the advantage of having significantly less variability over 24 hours compared to dipstick testing,[10] and leads to more clinical efficiency than a 24-hour urinary protein. Samples are sent to the laboratory and results are available within a few hours, making it a useful test for the obstetric day unit. The ability to detect the absence of significant proteinuria would lead to fewer 24-hour urine protein collections, fewer hospital admissions, and possibly fewer medical interventions. Significant proteinuria on PCR is defined by NICE as >30 mg/mmol.

Previously there has been no consensus on the PCR value that represents significant proteinuria. However, in a systematic review with pooled results, a cut off of 30 mg/mmol gave a sensitivity of 84% and specificity of 76% for predicting significant proteinuria on 24-hour urine collection in women with gestational hypertension.[11]

Spot albumin/creatinine ratio

Samples can be processed by an automatic analyser with results available within 5 minutes, making this a useful test in the obstetric outpatient clinic. Various studies have suggested different cut-offs for what is considered significant proteinuria, ranging from between 2 and 8 mg/mmol.[12] A recent systematic review suggested there was insufficient evidence about accuracy of albumin/creatinine ratio in pregnancy.[13]

Evaluations of the kidney

Microscopic urinalysis

Direct microscopic evaluation of the urinary sediment for specific urinary casts will often point to a specific disease process. These would include the following:[1]

- hyaline cast – concentrated urine, after exercise;
- red cell casts – glomerulonephritis;
- white cell casts – pyelonephritis, interstitial nephritis;
- renal tubular casts – acute tubular necrosis, interstitial nephritis.

Fractional excretion of sodium (FENa per cent) and urine osmolality (Uosm)

Urine electrolytes and osmolality may help in distinguishing prerenal azotaemia (the build up of waste products that accumulate in the blood and body when the kidney fails to function) from other intrinsic renal disease:[1]

- prerenal azotaemia – FENa (per cent) <1 and Uosm >500;
- acute tubular necrosis – FENa >1, Uosm 250–300;
- glomerulonephritis – FENa <1, Uosm variable;
- urinary obstruction – FENa variable, Uosm <400.

Ultrasound

Renal ultrasound scanning is the investigation of choice for the initial evaluation of new-onset renal disease. Although typical presentations of pre-eclampsia generally do not warrant a renal ultrasound, atypical presentation of proteinuria in pregnancy may benefit

from such evaluation. This non-invasive approach, which does not use any radiation, can identify a distended urinary collecting system, kidney size and echogenicity, renal mass lesions, and evidence of cystic renal disease. Transvaginal ultrasound can be a very successful adjunct in assessing for distal renal stones. Most cases of renal colic can be diagnosed with a combination of ultrasound and clinical features. It is only rarely that other imaging modalities will be required.

Intravenous urogram

Intravenous urogram (IVU) is used less commonly today to evaluate the renal collecting system and renal stones, unless specific information is required prior to surgical intervention. If an intravenous pyelogram (IVP) is required as an adjunct to other imaging modalities in pregnancy, the fetal radiation dose can be minimised with limited scans (including a preliminary plain abdominal X-ray, early and late post-contrast abdominal X-rays only). (See Breathless in pregnancy: respiratory causes.)

Computerised tomography scan

Non-contrast helical computerised tomography (CT) is 95 per cent sensitive and 98 per cent specific in detecting renal stones and has become the gold standard in investigating renal colic. In pregnancy, however, it delivers a significant radiation dose to the fetus, and alternative imaging modalities are therefore preferred. A targeted CT scan can be used as an adjunct to suboptimal renal ultrasound. (See Breathlessness in pregnancy: respiratory causes.)

Magnetic resonance imaging urography

Advances in magnetic resonance imaging (MRI) techniques have enabled MRI urography to be used as an adjunct to ultrasound in the investigation of renal colic/renal tract obstruction in pregnancy. There is no ionising radiation involved and the risks to the fetus are low.

Percutaneous renal biopsy

Renal biopsy is rarely warranted in pregnancy. Distinguishing between pre-existing renal disease and pre-eclampsia may be difficult, and therefore renal biopsy may be considered for diagnosis in pre-viable gestations where a definitive diagnosis will alter management.[14] While the risk of significant bleeding and blood transfusion is generally considered to be low, there have been studies suggesting significant morbidity.

Diagnosis

Urinary tract infection

Urinary tract infection can cause mildly elevated proteinuria on dipstick or spot urine protein/creatinine ratio. This generally can be easily distinguished from other causes of proteinuria through the evidence of pyuria and bacteriuria with associated urinary symptoms.

Pre-eclampsia

Pre-eclampsia is defined as hypertension with proteinuria occurring after 20 weeks of gestation,[15] and should be the primary initial diagnosis for new-onset proteinuria after 20 weeks' gestation. It is important, however, to realise that proteinuria is not seen in all cases of pre-eclampsia, and is not mandatory for the clinical diagnosis. Indeed, proteinuria has been found to be absent in 14 per cent of eclampsia[16] and 13 per cent of HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome.[17] Hypertension and other clinical characteristics that may be used for clinical diagnosis, in the absence of proteinuria, are the new onset of liver abnormalities, elevated serum creatinine, and platelet count <100,000 with evidence of haemolysis, neurological signs, such as headache or visual disturbance, epigastric pain, and fetal growth restriction.[18]

Owing to the discrepancy of random urine dipstick with other methods, a 24-hour urine protein analysis or PCR should be performed in all cases of suspected hypertensive disease.

Glomerulonephritis

Patients will present with oedema, hypertension, and acute renal insufficiency, making this difficult to distinguish from pre-eclampsia. Oedema is often found in the periorbital or vulval regions as well as the extremities. Since the management of pre-eclampsia requires a focused urgent plan, the clinician's primary goal is to exclude this from the differential. Urinalysis will demonstrate haematuria, red cell casts, white blood cells, and mild to moderate proteinuria. Specific aetiologies for glomerulonephritis will require exhaustive serologic examinations and possible renal biopsy. The treatment plan depends solely on the specific disease.

Acute tubular necrosis

The clinical setting for acute tubular necrosis (ATN) commonly occurs after sudden profound

hypotension due to hypovolaemia or septic shock. However, nephrotoxic agents may precipitate the tubular damage. This may involve an exogenous source, such as administration of aminoglycosides or radiographic contrast, or an endogenous source from rhabdomyolysis. A clinical history of 'muddy brown' urine or renal tubular casts on urinalysis, with an FENa of >1, will help in distinguishing ATN from other intrinsic renal diseases.

Treatment consists of strict fluid balance to avoid fluid overload, and supportive care. Although large doses of frusemide are commonly used to improve urine output, in randomised controlled trials this has not been shown to affect recovery time.[1]

Prerenal azotaemia

This is the most common type of renal failure outside pregnancy. Prerenal azotaemia in pregnancy can be to the result of a decrease in intravascular volume or a change in vascular resistance. A decrease in intravascular volume may be attributed to haemorrhage, dehydration, gastrointestinal loss, or trauma. An increase in renal vascular resistance may be caused by various drugs, such as non-steroidal anti-inflammatory drugs or angiotensin-converting enzyme inhibitors, or the decreased perfusion caused by renal artery stenosis. Urinalysis, FENa, and a blood urea nitrogen (BUN)/creatinine ratio (usually >20:1) can assist in distinguishing prerenal from intrinsic renal disease. Treatment is generally correcting the volume depletion or removing the inciting agent.

Obstructive uropathy

Obstruction of the genitourinary system can lead to post-renal azotaemia. This is an uncommon cause of proteinuria in pregnancy; however, it has been seen in multiple pregnancy where complete obstruction of the ureters can occur. The importance of identifying urinary obstruction as the cause of proteinuria is the fact that it is usually a readily correctable problem. Patients usually present with lower abdominal or flank pain. Urinary electrolytes demonstrate a low FENa, high osmolality, and a high BUN/creatinine ratio. Ultrasound in pregnancy will generally detect bilateral hydronephrosis or enlarged bladder. The severity of hydronephrosis will distinguish this from the physiologic hydronephrosis seen in most pregnancies. Post-obstruction diuresis will generally follow the release of the obstruction and fluid balance management is essential to prevent hypovolaemia.

Conclusion

New-onset proteinuria in pregnancy should alert the clinician to review for evidence of pre-eclampsia. The lack of proteinuria does not exclude the disease. However, not all cases of proteinuria in pregnancy are related to hypertensive disease, and the clinician should be familiar with the other causes and the appropriate evaluations.

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PSYCHOLOGICAL PROBLEMS IN PREGNANCY AND THE POSTNATAL PERIOD

Sujatha Thamban and Quazi Selina Naquib

Psychiatric disorders associated with childbirth are common, both the new episodes specifically related to childbirth and recurrences of pre-existing conditions. Pregnancy and childbirth have a combined psychological and physiological effect on a woman's life. Studies have shown that childbearing is associated with a marked increase in incidence and prevalence of psychiatric disorder, although the exact causal mechanisms remain unclear. Ten per cent of new mothers are likely to develop a depressive illness in pregnancy. Two percent of them will be referred to a psychiatric team during this time. Postnatal depression is consistently found in 10–15 per cent of mothers.[1] Postpartum psychosis is less common affecting 2 per 1000 deliveries. About 2 per cent of pregnant women using obstetric services have chronic mental health problems.[2]

The majority of women (50–75 per cent) who develop postnatal mental health problems will suffer from mild transitory depressive illnesses, often with accompanying anxiety (the 'blues'). The risk of developing a severe mental illness, either a severe depressive illness or a puerperal psychosis, is substantially increased, particularly in the first 3 months following delivery. These relative risks (RRs) compared to the rest of the female population can be summarised as follows:[3]

- developing a severe depressive illness following childbirth – RR X5;
- need to see a psychiatrist – RR X7;
- need for hospital admission due to a psychosis in the first 3 months following childbirth – RR X324.

The relative risk of developing a new-onset serious psychiatric disorder during pregnancy is lower than at other times; however, obsessive–compulsive disorder becomes worse or can start in pregnancy.

Psychiatric illness leading to suicide is a major cause of maternal death in the UK. The last 3 CEMACE reports found that over half of the women who died from suicide had a previous history of severe mental illness. Deaths from suicide, the leading cause of maternal death in 2000–2002, have dropped and are

now 0.57/100,000 maternities. This decrease in suicide during pregnancy and the year following delivery reported in 2003–2005 was largely due to a fall in the number of suicides between 6 and 12 months post delivery. Death rates from suicide were very low during pregnancy to within 42 days postpartum but trebled after 6 weeks to 12 months postpartum. However, death rates from suicide within a year after birth are substantially lower than in non-pregnant women (RR 0.09 for pregnancy to within 42 days postpartum group, and 0.31 for 6 weeks postpartum to 1 year postpartum group). The women who commit suicide are more likely to do so in a violent way and not as a 'cry for help'.[3]

The main psychiatric diagnoses contributing to suicide in 2006–2008 were:

- psychosis 38%;
- severe depressive illness 21%;
- adjustment/grief reaction 10%;
- drug dependency 31%;

the total number of deaths in pregnancy and late deaths from suicide were 29 in that period.

Postpartum psychiatric illness

Psychiatric disorders in the postpartum period are divided into three categories reflecting severity:

- maternity (baby) blues;
- postpartum depression;
- postpartum psychosis.

Maternity blues

This is a minor transitory mood disturbance occurring in 50–75 per cent of women in the first week following delivery, especially after a first baby. Women in the immediate postpartum period may experience mild 'highs' as well as depressive episodes.[4] The cause of 'blues' remains unknown, with the literature being inconsistent on associated factors, such as hormonal changes, and consequently no diagnostic blood tests are indicated.

The 'blues' may cause considerable distress to the mother but usually does not require any specific treatment other than reassurance. Symptoms typically last from a few hours to several days in the immediate postnatal period. These symptoms include tearfulness, sleeplessness, irritability, impairment of concentration, isolation, headache mood swings, and crying spells. The maternity blues are not considered a postpartum depressive disorder. The care of the baby is not affected and the women do not feel suicidal. It is defined by its brevity; should symptoms persist, then postnatal depression should be considered.

If the symptoms are extreme or prolonged, they must be distinguished from the prodromal features of a puerperal psychosis, which often commences in the same time period. If the symptoms persist over 2 weeks, then a diagnosis of depression should be considered.

Postnatal depression

Postnatal depression is regarded as any non-psychotic depressive illness of mild to moderate severity occurring during the first year following delivery. The peak onset of depression occurs in the first 6 weeks following childbirth. A recent meta-analysis of nearly 60 studies gives a prevalence rate for postnatal depression of 13 per cent.[1] The suffering caused by depression is profound yet often underestimated. Postnatal depression is particularly important because it is so common, and occurs at such a critical time in the lives of the mother, her baby, and her family. It is important that the term 'postnatal depression' should not be used as a generic term for all mental illness following delivery.

Psychosocial and biological factors have been postulated (see Box 1). These associations have been used by medical professionals to predict and identify women likely to develop postnatal depression and help them access early assessment and treatment. Each subsequent episode may commence earlier in the postpartum period.

Box 1 Risk factors for postnatal depression

- Depression during pregnancy
- History of previous depression, especially previous postnatal depression
- Discontinuation of antidepressant therapy
- Antenatal anxiety
- Low self-esteem
- Life stress (recent life events, unemployment, moving house)
- Poor family support
- Poor marital relationship
- Childcare stress (including difficulty in breast feeding)
- Infant temperament problems/colic
- Single parent
- Unplanned/unwanted pregnancy
- History of infertility and assisted conception

Earlier onset depression may in part have an endocrine cause. Massive endocrine changes in circulating sex steroids occur at childbirth. The hypothalamic–pituitary axis must adjust to the sudden loss of placenta and re-establish its regulatory functions in relation to ovarian activity as well as starting lactation.[5] Oestrogen may have mood-elevating properties: it has been found to be superior to a placebo in treating postnatal depression[6] and was shown to be an antidepressant in childbearing women.[7] The mechanisms of action, however, remain unclear. Cortisol dysregulation has also been postulated as being causative.[8]

Diagnosis of postnatal depression may be undetected in up to 50 per cent of cases.[9] The clinical picture is similar to other types of depression; however, other symptoms suggestive of postpartum depression include:

- difficulty with practical parenting, including handling or feeding;
- feelings of guilt that she is not coping;
- expressing excessive concern about the baby's health.

Treatment options are no different to depression occurring at other times. For mild to moderate depression, self-help strategies and non-directive counselling by health visitors can be helpful. For moderate to severe depression, medication and cognitive behavioural therapy (CBT) is recommended. Antidepressant medication such as selective serotonin reuptake inhibitors (SSRIs) are recommended. Fluoxetine is the SSRI with the lowest known risk during pregnancy. Citalopram and fluoxetine are present in breast milk at relatively high levels. It is important to reassure women that all antidepressants carry the risk of withdrawal or toxicity in newborn, but in most cases the effects are mild and self-limiting. Adequate doses should be used and treatment continued for an appropriate length of time. Breast-feeding may usually be continued with caution whilst monitoring the baby.[10] Drugs with low excretion into the breast milk should be preferentially used.

The lifetime risk of recurrence of further episodes of depression is >70 per cent, with a 25 per cent risk in a subsequent pregnancy.

Postpartum psychosis

Postpartum psychosis refers to a severe mental illness with a dramatic onset shortly after childbirth. The distinctive features are the sudden onset and the rapid deterioration of the woman's condition. For all mothers, the risk of admission to a psychiatric hospital is increased seven-fold in the month following delivery.[11] The peak time of onset of psychosis is within 2 weeks of delivery,[12] although there is a small but significantly elevated risk for at least 2 years postpartum, especially in first-time mothers.[11]

Postpartum psychosis affects women in 1–2 per 1000 births. Women with bipolar disorder have a 1 in 4 risk of developing postpartum psychosis (PP), which is increased to 1 in 2 if they have a previous history or family history of PP. Comparisons of rates across cultures and over time have shown remarkable consistency.[13] This figure has remained consistent in England and Wales over the last 50 years despite improvements in medical care and a reduction in maternal mortality rates.[13]

Presenting symptoms may vary (Boxes 2 and 3), but there is typically an initial 'lucid interval' lasting a few days following delivery, and prodromal features may coincide with the onset of the 'blues'. As mothers are now discharged early from maternity wards, initial symptoms may be observed by family members who notice sleeping difficulty, confusion, and odd behaviour.

A mother suffering from postpartum psychosis will require admission to a psychiatric unit, preferably a mother and baby unit where available. PP is

Box 2 Summary of puerperal psychotic symptoms

- Women with manic symptoms are excited, overtalkative, euphoric, uninhibited and intensely overactive. 'Patchy perplexity' is common and they may also have grandiose ideas, which may be delusional (e.g. conviction that she is 'chosen' or that the baby has special powers).
- Postnatally depressed women have more severe symptoms and may exhibit confusion, delusions, and stupor. Disorders of perception may be complex, taking the form of visions. Alternatively, these women can present with agitated depression, experiencing convictions of hopelessness and uselessness, which sometimes reach suicidal intensity. They can become preoccupied with rigid feeding routines or overwhelmed by minor health problems.
- Other symptoms suggesting psychosis include confusion or perplexity, catatonic features, thought disorder, auditory hallucinations and paranoid delusions or ideas of reference such as special messages. The picture may be labile with a mixture of depressive and manic symptoms.

Box 3 Screening for depression – Whooley questions

At a woman's first contact with primary care, at her booking visit, and postnatally (usually 4–6 weeks and 3–4 months postpartum), healthcare professionals (including midwives, obstetricians, health visitors and GPs) should ask two questions to identify possible depression:

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by having little interest or pleasure in doing things?

A third question should be considered if the woman answers 'yes' to either of the initial questions: 'Is this something you feel you need or want help with?'

a psychiatric emergency. Pharmacological treatment is dictated by the clinical picture and conventional treatments, including antidepressants, antipsychotics, mood stabilisers, and ECT (electroconvulsive therapy) are used in treatment. Child protection issues will arise when the woman may be a danger to the baby.

The short- to medium-term prognosis is good, with most patients responding well to treatment and making a complete recovery. The risk of relapse following a subsequent pregnancy, however, remains high, from 20 to 50 per cent.[14]

Chronic mental illness

Psychotic disorders

Psychosis during pregnancy

Studies have shown a slight but significant reduction in rates of contact with psychiatric services and admissions during pregnancy.[11,15–17] However, discontinuation of anti-depressants during pregnancy can precipitate a relapse of depressive symptoms.[18] For bipolar illness, pregnancy is usually a time of remission.[14,19] Pregnancy does not seem to cause a relapse in pre-existing schizophrenia.[20,21]

Psychosis following childbirth (up to 12 months)

A history of bipolar affective disorder, irrespective of whether the previous episode was puerperal or not, confers an extremely high risk of relapse following childbirth. The rate rises from a general population risk of 0.1–0.2 per cent to between 25 and 50 per cent (i.e. up to a 500-fold increase in risk).[14]

Table 1 Summary of positive and negative symptoms in schizophrenia

Positive	Negative
Delusions	Emotional apathy
Hallucinations	Slowness of thought and movement
Thought disorder	Underactivity
	Lack of drive
	Poverty of speech
	Social withdrawal

Childbearing women with chronic schizophrenia of the disorganised type[22] showed little variation in their symptoms. Women with paranoid psychoses with short episodes of illness or with periods of remission following treatment were at high risk (40 per cent) of recurrence or exacerbation of their illnesses.[21]

Postnatal management will depend on the type of their illness, with a better outcome for women with 'positive' symptoms (Table 1) of schizophrenia both in terms of their response to treatment and their ability to be primary carers for their babies. For mothers with marked negative symptoms, alternative carers will need to be identified as early as possible during the pregnancy, if it is considered that a mother is unlikely to be able to care for the baby.

Non-psychotic disorders

Non-psychotic disorders during pregnancy

Studies have been inconclusive with regard to exacerbation of pre-existing mood disorder during pregnancy. Some suggest an increase, especially in the early stages of pregnancy[23,24] but, in a comparison study with non-pregnant women, no such association was found.[25]

Symptomatic psychiatric illnesses have been associated with:

- poor antenatal care;
- inadequate nutrition;
- impulsive behaviour;
- substance abuse.

Depression during pregnancy has been associated with preterm delivery, smaller head circumferences, lower birth weights, and poorer Apgar scores.[18] Pregnancy may also trigger the onset of obsessive–compulsive disorder[26,27] or may cause it to worsen,[28] although the data on anxiety disorders is limited.

Non-psychotic disorder following childbirth (up to 12 months)

In women with a history of depression, the likelihood that they will become depressed following childbirth is raised about two-fold. Anticipatory support and/or preventive pharmacotherapy are possible options.[29] Other conditions, such as obsessive–compulsive disorders, anxiety and phobic states, and eating disorders may continue unchanged following delivery or may worsen.

In general, childbirth does not improve psychiatric outcomes in women with histories of mental illness. Recent studies have demonstrated adverse effects of postnatal mental illness on the following:

- the mother–infant relationship;[30]
- children's (particularly boys') later cognitive and social development;[31–33]
- attachments and emotional regulation.[31–33]

These effects highlight the need for early detection and effective intervention.

Medical conditions presenting as mental health problems

It should be remembered that systemic illnesses can present with psychiatric symptoms, and there is always a need for taking a history and examining the patient. Cerebral thrombosis, meningitis, viral encephalitis and thrombotic thrombocytopenic purpura (TTP) can all present with confusion, delusion or depressive symptoms. Cerebral thrombosis and TTP are both more common in pregnancy.[3]

In a woman who presents atypically (antenatally or with atypical symptoms) or who deteriorates despite treatment, full investigations should be performed. These should include full blood count, urea and electrolytes, liver function tests, coagulation with magnetic resonance angiography, or spiral computerised tomography of the skull.

Specific recommendations

1. Referral to specialised perinatal mental health services where available otherwise use general psychiatric services for the following:
   - current psychotic disorders, severe anxiety or depression, obsessive–compulsive disorders, and eating disorders;
   - previous history of bipolar disorder, schizophrenia, or puerperal psychosis;
   - women on complex psychotropic drug regimens;
   - illness of moderate severity if it develops late in the pregnancy or early postpartum period.
2. A minimum requirement for management should be regular monitoring and support for at least 3 months following delivery.
3. Psychiatric services should have priority care pathways for pregnant and postpartum women.
4. All mental health trusts should have specialised community perinatal mental health teams for the care of these women.

Maternity services need to ensure that appropriate communication with primary care and social services takes place for women who decline referral to specialist mental health services.

Useful organisations/websites

Association for Post-natal Illness – provides information and advice, and a network of local contacts; an information service for partners and families as well as sufferers (www.apni.org).

Meet a Mum Association – provides support for mothers who are or have been suffering from isolation and/or postnatal depression (www.mama.org.uk).

Newpin – a national organisation running a variety of projects in London, offering help and support to parents and carers of young children (e-mail: newpin@nationalnewpin.freeserve.co.uk).

Parentline Plus – provides a free confidential helpline for parents (www.parent-lineplus.org.uk).

www.cemach.org.uk (CEMACE report 2006–2008)

www.nice.org.uk/CG45

www.neuroscience.bham.ac.uk/research/app/

www.sign.ac.uk/guidelines/fulltext/60/evidence.html

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PUBERTY

Paramita Cifelli

Introduction

Puberty is a physiological sequence of events which occur when secondary sexual characteristics develop and the ability to reproduce is achieved.

Puberty generally starts in both sexes at around eleven years of age, but the timing varies and is dependent on socioeconomic status, ethnic origin, genetic factors, and nutrition. It tends to follow bone maturation more closely than the chronological age of the child.

These changes occur in response to the pulsatile secretion of gonadotrophin-releasing hormone (GnRH) from the hypothalamus stimulating the release of follicle-stimulating hormone (FSH) and luteinising hormone (LH) from the anterior pituitary. LH stimulates oestrogen production in girls and testosterone production in boys, and FSH stimulates the production of either ova or sperm from their respective gonads.

In boys, a testicular volume of 4 mL (measured in clinical practice with an orchidometer) is the first sign of puberty.

The appearance of palpable breast buds is the first sign of puberty in girls. This is usually followed by the appearance of pubic hair within the following 6–12 months. Menstruation starts within 2–2.5 years from the onset of breast budding.

Pubertal staging

This is conventionally done according to the Tanner clinical staging system proposed. In girls this involves assessment of breast development, in boys assessment of genital development and testicular volume, and in both sexes axillary and pubic hair development.

Breast development is caused by oestrogen secretion from the ovaries, while the growth of pubic and axillary hair is mainly under the influence of adrenal androgens. The stage of breast development usually correlates well with the stage of pubic hair development. However, since different endocrine organs control these two processes, the stages of each phenomenon should be classified separately. Growth of the penis and genitalia in the male correlates well with pubic hair development, since both features are regulated by androgen secretion, but stages for pubic hair and genital development should also be determined independently. For example, pubic hair growth without testicular enlargement suggests an adrenal rather than a gonadal source of androgens.

Girls: breast development

B1: Pre-pubertal.
B2: Breast budding.
B3: Development of breast mound (can be difficult to distinguish between B1 and B3 in obese girls).
B4: Areola projects at an angle to breast mound giving rise to secondary mound.
B5: Adult configuration.

Boys: genital development

G1: Preadolescent. The testes, scrotum and penis are of about the same size and proportions as in early childhood.
G2: Enlargement of the scrotum and testes. The skin of the scrotum reddens and changes in texture. There is little or no enlargement of the penis.
G3: Lengthening of the penis. There is further growth of the testes and scrotum.

G4: Increase in breadth of the penis and development of the glans. The testes and scrotum are larger; the scrotum darkens.
G5: Adult.

Both sexes: pubic hair staging

P1: No pubic hair.
P2: Fine hair over mons pubis.
P3: Coarse, curly hair confined to pubis.
P4: Extension to near-adult distribution.
P5: Adult distribution – covering the medial aspect of thighs.

Growth in puberty

Growth accelerates as soon as breast development starts and peak height velocity is attained 6–9 months after the appearance of breast stage 2 development. Menarche occurs after peak height velocity has been achieved. Post-menarche growth is usually no more than 5–7.5 cm, occasionally 10 cm, and menarche closely accords to a bone age of 13 years.

Peak height velocity occurs relatively late in puberty in boys compared with girls and coincides with a testicular volume of 10–12 mL. Voice changes in boys can be noted at 8 mL testicular volume and become obvious by 12 mL volume.

The pubertal growth spurt results from sex steroids exerting a direct effect on growing cartilage, as well as oestrogen, either from the ovary or aromatised from testicular testosterone, mediating an increased growth hormone response. While low concentrations of oestrogen stimulate growth, higher concentrations lead to fusion of the epiphyses and the end of growth. Normal thyroid function is also necessary.

Delayed puberty

This is seen much more commonly in boys and is conventionally defined in boys as the failure to develop a testicular volume of 4 mL by the age of 14 years.

Girls are defined as having delayed puberty when there is a failure to achieve Tanner stage II breast development (breast bud) by 13 years or a failure to achieve menarche (onset of menstrual periods) within 5 years of breast budding.

Delayed puberty, though rarer in girls, is much more likely to have an underlying pathology as a trigger.

The causes of delayed puberty are listed in Box 1 and can be subdivided according to the circulating levels of gonadotrophins.

Hypogonadotrophic hypogonadism

This is characterised by low levels of LH, FSH, and GnRH.

Box 1 Causes of delayed puberty

Hypogonadotrophic hypogonadism

- Constitutional delay
- Structural abnormalities of the brain (tumours, infiltrations infections)
- Isolated LH and FSH deficiency (includes Kallman syndrome)
- Chronic disease (includes hypothyroidism)
- Low BMI, eating disorders and excessive exercise
- Rare single genes defects
- Syndromes (includes Prader–Willi, Laurence–Moon, and Bardet–Biedl)

Hypergonadotrophic hypogonadism

- Gonadal dysgenesis
- Turner's syndrome
- Klinefelter's syndrome
- Noonan's syndrome*
- Disorders of sexual development, including complete androgen insensitivity syndrome
- Irradiation and chemotherapy
- Acquired autoimmune diseases, including autoimmune ovarian failure and autoimmune polyglandular endocrinopathies

*Noonan's syndrome: an autosomal dominant dysmorphic syndrome characterised by hypertelorism (increased distance between inner canthus of the eyes), downward slanting of the eyes, low-set posteriorly rotated ears, short stature, and right-sided cardiac anomalies. Incidence 1:2500 live births.
BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinising hormone.

By far the most common cause is a constitutional delay in growth and puberty. This is much more common in boys. There is often a strong family history, and most children will be short on presentation. Bone age is delayed in the majority of cases by more than a year. Investigations are often required to exclude chronic diseases.

However, simple delay is often difficult to distinguish from other, much rarer causes of isolated hypogonadotrophic hypogonadism, as the levels of LH and FSH will be prepubertal, with similar results on stimulation testing. Only follow-up, often after an initial treatment course, distinguishes the two groups. The majority of these children achieve their final height potential when they finally finish puberty.

Severe illnesses, especially those associated with steroid use and associated inflammation will also delay puberty. A low body mass index (BMI) (<17) secondary to either excessive exercise or an eating

disorder may result in delayed puberty or halt progression. Normal activation of the hypothalamo–pituitary–gonadal axis takes place after a variable period of time, once a normal eating pattern is established and weight gain is restored.

Hypergonadotrophic hypogonadism

This is associated with elevated LH and FSH levels and low oestrogen in girls and low testosterone in boys. Because of gonadal failure, feedback to the hypothalamo–pituitary axis is lost and the gonadotrophin levels rise rapidly from 8–9 years of age. The causes are related to end-organ failure, that is, of the ovary or testes. These conditions are responsible for nearly 30 per cent of cases of delayed puberty in girls.

The commonest cause of gonadal failure is Turner's syndrome (1:2000) in females. Short stature is the commonest clinical presentation in childhood; however, those missed in early childhood may present with pubertal delay or arrest (most commonly in chromosomal mosaic forms). The classic chromosomal abnormality is 45XO, which is present in about 50 per cent of cases, but 10–20 per cent of women with this syndrome have a mosaic karyotype. There is a similar presentation in gonadal dysgenesis (XX, XO/XY females and XO/XY males) of which Klinefelter's syndrome is the most common cause in males and often presents with slow pubertal progression rather than delayed puberty.

Irradiation and chemotherapy are becoming increasingly common causes of ovarian failure in children treated for cancer.

Androgen insensitivity syndrome in the 46XY individual may present with a completely female phenotype with sparse pubic hair and primary amenorrhoea.

Investigations

Investigations to consider:

- bone age;
- serum LH and FSH levels;
- oestradiol;
- karyotype;
- brain imaging (magnetic resonance imaging [MRI]);
- pelvic ultrasound;
- bloods to exclude systemic illness.

Treatment

- Treatment of any primary disease or nutrition problem is crucial.
- Observation and reassurance may be sufficient for some patients with constitutional delay.
- Pubertal induction with replacement testosterone and oestrogen should be considered.

In girls, this is undertaken very gradually with low-dose oestrogen. Low-dose ethinyloestradiol is commenced at a dose of 2 µg/d, and the dose should be increased 2 µg/d every 3–4 months until a final dose of 20 µg/d is reached. A progestogen in the form of norethisetrone (5 mg/d) is usually added for the first 5 days of each calendar month when the total daily dose of ethinyloestradiol has reached 20 µg/d.

Pubertal induction in boys is generally by testosterone intramuscular depot injections of 50–100 mg every month for an initial treatment period of 3–6 months, and this will generally be sufficient for those with simple constitutional delay.

Follow-up will determine whether spontaneous puberty is continuing. If it arrests, longer-term treatment will need to be considered, often after further investigation for permanent hypogonadism.

Lifelong treatment of hypergonadotrophic hypogonadism and permanent hypogonadism is usually required with either intramuscular testosterone or testosterone gels for males and oral oestrogen/progestogen combinations for females.

Precocious puberty

In the UK, any breast development, corresponding to Tanner stage II, before the age of 8 years in a girl and a testicular volume of 4 mL before the age of 9 years in a boy is defined as precocious, and is most frequently caused by premature activation of hypothalamo–pituitary–gonadal (HPG) axis when this follows a concordant sequence.

In the USA stage II breast development before the age of 8 years is not uncommon. However, a recent European survey did not find any definitive trend of precocious puberty in European girls. Young girls who have migrated from the developing world to the developed world show an increased incidence of precocious puberty.

Causes of gonadotrophin-dependent precocious puberty (GDPP)

Early puberty is much more frequently seen in girls and by far the most common cause is idiopathic true central precocious puberty, triggered by GnRH stimulating the release of LH and FSH (Box 2). On examination there will be breast development and hair growth, and on investigation bone age will be advanced and pubertal changes seen on a pelvic ultrasound scan.

Box 2 Causes of precocious puberty

Causes of true central precocious puberty (gonadotrophin-releasing hormone (GnRH) dependent)

- Constitutional or idiopathic (responsible for about 80 per cent of cases in girls)
- Central nervous system (CNS) tumours around pituitary and hypothalamus, especially hamartomas
- Structural brain abnormalities: hydrocephalus, septo-optic dysplasia
- Neurofibromatosis, tuberous sclerosis
- CNS damage: infection, hypoxic insult, trauma, irradiation
- Hypothyroidism

Causes of GnRH-independent precocious puberty

Peripheral oestrogen secretion

- Ovarian tumour
- Autonomous ovarian cysts
- Liver tumours
- Thelarche and thelarche variant
- Drug and dietary sources

Peripheral androgen secretion

- Adrenarche
- Congenital adrenal hyperplasia
- Adrenal tumours, including Cushing's syndrome
- McCune–Albright syndrome
- Exposure to exogenous sex steroids

By comparison boys are much more likely to have a pathological trigger for early puberty, and an MRI scan in these cases is required to exclude the second most common cause of precocious puberty, that is, tumours in the hypothalamus or around the pituitary stalk. About 10 per cent of girls and more than 50 per cent of boys present this way. Most tumours, with the exception of the optic gliomas seen in neurofibromatosis, tend to be benign hamartomas, which may secrete cytokines that promote pulsatile secretion of gonadotrophins.

Causes of gonadotrophin-independent precocious puberty (GIPP)

Secondary to peripheral oestrogen

Premature thelarche

This is isolated breast development in the absence of other signs of puberty. It is commonly seen in infants and almost always happens before the age of 3 years. Breast size may wax and wane, but it does not progress, regresses by school age, and requires no treatment.

Thelarche variant

In some girls with thelarche, the breast development persists or even progresses slowly. Occasionally, there could be an associated increase in height velocity and can be considered midway to central precocious puberty, and again treatment is not indicated.

Other causes

Ovarian (and adrenal, testicular and liver) tumours secreting oestrogen are rare and often present with a palpable mass and prominent breast development but no other sign of puberty. Occasionally gonadal tumours secrete testosterone which produce androgenic effects.

The McCune–Albright syndrome, a syndrome of GIPP, has café-au-lait pigmentation with an irregular border and bony X-ray changes and ovarian cysts. Oestrogen-containing pills and creams soy formulas, and ginseng cream are potential sources of oestrogens.

Secondary to peripheral androgen

Adrenarche

Adrenarche is the normal maturation of the adrenal glands. Adrenal androgen production commences around mid-childhood (6–8 years), and dehydroepiandrosterone (DHEA) becomes the predominant adrenal steroid during this time.

Some individuals produce enough adrenal androgens to cause signs and symptoms of mild androgenicity, such as pubic and axillary hair, body odour, mild acne, and a small advance in bone age, known as *exaggerated adrenarche*.

Premature adrenarche describes early activation of DHEA production for those who develop adrenarche before the age of 6 years. In more severe cases virilisation is more pronounced and progressive.

Congenital adrenal hyperplasia (CAH)

The mild form of non-salt-losing congenital adrenal hyperplasia can mimic adrenarche so bloods to check 17-hydroxyprogesterone (17-OHP) and/or a urinary steroid profile may be indicated.

Other causes

Adrenal adenomas and adenocarcinomas can secrete huge amounts of adrenal androgens.

Exogenous steroids and non-iatrogenic Cushing's syndrome, which tends to show excess androgen secretion and hirsuitism, are well-documented causes of sexual precocity.

Investigations to consider

- *Bone age*: in the majority of the cases, bone age is advanced – usually by more than 2 years.
- A *pelvic ultrasound scan* of the pelvis confirms an enlarged, pear-shaped uterus with a prominent endometrial echo. In GDPP, the ovaries are active with >6 cysts that are greater than 4 mm in diameter. Larger cysts are sometimes seen in premature thelarche (<3 cysts), and the thelarche variant (3–6 cysts). The uterus changes in shape from a tubular structure to a pear-shaped structure, where the fundus expands so that its diameter exceeds that of the cervix. In GDPP, the changes resemble those of normal puberty, whereas in premature thelarche or thelarche variant, the uterus remains prepubertal in shape.
- *Dynamic test of the HPG axis*: a GnRH stimulation test shows a pubertal response (luteinising hormone >7 IU/L) in GDPP and prepubertal response in others.
- The *serum oestradiol* is elevated to pubertal level in both GDPP and GIPP.
- In selected cases, *thyroid function, liver function, adrenal androgens, and urinary steroid profile* may be needed.
- *Pituitary imaging*: an MRI scan of the hypothalamus and pituitary should be performed in confirmed GDPP in all boys with early puberty and all girls below 7 years of age.

Treatment options

Adrenarche, thelarche, and thelarche variant do not require treatment. Hypothyroidism is treated with a cautious introduction of thyroxine with subsequent increase to standard maintenance doses. Non-classical CAH is treated with hydrocortisone and fludrocortisone in most cases.

While an underlying abnormality triggering precocious puberty needs treatment, the decision to treat precocious puberty itself is based on several factors, such as the age of onset, the rate of progression, and the emotional impact of experiencing early puberty. Treatment will halt pubertal progress and the pubertal growth spurt, but significant regression of the signs of sexual precocity does not usually occur.

GnRH analogues (GnRHa) down-regulate GnRH receptors and hence inhibit secretion of luteinising hormone and follicle-stimulating hormone. Triptorelin is the only licensed product for children in the UK. However, leoprorelin and goserelin preparations are also available and are used in children. These preparations are given subcutaneously/intramuscularly every 4–12 weeks. Treatment is usually continued up to the age of 10–11 years. A consensus document was published in 2009 (Carel et al.) regarding their use.

Initial stimulatory effects of treatment can be prevented by the use of cyproterone acetate in conjunction with the GnRHa over the first 4–6 weeks at a dose of 50 mg/d.

Although it has been suggested that treatment with GnRHa improves final adult height, the age of onset of treatment is a crucial factor, with a more clear-cut effect in younger children. GnRHa and cyproterone acetate cannot recover lost height potential.

It has been suggested that a combination of growth hormone and GnRHa may result in an increase in final height. Although the combination treatment leads to an initial increase in height velocity, there is limited data to support an increase in final height.

GnRH-independent sexual precocity

Removal of any primary cause, such as an ovarian cyst/tumour, hepatoma, or adrenal tumour, is crucial. Otherwise, treatment is difficult. Options include androgen receptor blockers (cyproterone, flutamide, spironolactone), aromatase inhibitors (testolactone), and testosterone biosynthesis inhibitors (ketoconazole).

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PUBIC BONE PAIN IN PREGNANCY

Anushka Thalayasingam and Sharmistha Williams

Pubic bone pain is becoming an increasingly common complaint in pregnancy. This can be due to pre-existing disease that has been exacerbated during pregnancy or be peculiar to pregnancy itself. There are many physiological changes in the pelvis during pregnancy that can account for this symptom. These include the increase in mechanical stress on the pelvis due to the increasing weight, the increase in laxity of the ligaments and fibrocartilaginous joints as a result of the hormonal changes in pregnancy, and the changes in posture that are associated with advancing pregnancy.

Pubic bone pain may vary in severity. In extreme cases the pain may be so severe and debilitating as to cause difficulty in weight-bearing and walking. An early diagnosis of the cause of the pubic bone pain is important, as early intervention has been shown to reduce the morbidity associated with the underlying disease. Difficulties in diagnosis of musculoskeletal disorders in pregnancy arise from the limited use of imaging modalities owing to their potential harmful effects on the unborn fetus (see Breathlessness in pregnancy: respiratory causes).

The causes of pubic bone pain in pregnancy are summarised in Box 1.

Box 1 Causes of pubic bone pain in pregnancy

Musculoskeletal conditions

- Disease involving the pubic bones and pubic symphysis
  - symphysis pubic dysfunction
  - osteomyelitis of the pubis
  - osteitis pubis
  - pregnancy induced osteomalacia
- Referred pain
  - transient osteoporosis of pregnancy affecting the hip joint
  - mechanical back pain and sciatica

Other conditions

- Urinary tract infection

Musculoskeletal conditions

Diseases involving the pubic rami and/or the symphysis pubis may be mechanical (symphysis pubis dysfunction), idiopathic (osteitis pubis), inflammatory (osteomyelitis), or metabolic (osteomalacia). The commonest condition in pregnancy is symphysis pubis dysfunction.

Symphysis pubis dysfunction (SPD)

SPD results from instability of the pelvic girdle due to laxity and diastasis of the pubic symphysis joint (Figs 1 and 2). The reported incidence of SPD has a wide geographical variation, ranging from 1:36 to 1:300 within the UK because of the lack of objective or subjective diagnostic criteria.[1] While in Scandinavia most women with SPD present in the first trimester of pregnancy, in the UK presentation is usually in the second half of the pregnancy. Recurrence rates in future pregnancies may be as high as 85 per cent.[2]

Symptoms include pubic bone pain on walking, turning over in bed, climbing stairs, standing on one leg and lifting or parting the legs. Although the pain is commonly localised to the symphysis pubis it may radiate to the lower abdomen, groin, perineum, thigh, leg, and lower back. Pain may be described as shooting, burning, stabbing, or grinding in nature.

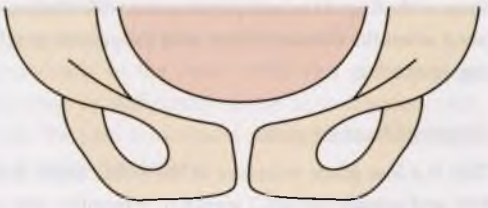

Figure 1 Pubic symphysis diastasis in pregnancy. The normal gap is 6–8 mm in the second half of pregnancy. Diastasis is said to occur if the gap is greater than 10 mm.

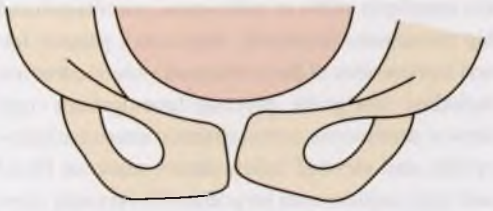

Figure 2 Upward displacement of the pubic rami when the patient lifts one leg. It is this instability of the symphysis pubis that results in difficulty in weight bearing and walking.

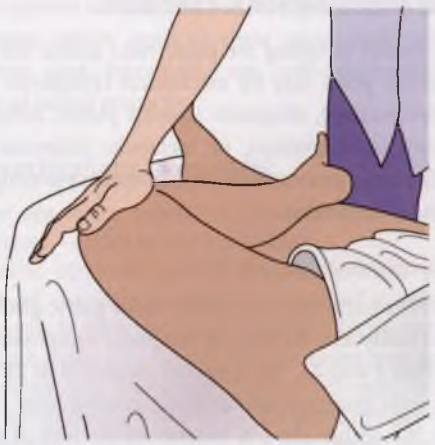

Figure 3 The Patrick's fabere test.

A waddling gait may be seen in extreme cases. This is due to the loss of abduction of the thigh. The commonest clinical sign is tenderness over the pubic symphysis or the sacroiliac joint. Active straight leg raising is usually restricted by pain and may cause a palpable displacement of the pubic symphysis. Hip movements are also restricted by pain, especially abduction and lateral rotation.

Tests usually carried out by obstetric physiotherapists include placing the ankle on the contralateral knee with the leg falling passively outwards; pain in either sacroiliac joint is a positive test (Fig. 3).[3]

Plain antero-posterior films of the pelvis may show widening of the symphysis pubis with displacement when the films are taken with the patient standing on one leg.

Osteomyelitis of the pubis

This is a low-grade infection of the pubic bone. It is rare and usually occurs 2 weeks to 3 months after a urogenital procedure, gynaecological surgery, or parturition. More uncommonly it results from spread of bacteria from a distant site in intravenous drug users. Symptoms usually include tenderness over the symphysis pubis or pubic rami, painful reduced hip movements (especially abduction), pain on lateral compression of the pelvis, and systemic features including low-grade pyrexia. Investigations may show a normocytic normochromic anaemia, leucocytosis, and elevated inflammatory markers. Blood and urine cultures may be positive. X-rays may show widening and bony erosions of the symphysis pubis (Fig. 4). Bone scans would show an increased uptake though they are not used in pregnancy.

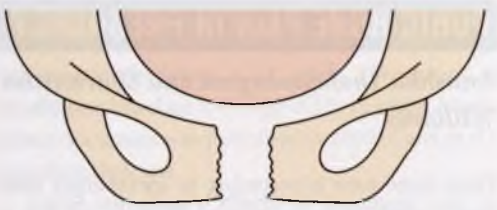

Figure 4 Erosions of the medial margins of the symphysis pubis seen with osteomyelitis of the pubis.

Osteitis pubis

This is a painful inflammatory condition involving all the structures in the region of the symphysis pubis in a symmetrical fashion. It is most commonly idiopathic but sometimes is associated with pregnancy, seronegative spondyloarthritis, urogenital procedures, and trauma.

Symptoms of this condition include pain in the pubis with radiation to the groin, thigh, and lower abdomen. Pain is aggravated by climbing stairs, kicking, lying on one side, and pivoting on one leg. Coughing and sneezing may also aggravate the pain. Palpation over the pubic symphysis and bilateral compression of the greater trochanters cause tenderness. Weakness in abduction of the thigh gives rise to a waddling gait, and there may also be hip flexor weakness.

Erosions, cystic changes, and rarefaction of the medial margins of the pubic rami are typical (Fig. 5). The X-ray of the pelvis shows diastasis of the pubic symphysis with displacement when the patient is asked to stand on one leg. Sclerosis of the margins may be a later feature. White cell counts and inflammatory markers are usually not elevated. Bone scans may be negative.

Pregnancy-induced osteomalacia

This is a metabolic disorder of bone caused by vitamin D deficiency. Vitamin D requirements are increased in pregnancy, and if these are not met by dietary intake, osteomalacia may result. Vegetarians are particularly at risk of this problem.

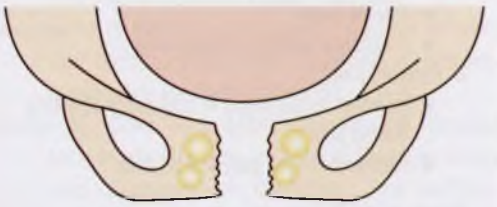

Figure 5 Rarefaction and cyst formation of the pubic rami and erosions of the medial margins of the symphysis pubis, which are characteristic features of osteitis pubis.

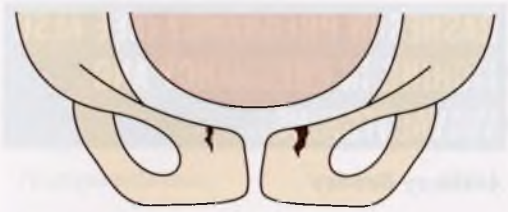

Figure 6 Looser's zones (pseudo fractures) in the pubic rami are characteristic of osteomalacia. Vegetarians are at high risk as they may not be able to compensate for the increased vitamin D requirement of pregnancy.

Symptoms are vague and can often be misdiagnosed. Bone pain usually occurs in the axial skeleton. Localised pain in the pubic area may be from pseudo fractures (Looser's zones; Fig. 6).

The gait may be waddling owing to a proximal myopathy. There may be bony tenderness localised to the pubis but also present over the spine, ribs, and sternum.

Diagnosis is usually made by biochemical investigations. Serum calcium may be low or normal. Alkaline phosphatase is usually raised in nearly all patients, though this is a usual finding in pregnancy. The diagnostic test is a low serum vitamin D level. X-rays show Looser's zones in the pubic and ischial ramii. Biochemistry usually returns to normal with oral vitamin D replacement therapy. If this does not occur, malabsorption should be excluded.

A summary of these conditions and differential diagnosis characteristics are given in Table 1. This illustrates the similarities in presentation. Since X-rays are only rarely used in pregnancy, diagnostic confusion may occur. This explains why the exact incidence of any of these conditions in pregnancy has not been well documented.

Referred pain

Musculoskeletal conditions that affect the spine and the hip joint can sometimes present with pubic bone pain. There are usually other symptoms and signs that help distinguish them from the conditions that directly affect the pubic bone and symphysis pubis. These are described below.

Transient osteoporosis of pregnancy affecting the hip joint

This is a rare but recognised condition. In pregnant women the left hip is typically affected, but the right hip and other joints may also be involved.

Symptoms are usually hip pain, either localised to the groin or referred to the anterior aspect of the knee, especially on weight bearing. The white cell count and inflammatory markers are only marginally raised and may be within the normal range seen in pregnancy.

X-rays reveal localised osteopaenia that may involve the femoral head and acetabulum. Ultrasound may demonstrate an effusion in the hip joint. The condition is usually distinguished from conditions that affect the pubic bone by the lack of localised tenderness when the pubic symphysis is palpated.

Mechanical back pain and sciatica

The late stages of pregnancy are associated with an increase in lumbar lordosis and angulation of the lumbosacral junction. Up to 50 per cent of women may complain of lumbar backache in the later stages of pregnancy. The pain radiates to the buttocks and occasionally to the lower limbs and pubic region. This may be sufficiently severe as to interfere with sleep. The pain is increased during labour but disappears soon after delivery.

Table 1 Characteristics of musculoskeletal diseases of the pubic bone in pregnancy

	PSD	Osteitis pubis	Osteomyelitis	Osteomalacia
Pain over pubis	Yes	Yes	Yes	Yes
Loss of thigh abduction	Yes	Yes	Yes	Yes
High ESR	No	No	Yes	No
Abnormal biochemistry	No	No	No	Yes
Systemic symptoms	No	No	Yes	Yes
Pubic diastasis	Yes	Yes	No	No
Pubic displacement	Yes	Yes	No	No
Erosions	No	Yes	Yes	No
Cysts/rarefaction	No	Yes	No	No
Looser's zones	No	No	No	Yes

ESR, erythrocyte sedimentation rate.

Gait is usually not affected and there is no myopathy. Lumbar movements may provoke the pain. If associated with disc prolapse, straight leg raising would be affected, and localising neurological changes may be present. There is usually no localised tenderness of the pubic symphysis. The diagnosis is usually made on clinical grounds and X-rays of the lumbosacral spine are performed only if pain is persistent and worsens.

Other conditions

Lower urinary tract infection usually presents with dysuria, frequency, and urgency of micturition. However these symptoms are less prominent in pregnancy. Women may present with pain behind the symphysis pubis.

Urinary tract infection

A lower urinary tract infection may present with pain behind the pubic bone which may be confused with the conditions that directly involve the pubic bone. Urinary frequency in the third trimester is common, and therefore the diagnosis is usually made by routine dipstick of a urine sample that shows proteinuria. A mid-stream specimen of urine would then confirm a urinary tract infection with the growth of 10^5 organisms per mL of urine. Clinical examination usually fails to elicit tenderness over the symphysis pubis. There is no abnormality of gait, and abduction of the thigh is normal. Rapid symptomatic relief is obtained with appropriate antibiotic therapy.

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Useful website

www.pelvicpartnership.org.uk

RASHES IN PREGNANCY (SEE ALSO ITCHING IN PREGNANCY AND VULVAL ITCHING)

Anthony Bewley

Rashes in pregnancy fall into two categories: those directly related to pregnancy, and those unrelated to the pregnancy. Rashes unrelated to pregnancy, such as eczema, psoriasis, and lichenoid skin disease, are discussed in Itching in pregnancy and Vulval itching.

Rashes directly related to the pregnancy

There are five distinct dermatological conditions that can be induced by pregnancy (Table 1), and all seem to have an abundance of the letter 'P', which combined with the word 'pregnancy' may have the clinician performing a tongue twister just to say the diagnosis. However, once familiar with the conditions (and once seen, they are rarely forgotten), the nomenclature and its potential confusion become clearer. Apart from impetigo herpetiformis, they are all pruritic, and it is the itching rather than the appearance that is often most debilitating.

Polymorphic eruption of pregnancy

This intensely itchy condition is thought to be associated with the exposure of skin antigens from the stretched abdominal skin of pregnancy. Hence it is commoner in the third trimester, multiple pregnancies, and polyhydramnios. The rash distinctively appears as urticated (nettle-rash-like) lesions in stretch marks and spares the umbilicus (Fig. 1). It is most often primagravidae who are affected. Delivery of the child (which is almost always unaffected by rash) is curative, although the symptoms may persist for a few weeks. Treatment is of the itch (Box 1) and reassurance that the condition is unlikely to recur in subsequent pregnancies.

Pemphigoid gestationalis

Pemphigoid gestationalis, also known (unhelpfully) as herpes gestationalis, is much rarer than polymorphic eruption of pregnancy. Characteristically, unlike any other pregnancy-related rash, there are true fluid-filled blisters, as the pathophysiology is immunobullous, i.e., autoantibodies are formed at the

Table 1 Rashes directly caused by pregnancy

Condition	Frequency	Distinctive feature	Other features	Treatment
Polymorphic eruption of pregnancy	Common	Umbilical sparing	3rd trimester Polyhydramnios, >1 fetus	Itch, see p.16
Pemphigoid gestationalis	Uncommon	Blisters	2nd/3rd trimester Recurs; may affect baby	Systemic steroids, refer to dermatology
Prurigo of pregnancy	Common	No urticaria-like itchy lesions	2nd/3rd trimester	Itch
Pruritic folliculitis of pregnancy	Uncommon	Folliculitis	2nd/3rd trimester	Itch, UVB
Impetigo herpetiformis	Very rare	Pustules, scaling	Very serious	Refer to dermatology

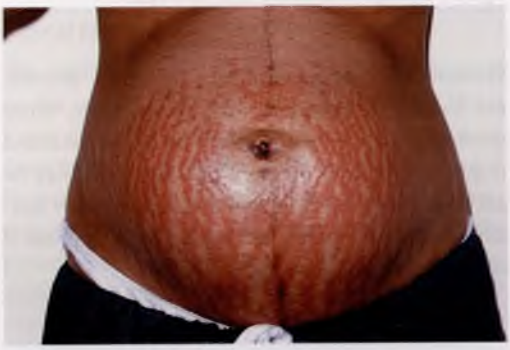

Figure 1 Polymorphic eruption of pregnancy. Note the periumbilical sparing.

Box 1 Management of itching in pregnancy

- Emollients (into the bath or on to the skin)
  - bath additives containing lauromacrogols (e.g. Balneum Plus®) or oat extract (e.g. Aveeno®) may be additionally antipruritic
  - topical emollients range from creamy (e.g. Cetraben) to very greasy (e.g. white soft paraffin) – let the patient decide which is best
- Avoidance of soaps and detergents – use soap substitutes (e.g. Dermol 500)
- Non-sedating antihistamines (e.g. loratidine) are usually not licensed for pregnancy but are probably safe
- Sedating antihistamines (e.g. chlorpheniramine) have been used safely in pregnancy
- Topical steroid ointments (rather than creams) are probably safe (although not licensed) in pregnancy. Try to keep to the lowest strength possible (usually clobetasone or betamethasone 0.1%) for no longer than 6 weeks
- (Rarely) phototherapy (usually narrow-band ultraviolet B)
- Information available at www.bad.org.uk

basement membrane of the skin, causing fluid-filled dermoepidermal separation (Figs 2 and 3). It is intensely itchy, may affect the periumbilical skin, and may appear in the second and third trimester. Unfortunately, even though delivery is curative, the child may be born with a similar rash, although this is very rarely dangerous. The mother's rash may persist for several weeks, and the condition typically recurs in subsequent pregnancies. Treatment is with systemic steroids – the lowest dose to suppress the condition with treatment of itch.

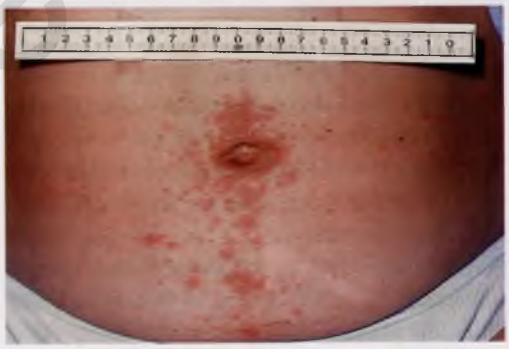

Figure 2 Pemphigoid gestationalis. Note the periumbilical involvement.

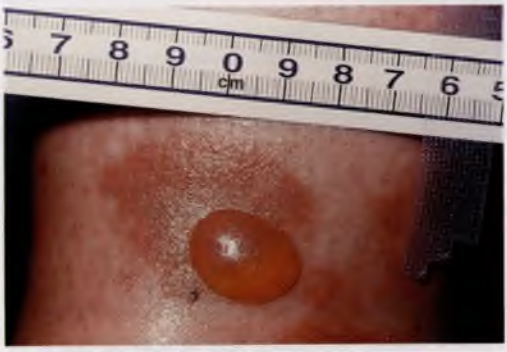

Figure 3 Blistering in pemphigoid gestationalis.

Prurigo of pregnancy

The main differences between this common condition and polymorphic eruption of pregnancy are that it starts earlier and there are no urticated (hives-like) lesions. In fact, the condition looks like, and is frequently mistaken for, eczema (excoriations, papules and redness, often over the extensors) and scabies. However, the patient does not usually have a history of eczema, and it is the extensor surfaces that are affected (rather than the flexures in eczema, and the groin and web spaces in scabies). The child is unaffected, but recurrence in subsequent pregnancies is common. Treatment is of the itch (Box 1).

Pruritic folliculitis of pregnancy

Aptly named, this condition causes an intensely itchy sterile folliculitis and looks like a widespread, fine, itchy acne except it is more generalised (on the head and chest). It often starts in the second trimester and continues to the delivery of the child, which is curative. The child is unaffected, and the condition may or may not recur. Treatment is of the itch (Box 1), although topical steroids are mostly avoided.

Impetigo herpetiformis

Impetigo herpetiformis looks similar to pustular psoriasis, except it is directly related to the pregnancy. It is the most dangerous of the pregnancy-related rashes and carries a small risk of maternal mortality. Clinically, skin lesions are tender, scaly, and red with a broad sheet or surrounding ring of studded pustules (Figs 4 and 5). The lesions may be widespread, but frequently affect flexural (especially the groin) and acral (hands and feet) areas. The patient can be quite unwell with pyrexia, a mild inflammatory hepatitis and general malaise.

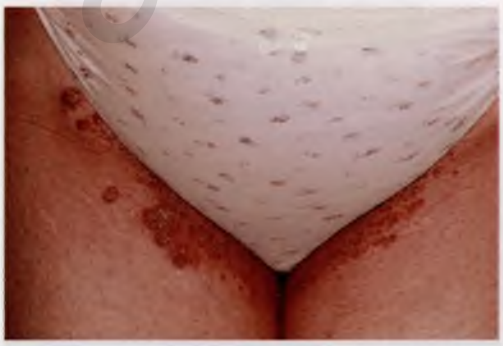

Figure 4 Impetigo herpetiformis. Note the scaly red rash in the groin with a pustular rim.

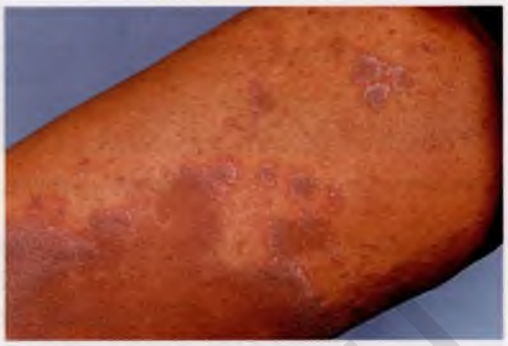

Figure 5 Impetigo herpetiformis: close-up of rash.

Treatment is often difficult. Systemic steroids are frequently necessary and, occasionally, other second-line, potentially more toxic preparations (e.g. methotrexate) are required. The fetus may be affected. Once the child is delivered, the rash usually settles. Fortunately, the condition is rare, but it can recur in subsequent pregnancies.

THYROID PROBLEMS IN PREGNANCY

Alice Hurrell and Rina Davison

Physiological changes in pregnancy

The structure and function of the thyroid gland alters during pregnancy. In areas of relative iodine deficiency, e.g., Belgium, the thyroid gland often hypertrophies due to an increased iodide clearance by the kidney and increased maternal iodine requirement because of active transport to the fetal placental unit. Hence the thyroid gland enlarges in order to trap adequate amounts of iodine.

Thyroid-stimulating hormone (TSH) levels drop in the first trimester corresponding to the peak serum human chorionic gonadotrophin (HCG) during this period. Free thyroxine (FT4) levels may rise early in pregnancy and this is attributable to the thyrotrophic action (TSH-like activity) of HCG (usually inconsequential Vomiting in pregnancy).

Hypothyroidism

This can occur in up to 1 per cent of pregnancies and is usually caused by an autoimmunity (Hashimoto's thyroiditis) or iodine deficiency (see Box 1).

Box 1 Causes of hypothyroidism in pregnancy

- Autoimmunity
- Iodine deficiency
- Thyroidectomy
- Post-radioiodine therapy
- Iatrogenic, e.g. amiodarone, lithium anti-thyroid drugs

Clinical features

The expression of various clinical features depends on the severity of the condition, and whether this is a new diagnosis or the patient is already on replacement therapy. Symptoms include weight gain, fatigue, forgetfulness, myalgia, goitre, dry skin, fluid retention, bradycardia and cold intolerance (Box 2). The patient may have coexisting autoimmune diseases, such as type 1 diabetes.

Box 2 Symptoms or signs of hypothyroidism

- Goitre
- Carpel tunnel syndrome
- Constipation
- Fluid retention
- Lethargy
- Weight gain

Diagnosis

Primary hypothyroidism is diagnosed if elevated TSH and low FT4 are detected. If the TSH is elevated and FT4 normal, the diagnosis is subclinical hypothyroidism. In this case, the patient may or may not have symptoms, but evidence suggests that treatment with thyroxine improves obstetric outcome. Low TSH and low FT4 are found in secondary (or central) hypothyroidism. The patient is likely to have pituitary or hypothalamic dysfunction, and is unlikely to become pregnant owing to impairment of gonadotrophin secretion.

Treatment

Pre-pregnancy counselling is recommended with the goal of achieving euthyroidism prior to conception. Hypothyroidism during pregnancy is treated vigorously with thyroxine in order to achieve a TSH of <2.5 mU/L. In established hypothyroidism, thyroxine dosage usually needs to be increased by 4–6 weeks' gestation and a may require a 30 per cent or more increase in dosage. Hence patients need thyroid function tests before trying to conceive and at least each trimester, with dose adjustments as necessary. If hypothyroidism is newly diagnosed in pregnancy, thyroid function tests should be rapidly normalised, with thyroxine dosage titrated to achieve a TSH of <2.5 mU/L. Thyroid function tests should be repeated within 30–40 days and then every 4–6 weeks. After delivery, the dose of thyroxine returns to pre-pregnancy requirements almost immediately.

Effects on conception, pregnancy, and the fetus

Hypothyroidism decreases ovulation and thereby reduces fertility. There is an associated risk of an increased rate of miscarriage, anaemia, hypertension, and low birth weight. Fetal thyroid function only begins at 10–12 weeks' gestation, and there is increasing evidence that, early in pregnancy, maternal thyroxine crosses the placenta and exerts an effect on brain development. Studies suggest untreated or undertreated maternal hypothyroidism can effect psychomotor development and IQ in offspring. These findings argue strongly for prompt recognition and treatment of hypothyroidism in pregnancy, which will usually lead to good maternal and fetal outcomes.

There is an association between anti-thyroid antibodies and pregnancy loss. Women with elevated thyroid peroxidase (TPO) antibody titres may be at increased risk of miscarriage, preterm birth, progression to overt hypothyroidism, and postpartum thyroiditis. Universal screening for TPO antibodies is not recommended. However, if TPO antibodies are detected, women should be screened for TSH abnormalities before pregnancy and during the 1st and 2nd trimesters.

Hyperthyroidism

The incidence of thyrotoxicosis during pregnancy is about 1 in 500 pregnancies. Graves' disease is the most common cause (95 per cent), although less commonly, toxic multinodular goitre, toxic adenoma, drugs or, rarely, gestational trophoblastic disease may lead to thyrotoxicosis.

Symptoms and signs

Most cases of hyperthyroidism in pregnancy will have already been diagnosed and will be on maintenance treatment. In cases of poorly controlled or newly diagnosed hyperthyroidism, typical features include heat intolerance, tachycardia, palpitations, goitre, weight loss, tremor, and lid retraction (Box 3). Lid lag and exophthalmos indicate Graves' ophthalmopathy.

Box 3 Symptoms or signs of hyperthyroidism

- Amenorrhoea
- Heat intolerance
- Increased appetite
- Anxiety
- Nausea
- Palpitations
- Sweating
- Tachycardia
- Tremor
- Vomiting
- Goitre

Diagnosis

Typically there is a raised serum FT4 and/or free tri-iodothyronine (FT3) and suppressed TSH. If low TSH is detected during pregnancy, hyperthyroidism must be distinguished from normal physiology of pregnancy and gestational thyrotoxicosis.

Management

Hyperthyroidism may cause maternal heart failure, infertility, miscarriage, intrauterine growth retardation (IUGR), premature labour, and increased perinatal mortality. Graves' disease, after a transient exacerbation of clinical symptoms, usually tends to remit in the second half of pregnancy.

The primary therapeutic objective is restoration to maternal euthyroidism using carbimazole or propylthiouracil (PTU) at the lowest dose to maintain the maternal FT4 in the upper normal range through periodic titration. Both drugs cross the placenta and, in high doses, may cause fetal hypothyroidism and goitre. Both drugs can also, rarely, cause a skin defect of the child's scalp known as aplasia cutis. PTU is recommended as first line in the 1st trimester, because of a possible association between carbimazole and specific congenital anomalies if exposure occurs during organogenesis. PTU may rarely be associated with severe liver toxicity and therefore it is recommended that PTU is changed to carbimazole after completion of the first trimester. Ten mg of carbimazole is considered equivalent to 100–150 mg of PTU, and both are equally efficacious in treating hyperthyroidism. When switching from PTU to carbimazole, thyroid function tests (TFTs) should be repeated after 2 weeks and then at 2–4 week intervals. If continuing on PTU, liver function should be monitored every 3–4 weeks. Doses of PTU <150 mg/d or carbimazole <15 mg daily are unlikely to cause problems, and breast-feeding is safe.

As transplacental transfer of thyroxine (T4) from mother to fetus is only minor, it would be inappropriate to treat the mother with an antithyroid drug/thyroxine combination, i.e., block and replace. Beta-blockers are used only in the short term for the relief of adrenergic symptoms associated with acute thyrotoxicosis. As pregnancy is an immunosuppressant, hyperthyroidism usually becomes easier to manage as gestation advances. Antithyroid drugs can sometimes be withdrawn after 4–12 weeks of treatment, but thyroid function tests and clinical assessment should still performed each trimester. Women should also be warned of relapsing hyperthyroidism postpartum.

Subtotal thyroidectomy is usually reserved for large goitres causing compressive symptoms or for suspected carcinoma. Other indications include severe adverse reaction to anti-thyroid drug treatment, persistent high dose requirement (>450 mg/d PTU or >30 mg/d carbimazole) and non-compliance and uncontrolled hyperthyroidism. The optimal timing for surgery is in the 2nd trimester. Radioiodine scans and therapy are contra-indicated in pregnancy and breast-feeding.

Neonatal hyperthyroidism

Neonatal hyperthyroidism occurs in 2–10 per cent of babies born to women with active Graves' disease. Thyroid receptor antibodies freely cross the placenta and can stimulate the fetal thyroid. It can be predicted by determining maternal TSH receptor antibodies (TRAb) at 22 weeks in women with 1) current Graves' disease, 2) history of Graves' disease and treatment with iodine/surgery pre-pregnancy, 3) a previous neonate with Graves' disease, or 4) previously elevated TRAb. In patients at risk, fetal thyroid status should be assessed at the anomaly scan

and then every 4–6 weeks or as clinically indicated. Signs of fetal thyroid dysfunction include fetal thyroid enlargement, advanced bone age, tachycardia, IUGR, hydrops, and cardiac failure. Cordocentesis for thyroid hormone assay should be reserved for cases where the diagnosis is not clear from the clinical picture. Treatment is with anti-thyroid drugs given to the mother (in fetal thyrotoxicosis) or to the neonate. Treatment in the neonate is needed only for a few weeks while the maternal antibodies clear from the circulation.

For women with good control on anti-thyroid drugs, the maternal and fetal outcomes are usually good.

Hyperemesis gravidarum

Hyperemesis gravidarum is characterised by prolonged and severe nausea and vomiting in early pregnancy, which can lead to a loss of 5 per cent body weight, dehydration, and ketosis, together with electrolyte abnormalities. Management may include hospitalisation, intravenous fluids, anti-emetics, thiamine, high-dose folic acid, and prophylactic dose low-molecular-weight heparin. In up to 50 per cent of admissions, disruption of thyroid function occurs. The TSH level is usually low and the FT4 may be increased, although the FT3 is rarely raised. These effects are usually due to the thyrotrophic action of HCG. In women symptomatic of hyperthyroidism, a careful history and examination, thyroid function tests, and TSH receptor antibodies help to distinguish between hyperemesis and thyrotoxicosis. Increased thyroid function of hyperemesis gravidarum is self-limiting, and treatment is usually supportive.

Postpartum thryoiditis

Postpartum thyroiditis is defined as an exacerbation of autoimmune thyroiditis during the postpartum period. Patients usually suffer from subclinical autoimmune thyroiditis beforehand, which is exacerbated after delivery. However, Graves' disease may also occur or recur in the postpartum period. About 1 in 20 pregnant women develop disordered thyroid function in the postpartum period, but many cases are asymptomatic. This may take the form of persistent or transient thyrotoxicosis, destructive thyrotoxicosis followed by transient hypothyroidism, and/or persistent hypothyroidism. There is often hyperthyroidism at approximately 3 months postpartum, followed by hypothyroidism at 6 months postpartum.

There is insufficient evidence to recommend routine screening for postpartum thyroiditis. However, women known to have thyroid peroxidase antibodies should have thyroid function tests measured at 3 and 6 months postpartum. Similarly, the prevalence of postpartum thyroiditis is higher in women with type 1 diabetes, Graves' disease in remission, and chronic viral hepatitis, in which cases screening by TSH is recommended at 3 and 6 months postpartum.

Pathogenesis

There is a destructive autoimmune thyroiditis causing an outpouring of preformed thyroxine from the thyroid gland followed by hypothyroidism owing to depletion of thyroid hormone within the gland.

Clinical features

Thyroid dysfunction is most often subclinical, and presentation is usually between 3 and 4 months postpartum. However, in the hyperthyroid state, there may be typical symptoms of thyrotoxicosis and, similarly, in the hypothyroid phase, there may be lethargy, tiredness, or depression. Hypothyroidism is a reversible cause of depression and should be screened for in women presenting with posttnatal depression. However, there is insufficient evidence for a link between postnatal depression and postpartum thyroiditis or thyroid antibody positivity.

Diagnosis

Diagnosis of postpartum thyroid dysfunction is simple when the patient shows abnormal thyroid function tests and positive thyroid antibodies. In overt thyrotoxicosis, it is essential to distinguish between postpartum Graves' disease and destructive thyrotoxicosis, as the management is different. Radioactive iodine scanning can distinguish the two: showing a low uptake in the thyroid with destructive thyroiditis and a high uptake with Graves' disease. Anti-TSH receptor antibodies are usually absent in postpartum thyroiditis.

Management

In postpartum hyperthyroidism, treatment is with antithyroid drugs to render the patient euthyroid as quickly as possible. Radioactive iodine is rarely used owing to the practical limitations of limited close contact between mother and baby. Beta-blockers are used to treat cardiovascular hyperdynamic symptoms in the thyrotoxic phase.

In postpartum hypothyroidism, no treatment is necessary for asymptomatic women with an elevated TSH, but thyroid function should be rechecked in 6 weeks. Thyroxine is used to treat persistent hypothyroidism, including women who are symptomatic with hypothyroidism or who are planning a subsequent pregnancy. Thyroid function should be rechecked in 6 weeks to see if it is possible to discontinue treatment.

Prognosis

In destructive postpartum thyroiditis causing thyrotoxicosis or hypothyroidism, thyroid dysfunction is transient and most patients recover spontaneously to euthyroidism. Only in a few cases does hypothyroidism persist, and high titres of antibodies are risk factors for persistent hypothyroidism. However, late development (after 5 years or more) of permanent hypothyroidism is found in 25 per cent of patients with postpartum thyroiditis. Therefore, these patients should be followed up with a yearly TSH in primary care, and TFTs should be measured prior to trying to conceive.

TIREDNESS IN PREGNANCY

Jai B Sharma

Pregnancy is a state in which there are considerable hormonal, physiological, and emotional changes, all of which can have profound effects. There are many physiological changes, which can manifest as excessive nausea and vomiting, morning sickness, tiredness, lack of appetite in early pregnancy and excessive appetite in later pregnancy, slight dyspnoea, mild palpitation, constipation (owing to the effects of progesterone), and backache. These occur as a result of hormonal changes, as concentrations of oestrogens, progestogens, and other placental hormones (e.g. human chorionic gonadotrophin) increase significantly during pregnancy.

Mild tiredness during pregnancy is a common physiological symptom and may not be of any significance. Along with physiological changes, increasing fetal movements, Braxton–Hicks contractions, and urinary frequency can lead to broken sleep, resulting in headaches and tiredness. However, excessive tiredness can be a symptom of abnormal pathology during pregnancy, which must be carefully assessed for any cause, and should be appropriately treated.

Causes of tiredness in pregnancy

The various causes of tiredness in pregnancy are given in Box 1. Mild tiredness is almost universal in most pregnant women, possibly owing to hormonal changes. It does not require any specific treatment. However, if the patient is concerned, it is worthwhile examining and investigating her fully to avoid missing any pathological cause of tiredness.

Box 1 Causes of tiredness in pregnancy

Physiological
- Mild tiredness is common in all women

Nutritional causes
- Anaemia
  - iron-deficiency anaemia
  - folate deficiency
  - cyanocobalamin deficiency
- Protein-energy malnutrition
- Micronutrient deficiencies

Infections and infestations
- Upper respiratory tract infections
- Urinary tract infections
- Genital infections
- Malaria
- Typhoid
- Hepatitis A, B, C and E infections
- Tuberculosis
- Worm infestations
- Intestinal infections

Endocrinological causes
- Diabetes mellitus
- Thyroid disorders (hypothyroidism and hyperthyroidism)
- Hyperparathyroidism
- Adrenal insufficiency
- Cushing's syndrome

Systemic diseases
- Heart disease
- Respiratory diseases (asthma, bronchitis, bronchiectasis)
- Rheumatoid arthritis
- Systemic lupus erythematosus and other collagen disorders
- Neuromuscular, including multiple sclerosis

Malignancies
- Leukaemia
- Lymphoma
- Gynaecological malignancies (ovarian, cervical)
- Other malignancies

Miscellaneous causes
- Chronic fatigue syndrome
- Hyperemesis
- Pre-eclampsia and other pregnancy disorders

Nutritional causes of tiredness

As shown in Box 1, anaemia resulting from iron deficiency, folate deficiency, or cyanocobalamin deficiency can cause tiredness in pregnancy. Even protein energy malnutrition during pregnancy can cause tiredness during this period. Deficiencies of various micronutrients and trace elements, such as zinc and selenium, can be other causes. All pregnant women must ensure they consume sufficient calories during pregnancy (2500 kcal/d) and an optimum amount of protein (60 g/d). In developing countries, it is not uncommon to see pregnant women with inadequate calorie and protein intake, which can result in tiredness. Treatment is by advising the women to ensure they have an adequate intake of calories, proteins, trace elements, and calcium during pregnancy.

Calcium deficiency is common, especially in developing countries, where most women are vegetarians. They should be advised to take adequate milk and milk products to give them about 1200 mg of calcium/d. If they are unable to take milk and milk products in the desired amount, they should be prescribed calcium tablets at a dose of 1 g/d. The recommended daily dietary allowances of various nutrients are given in Table 1.

Table 1 Recommended daily dietary allowances in pregnancy

Nutrients	Requirement
Calories	2500 kcal
Proteins	60 g
Iron	30 mg
Calcium	1200 mg
Folic acid	800 µg
Cyanocobalamin	1–2 µg
Vitamin A	2000 units
Vitamin D	300 units
Vitamin C	40 mg

Anaemia in pregnancy

Anaemia is an important cause of tiredness during pregnancy, especially in developing countries, where its prevalence is very high (up to 80 per cent). Even women with normal haemoglobin but with low iron stores can have excessive tiredness and feel unwell during pregnancy. When given iron supplementation, they experience a dramatic improvement in well-being, and start feeling much better and more energetic owing to the improvement in various iron-dependent enzymes in the body. All types of anaemia-like nutritional deficiency (iron, folate, cyanocobalamin), haemoglobinopathies, and anaemias of chronic disease and inflammation cause tiredness and malaise. For further details, see Anaemia in pregnancy.

Infections and infestations

Various infections (bacterial, viral, and others) and infestations (worm) are common and an important cause of tiredness in pregnancy, especially in developing countries (see Box 1). The attending doctors should be aware of this and must take a careful history, perform a detailed examination, and investigate properly for appropriate management.

Upper respiratory tract infections

These are common causes of morbidity during pregnancy throughout the world, including the developed nations. In cold countries, flu (viral infection) is common and can happen during pregnancy, causing tiredness, fever and malaise. The management is symptomatic by paracetamol, and adequate nutrition and hydration. The management of other respiratory infections, such as bronchitis and pharyngitis, is by use of antibiotics, such as erythromycin or azithromycin, and paracetamol with or without cough suppressants. Steam inhalation is useful as an adjunctive therapy.

Urinary tract infections

Urinary tract infections (UTIs) are common during pregnancy owing to the short urethra in women, the proximity of the anus, stasis of urine due to progestogens during pregnancy, and compression of the bladder by the enlarging uterus. UTIs present as a burning sensation and frequency of micturition, and

are easy to diagnose. However, many women may not have typical symptoms during pregnancy. These may manifest instead as tiredness and other vague symptoms, such as feeling unwell and pain in the abdomen, especially if recurrent. A very high index of suspicion is required on the part of the attending doctor to diagnose and treat UTIs at an early stage, as untreated UTI can cause serious pyelonephritis, intrauterine growth restriction, intrauterine death, and preterm labour. The treatment depends upon the culture and sensitivity report, which should always be done on a mid-stream urine specimen.

Genital infections

These are uncommon during pregnancy but can cause tiredness, fever, and abdominal and pelvic pain. Pelvic inflammatory disease is usually due to *Chlamydia trachomatis* infection, but can be from gonorrhoea, *Mycoplasma*, or other microorganisms. Treatment is with erythromycin or azithromycin. Tetracycline and doxycycline are contraindicated in pregnancy. Lower genital infections, such as trichomonal and candidal vaginitis, and bacterial vaginosis, usually present as itching with vaginal discharge and have no systematic effects, but may, though rarely, cause tiredness. They can be easily treated with clotrimazole or metronidazole.

Malaria

Malaria is a rare infection in Western countries, but is rampant in many developing countries in Asia and Africa, especially in tribal and rural areas where mosquitoes are in abundance. It causes high-grade remittent fever with rigor and chills with body aches and tiredness. *Falciparum* malaria is particularly hazardous, and can cause abortions, intrauterine growth restriction, intrauterine death, and preterm labour. Diagnosis is by peripheral blood film for malaria parasites, and treatment is with chloroquine and other malaricidal drugs.

Typhoid and other intestinal infections

Typhoid is an important cause of fever and morbidity in developing countries. Diagnosis is by blood culture and the Widal test. Treatment is with cephalosporins (cefuroxime), depending upon the culture sensitivity report. Other intestinal infections can present as diarrhoea, fever, pain in the abdomen, and tiredness. Oral rehydration therapy with or without antibiotics is required, as the infection often settles down with time.

Hepatitis infections

These are important causes of maternal morbidity in certain geographic areas, such as Asia and Africa, where the prevalence of hepatitis A, B, C, and E is high. Hepatitis can be made worse by pregnancy, and some patients can present with jaundice and hepatic coma, which has very high mortality. Mild cases can manifest as tiredness and other vague symptoms; a high index of suspicion is required for timely diagnosis and management. Details of liver disorders during pregnancy are given in Jaundice and liver disease in pregnancy.

Tuberculosis

Tuberculosis can be pulmonary (more common) or extrapulmonary. It is an important and common disease in developing countries in Asia and Africa, but is becoming more common in Western countries owing to infection with the human immunodeficiency virus. It presents with fever, anorexia, loss of weight, and cough with expectoration not responding to routine antibiotics. Diagnosis is by sputum examination for acid-fast bacilli on 3 consecutive days. Treatment is with antituberculous therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol, which should be continued in pregnancy for optimum maternal and fetal outcome. As most of these women are anaemic and hypoproteinaemic, adequate protein, calories, and iron therapy should supplement the antituberculous therapy.

Parasitic infestations

Amoebiasis, giardiasis, hookworm, and other worm infestations are rare in Western countries, but are still rampant in developing countries. They are an important cause of malnutrition, anaemia and tiredness during pregnancy in these countries. Diagnosis is by stool examination for ova and cysts on 3 consecutive days. Treatment is with metronidazole (for amoebiasis and giardiasis) and mebendazole or albendazole (single dose), which can be given safely in the second and third trimester of pregnancy.

Endocrinological causes

Diabetes mellitus

Rarely, diabetes can manifest as tiredness during pregnancy. In the early stages, the typical symptoms – polyuria, polydipsia, and polyphagia – may not be apparent. The diagnosis of diabetes should always

be kept in mind. Fortunately, most units screen for diabetes in their antenatal protocol, where most patients with high blood sugar are picked up and treated. The details of diabetes in pregnancy are given in Glycosuria in pregnancy.

Thyroid disorders during pregnancy

A severe degree of hypothyroidism often causes infertility and is unlikely to be associated with pregnancy. Thyroid disorders, especially mild to moderate hypothyroidism, are important causes of tiredness during pregnancy, especially in certain geographic areas where iodine deficiency is common. There may be a past history of hypothyroidism before pregnancy, in which case the diagnosis is not difficult to make. However, many patients manifest symptoms of hypothyroidism for the first time during pregnancy, making diagnosis difficult and delayed. The attending doctors must keep hypothyroidism in mind in all pregnant women who present with tiredness, feeling unwell, feeling cold, and having a lack of energy.

Hyperparathyroidism

Hyperparathyroidism is very rare in pregnancy, but can cause generalised weakness and hyperemesis with renal stones and psychiatric disorders. It requires surgical removal of the parathyroid adenoma.

Adrenal disorders

These disorders are very rare in pregnancy, since many patients with them are infertile. However, mild disorders can be associated with pregnancy, and their diagnosis may be missed. Adrenal insufficiency can cause weakness and fatigue. Diagnosis is by blood cortisol levels, and treatment is with corticosteroids (hydrocortisone). Cushing's syndrome is excessive production of corticosteroids and can cause tiredness. It needs treatment of the basic condition, such as adrenalectomy.

Systemic diseases

Various systemic diseases, manifest, albeit rarely in pregnancy, as tiredness, fever, and other general symptoms, such as anorexia and weight loss. The attending doctors should always keep a high index of suspicion of these conditions to avoid missing the diagnosis and delaying treatment.

Heart disease

Rheumatic heart disease is very rare in Western countries owing to the more liberal use of antibiotics, but continues to be a major health problem in developing countries. Mitral stenosis is the commonest lesion and can cause severe morbidity and mortality in pregnancy. Many patients conceive after mitral valve replacement and while they are on anticoagulation therapy. Patients with heart disease present with tiredness, weakness, palpitations, and breathlessness in pregnancy. Further details on breathlessness are given in Breathlessness in pregnancy: cardiac causes.

Even patients with congenital heart disease are now venturing into pregnancy after surgical correction of their heart lesion. These patients are at high risk and must be handled in consultation with a dedicated cardiologist, as morbidity and mortality can be very high.

Respiratory diseases (asthma, bronchitis, bronchiectasis)

Asthma is common in the general population and can be associated with pregnancy; it can present as a cough, dyspnoea, and tiredness. Treatment is the same as for the non-pregnant state, using salbutamol and steroid inhalers. Bronchitis, bronchiectasis, and other respiratory diseases are rare. They present with serious illness and tiredness and need treatment in consultation with a chest physician. Further details on breathlessness are given in Breathlessness in pregnancy: respiratory causes.

Rheumatoid arthritis

Rheumatoid arthritis can be associated with pregnancy, causing symptoms of arthritis and tiredness that require medical treatment in consultation with a physician.

Systemic lupus erythematosus and other collagen disorders

Collagen disorders, though rarely associated with pregnancy, can cause generalised symptoms of systemic lupus erythematosus, and can lead to abortions, intrauterine growth restriction, and intrauterine death. They can be treated with steroids and other specific medicines in consultation with a physician.

Neuromuscular diseases

Various neuromuscular disorders, such as multiple sclerosis and myasthenia gravis, can be associated with pregnancy, causing generalised neuromuscular symptoms and tiredness. They require treatment in consultation with a physician.

Malignancies

Leukaemia, lymphoma, and gynaecological (ovarian, cervical) and other malignancies can very rarely be associated with pregnancy. They can manifest as tiredness, generalised weakness, spongy and bleeding gums, lymph adenopathy, vaginal bleeding, and abdominal mass, depending upon the site of malignancy. They need specific surgical and oncological treatment in consultation with a medical oncologist and radiation oncologist, depending on the site of cancer, the gestation of the fetus, and maternal expectations.

Miscellaneous conditions

Chronic fatigue syndrome

This is a rare condition during pregnancy, which can present as severe tiredness. It is a syndrome in which the patient feels very weak and tired and usually follows viral illnesses, such as infections with Epstein-Barr virus, Coxsackie virus, and cytomegalovirus. The cardinal symptom is fatigue with poor concentration, poor memory, irritability, and neuraesthenia. Treatment is by treating the viral infection, general treatment including paracetamol, proper hydration and nutrition, and psychological and psychiatric therapy, usually in consultation with a physician.

Hyperemesis gravidarum

Slight nausea and vomiting are common in pregnancy, but excessive vomiting (hyperemesis) can present as tiredness along with dehydration and weakness, necessitating intravenous hydration and antiemetic therapy. Further details can be seen in Vomiting in pregnancy.

Pre-eclampsia and other pregnancy disorders

Pre-eclampsia presents after 20 weeks of pregnancy with hypertension and proteinuria, and is a cause of significant morbidity and mortality both in the mother and the fetus. It can present as tiredness. The treatment is with antihypertensive drugs, with or without magnesium sulphate, depending upon the severity of hypertension and gestation of the fetus.

Conclusion

Tiredness in pregnancy is not an isolated condition, but can be a manifestation of various disorders during pregnancy. It requires careful history-taking and examination, detailed investigations and appropriate treatment of the underlying condition, often in consultation with other specialists for optimum management.

Key points

1. Tiredness is a common problem in pregnancy and can be physiological.
2. There can be a variety of causes for tiredness, which include anaemia and other nutritional disorders, infections and infestations, diabetes mellitus and other endocrine diseases, systemic diseases, malignancies, and miscellaneous causes.
3. The attending doctor must take a detailed history of the patient, should perform a thorough clinical examination, and should investigate the patient properly to reach an accurate diagnosis.
4. The management is dependent upon the cause, often in consultation with specialists of other disciplines.
5. General treatment includes adequate nutrition, hydration, and symptomatic therapy.

TUMOUR MARKERS IN GYNAECOLOGY

Fredric Willmott

Tumour markers are macromolecular tumour antigens used to investigate patients presenting with either symptoms suggestive of a pelvic lesion or the presence of one on clinical examination. They are also used in monitoring treatment response of malignant disease and may detect an early recurrence.

CA-125

The most widely use marker in gynaecology is cancer-associated antigen (CA) 125. This was first described in 1981 (Bast). The CA-125 antigen is a large transmembrane glycoprotein derived from coelomic (pericardium, pleura, peritoneum) and Müllerian (fallopian tubal, endometrial, endocervical) epithelia.

About 85 per cent of women presenting with epithelial ovarian cancer will have a raised CA-125 level (>35 U/mL). CA-125 is >35 U/mL in only 50 per cent of patients with FIGO stage I disease at the time of surgery; therefore, for stage I, it has a 50 per cent false-negative rate.

Investigating symptoms of pelvic mass

Within primary care, access to imaging is not always readily available. Therefore NICE suggests carrying out

tests in primary care if a woman (especially if 50 years or over) reports having any of the following symptoms on a persistent or frequent basis – especially more than 12 times per month:

- persistent abdominal distension ('bloating');
- feeling full (early satiety) and/or loss of appetite;
- pelvic or abdominal pain;
- increased urinary urgency and/or frequency.

NICE also recommends performing a serum CA-125 level in any woman of 50 or over if she experiences symptoms within the last 12 months that suggest irritable bowel syndrome (IBS), because IBS rarely presents for the first time in women of this age.

If serum CA-125 is raised, an ultrasound scan of the abdomen and pelvis should be arranged. If the scan findings are normal, it is essential that a careful clinical assessment be undertaken. Other causes of a raised CA-125 should be excluded (see below), and the patient should know to re-present if the symptoms persist or worsen.

Investigating a known pelvic mass

In postmenopausal women, a simple ovarian cyst that is unilateral/unilocular and less than 5 cm in diameter has a low risk of malignancy (<1%). The RCOG recommends that, in the presence of a normal serum CA-125 level, these cysts be managed conservatively with follow-up scanning and CA-125 levels.

In premenopausal women a serum CA-125 assay does not need to be performed when a radiological ultrasound diagnosis of a simple ovarian cyst has been made. This is because CA-125 is unreliable in distinguishing benign from malignant ovarian masses in premenopausal women, as CA-125 can be raised in numerous conditions. Consequently, a raised serum CA-125 should be interpreted cautiously. However, only in advanced endometriosis (stages III–IV) is it likely to be raised to several hundreds or thousands of units/mL. If a serum CA-125 is raised but less than 200 units/mL, it is acceptable for further investigation to exclude and treat the common differential diagnoses (see Boxes 1 and 2).

In secondary care, CA-125 should be checked in all women with suspected ovarian cancer. With this result, the risk of malignancy index I (RMI) score should be calculated (see Ovarian swellings). This guides management, as an RMI score of 250 or greater will need referral to a specialist multidisciplinary team.

Serial monitoring of raised CA-125 may show rapidly rising levels. These are more worrying, as they are more likely to be associated with malignancy than a raised level which remains static. Consultation with a gynaecological oncologist is suggested if serum

Box 1 Benign causes of a raised CA-125

Pelvic-mass associated

- Pregnancy
- Endometriosis (+/– endometriomas)
- Pelvic inflammatory disease (+/– tubo-ovarian collections)
- Adenomyosis
- Uterine leiomyoma
- Multivisceral tuberculosis
- Meigs and pseudo-Meigs syndrome
- Ovarian hyperstimulation syndrome

Non-pelvic-mass associated

- During menstruation
- Urinary tract infection
- Pelvic/abdominal trauma
- Liver cirrhosis
- Tuberculosis peritonitis
- Uremia and renal failure
- Nephrotic syndrome
- Fulminant hepatic failure
- Pancreatitis
- Cardiac failure
- Budd–Chiari syndrome

Box 2 Malignant causes of a raised CA-125

Primary pelvic tumour

- Ovarian cancer
- Advanced uterine cancer
- Advanced fallopian-tube cancer
- Advanced rectal or bladder cancer

Secondary pelvic involvement

- Lymphoma with peritoneal involvement
- Pancreatic carcinoma
- Breast cancer with peritoneal metastasis
- Gastric cancer with peritoneal metastasis
- Advanced hepatocellular carcinoma

CA-125 is more than 200 U/mL, as the first aim of pre-operative assessment should be to triage women in order to decide the most appropriate place for them to be managed.

Most of the borderline tumours (such as teratomas and dysgerminomas) are not of epithelial origin and are not associated with increased levels of serum CA-125.

CA-125 is not a diagnostic certainty and can only guide the diagnosis and treatment. Following treatment for ovarian malignancy, CA-125 is a useful tool for monitoring recurrence. However, this depends upon the original tumour being in the 50–80 per cent of CA-125-producing masses.

Other tumour markers in gynaecology

Given the complex nature of the ovary, many substances and therefore tumour markers are produced. Lactate dehydrogenase (LDH), α-fetoprotein (α-FP), and human chorionic gonadotropin (HCG) are such compounds. It is recommended that these markers be measured in all women under the age of 40 with a complex ovarian mass because of the possibility of germ cell tumours.

In cases of suspected widespread abdominal malignancies, additional tumour markers should be used to investigate the possible primary. Corcinoembryonic antigen (CEA), CA 19.9, and CA 15.3 may point towards a gastro-intestinal primary.

Inhibin is secreted by adult granulosa cell tumours (AGCTs) and is therefore a useful tumour marker for this uncommon neoplasm. AGCTs commonly secrete oestrogen and may present with abnormal uterine bleeding associated with endometrial hyperplasia or even cancer.

Further reading

Green-top Guideline 62: Management of suspected ovarian masses in premenopausal women. RCOG/BSGE Joint Guideline, November 2011.

Kumar B, Davies-Humphreys J. Tumour markers and ovarian cancer screening. *Obstetrician and Gynaecologist* 2000; **2**(4): 41–44.

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RCOG Guideline 34: Ovarian cysts in postmenopausal women. October 2003, reviewed 2010.

Sevinc A, Adli M, Kalender M, Camci C. Benign causes of increased serum CA-125 concentration. *Lancet Oncology* 2007; **8**(12): 1054–55.

URINARY RETENTION

James Green

Urinary retention is the lack of the ability to urinate. It can occur in the following situations:

- the detrusor muscle in the bladder wall is unable to contract effectively;
- the bladder outlet fails to relax sufficiently;
- contraction of the detrusor and relaxation of the sphincter are uncoordinated, e.g. in detrusor sphincter dyssynergia.

The causes for these situations can be divided into two main groups: neurogenic and non-neurogenic.

Non-neurogenic causes of urinary retention

There are many non-neurological conditions that should be considered as a cause for urinary retention (see Box 1). These range from obstruction to failure of the ageing detrusor muscle (myopathy).

Neurogenic causes of urinary retention

More unusual causes for urinary retention involve the nervous system. In general, the anatomical level of the neurological injury determines the functional effect on the urinary system (Box 2). Spinal lesions may result in dyssynergia, an uncoordinated muscle contraction (see detrusor sphincter dyssynergia above), whereas sacral, cauda equina, or other peripheral nerve injuries may produce detrusor areflexia or absence of reflex. However, the situation is often more complex than this, as multiple or incomplete injuries can produce mixed patterns. Consequently, the functional result of the injury can often only be determined by video cystometrogram. This has the added bonus of allowing the measurement of the estimated pressure generated by the detrusor muscle during filling and micturition phases. This is important because, if the urinary system is exposed to an abnormally high functioning pressure,

Box 1 Non-neurogenic causes of urinary retention

Obstructive
- Urethral stenosis
- Urethral oedema
- Foreign body (including calculus)
- Post-stress incontinence surgery (including sling and injectables)
- Prolapse
- Pelvic mass, e.g. haematocolpos, extroverted gravid uterus, uterine fibroid, ureterocoele, benign and malignant tumours, faecal impaction

Post surgery
- Overdistension leading to detrusor muscle injury

Inflammatory
- Urethritis (infective and chemical)
- Vulvovaginitis (including herpes)
- Allergy
- Anogenital infection

Pharmacological
- Anticholinergic agents
- Epidural and spinal anaesthetics
- Ganglion-blocking agents
- Alpha-adrenergic agents
- Tricyclic antidepressants

Endocrine
- Hypothyroidism

Other causes
- Iatrogenic
- Urethral sphincter dysfunction/hypertrophy (Fowler)
- Detrusor myopathy
- Psychogenic

Box 2 Neurogenic causes of urinary retention

Conditions affecting the brain
- Cerebrovascular accident
- Parkinson's disease

Conditions affecting the spinal cord
- Spinal cord injury
- Multiple sclerosis
- Intervertebral disc disease (central)
- Ankylosing spondylitis
- Guillain–Barré syndrome
- Tabes dorsalis
- Acquired immunodeficiency syndrome (AIDS)
- Lyme disease
- Tropical spastic paraparesis
- Transverse myelitis
- Herpes zoster
- Poliomyelitis
- Tethered cord syndrome, short filum terminale, spinal dysraphism

Conditions affecting the peripheral nervous system
- Diabetic neuropathy
- Pelvis plexus injury, e.g. after abdominoperineal resection, hysterectomy

this can damage the upper urinary tract, leading to renal dysfunction and subsequent renal failure.

Diagnosis

Urinary retention can be diagnosed clinically or by ultrasound scanning. To identify the cause of retention, a detailed clinical history should be obtained and a clinical examination performed, including the nervous system if a neurological cause is suspected. Infection should be identified by urine culture and serum analysis. Renal dysfunction, although rarer in women, should be excluded.

Treatment

The best treatment is to avoid precipitating causes in the first place. Classic examples of this include avoiding faecal impaction and overdistension after surgery.

Once retention has occurred, decompression via a urinary catheter is indicated. An obstructed urinary system that is infected should be treated as an emergency, as septicaemia can result. If the obstructed lower urinary tract has resulted in renal dysfunction, an exact measurement of fluid input and urine output is undertaken to exclude a post-obstructive renal diuresis. If the urine output is excessive after catheterisation (>200 mL/h), intravenous fluids (normal saline) should be commenced to stop dehydration from occurring by initially balancing fluid input against the measured output.

In the majority of patients with normal renal function and no urinary infection present, clean intermittent self-catheterisation is the method of choice, providing manual dexterity is adequate. The frequency of catheterisation should be tailored to

the individual's bladder capacity. The aim is to avoid overflow incontinence and urinary stasis leading to potential urinary tract infection.

Some conditions, such as overdistension injury to the detrusor muscle, will often recover in a few days, but detrusor areflexia due to incomplete pelvic plexus injury after major pelvic surgery often takes at least 6 weeks to resolve.

Pharmacotherapy in the form of cholinergics and prostaglandins (PGs), e.g. bethanechol and PGE2, respectively, occasionally has beneficial results on the detrusor muscle. Surgery has a place in specific patient groups. If urethral stenosis exists, then urethral dilatation can be helpful. Neuromodulation of the S3 nerve root via the S3 foramen has had success in specialist centres in patients with sphincter hypertrophy.

UTERINE SWELLINGS

Sotiris Vimplis

The main function of the uterus (womb) is to contain a developing pregnancy (Fig. 1). Its anatomy is, therefore, adapted to fulfil this function by comprising a cavity encased by involuntary muscle fibres. These are arranged in a herring-bone pattern allowing expansion and contraction. When contracting, the fibres act as living ligatures, constricting the blood vessels to the cavity. The uterus is covered by peritoneum and lined by a glandular epithelium, which allows implantation of a fertilised egg.

Swellings of the uterus can be divided into:

- those that are pregnancy related;
- those that are non-pregnancy related or anatomically related.

These can essentially be considered benign or malignant, the latter usually being primary tumours, although secondary uterine malignancies do occasionally occur.

Pregnancy-related uterine swellings

Normal pregnancy

The most common cause of uterine swelling is pregnancy, and this must always be considered during the reproductive years, particularly when associated with a history of amenorrhoea or menstrual upset. The size is dependent on the gestational age, but will usually become palpable abdominally from 12 weeks' gestation.

Trophoblastic disease

This is an abnormal proliferation of trophoblastic tissue with an incidence of 1 per 714 live births in the UK. Gestational trophoblastic disease covers a spectrum of diseases, including complete and partial hydatidiform mole and the malignant conditions of invasive mole, choriocarcinoma, and placental site trophoblastic tumour. The presenting symptoms and signs include first-trimester bleeding, hyperemesis, excessive uterine enlargement, and early failed

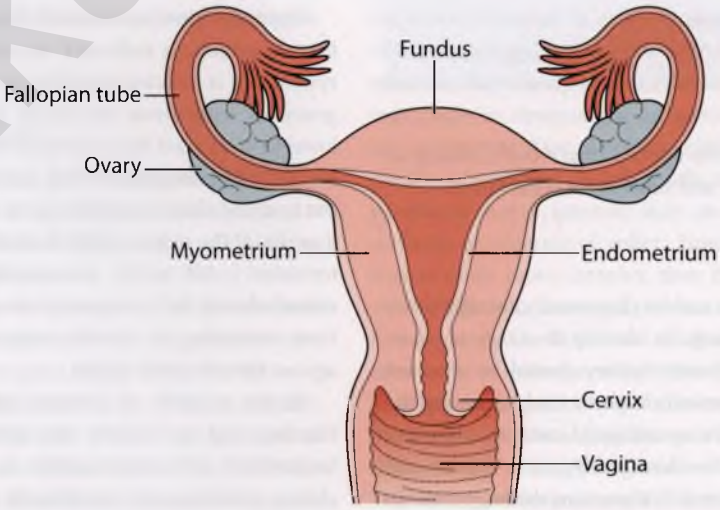

Figure 1 Diagram of the female genital organs/tract.

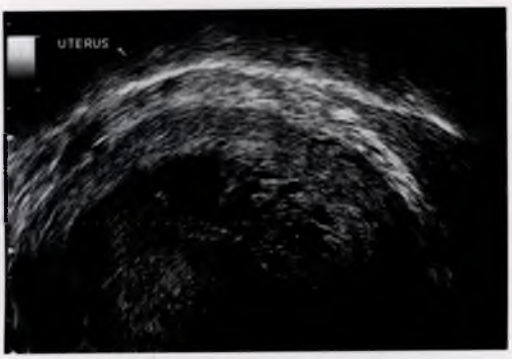

Figure 2 Ultrasound scan of hydatidiform mole showing typical snowstorm appearance.

pregnancy. Rarer presentations include hyperthyroidism, early onset pre-eclampsia, and abdominal distention due to theca lutein cysts. Ultrasound examination is helpful in making a pre-evacuation diagnosis, but the definitive diagnosis is made by the histological examination of the products of conception. An excessive amount of beta-human chorionic gonadotrophin (β-HCG) is produced, providing a 'tumour marker' to monitor regression or progression. Management of choice for molar pregnancy is suction curettage. All women diagnosed with molar pregnancy should be registered at one of the three trophoblastic treatment and screening centres (Charing Cross Hospital in London, Weston Park Hospital in Sheffield, and Ninewells Hospital in Dundee). Hydatidiform mole precedes choriocarcinoma in 50 per cent of cases (Fig. 2). This condition is highly chemosensitive and, when managed appropriately, has an excellent prognosis even in the presence of metastatic disease.

Clot retention

This can occur following spontaneous miscarriage, termination of pregnancy, or delivery, and is due to inadequate uterine contraction that does not cut off the blood supply to the placental bed in the uterine cavity. Bleeding may persist and be either revealed or concealed. Evacuation of the uterus may be required.

Retained products of conception

These are discussed under Bleeding during early pregnancy and Collapse in the puerperium.

Non-pregnancy-related uterine swellings

Uterine swellings have varying implications, depending on the age of presentation. The diagnosis is usually based on history and physical examination. Ultrasound scanning is the main imaging modality, although magnetic resonance imaging (MRI) is proving useful in defining the extent of surgery required for management of endometrial malignancies. Hysteroscopy and endometrial sampling are considered when patients present with abnormal vaginal bleeding.

Benign

Müllerian malformations

Adolescent girls, unlike women in other age groups, may present with a uterine mass that is secondary to a Müllerian malformation, such as imperforate hymen, vaginal agenesis with a normal uterus and functioning endometrium, vaginal duplication with obstructing longitudinal septa, and obstructed uterine horns. Cases of outflow obstruction remain asymptomatic until after the menarche. The uterine mass is due to the development of a haematometra (uterus distended with blood) and/or a haematocolpos (vagina distended with blood) owing to accumulating menstrual loss. A frequent presentation of genital obstruction is primary amenorrhoea with normal secondary sexual characteristics plus cyclical abdominal pain. Genital tract abnormalities in general may also present with severe dysmenorrhoea, dyspareunia, and infertility, and recurrent miscarriage, ectopic pregnancy, and obstetric complications if pregnancy occurs.

Investigation of Müllerian anomalies may include assessment of both the internal and external uterine contours with ultrasound, and often MRI, hysterosalpingography, hysteroscopy, and even laparoscopy may need to be performed.

In adolescents, pregnancy should always be considered a cause of uterine mass, unlike uterine leiomyomas, which are uncommon in women under 30 years of age, although the youngest patient on record was 13 years old.

Physical examination, pelvic ultrasound, and serum β-HCG levels will clinch the diagnosis if there is any doubt. As in all age groups, the primary diagnostic technique for the assessment of uterine swellings is ultrasonography, which if inconclusive is followed by computerised tomography of the abdomen/pelvis and/or MRI of the pelvis.

Fibroids

Fibroids or leiomyomata are the commonest tumours of the female genital tract, occurring in almost one

in three women over 30 years of age (Figs 3 and 4). They occur most frequently in middle-aged women of Afro-Caribbean origin. Fibroids are benign tumours arising from the myometrium of the uterus. They develop in women of reproductive age, promoted and maintained by exposure to oestrogen and progestogen. They increase in size during pregnancy and with administration of oestrogen and shrink when gonadotrophin-releasing-hormone analogues are given and after the menopause. Their size can range from a few millimetres to several centimetres, and they are usually present in the main body of the uterus, occasionally occurring in the cervix or the broad ligament. Confirmation of diagnosis is generally straightforward with physical examination and pelvic ultrasonography.

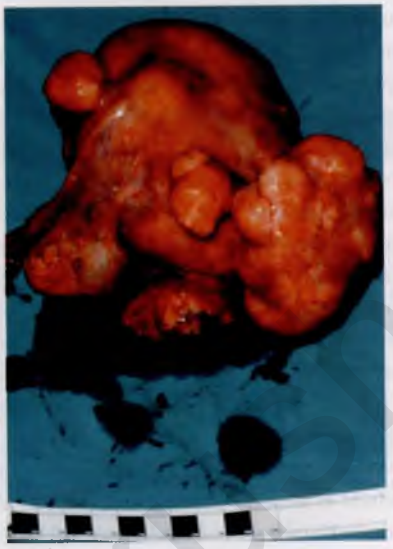

Figure 3 Hysterectomy specimen showing enlarged uterus due to fibroids.

Figure 4 Transverse section across a fibroid showing a whorled appearance.

Fibroids are usually asymptomatic but can cause symptoms depending on their size and location in the uterus. The most common symptoms and signs include:

- menorrhagia, especially with submucosal and intramural fibroids;
- awareness of a pelvic/abdominal mass;
- pressure symptoms – urinary frequency, retention or hydronephrosis
- pregnancy – fibroids may increase in size or degenerate (red degeneration) resulting in pain; they can also cause premature labour, malpresentation, obstructive labour, and postpartum haemorrhage.

Leiomyomas can be divided into four categories based on their position in the myometrium (Fig. 5).

- *Intramural leiomyomas* are the most common and, when large, may distort the uterine outline, resulting in a large, irregular mass. This type of myoma can give rise to menstrual problems and to complications of pregnancy.
- *Submucosal leiomyomas* are found beneath the mucosal surface of the uterus and can cause bleeding, even when small, secondary to compression of the overlying endometrium and compromise of its vascular supply. As they become larger, they may bulge into the endometrial cavity and increase the surface area of the endometrium. Fertility may be affected as they may interfere with implantation. Rarely, this kind of myoma can become pedunculated and prolapse through the cervix.
- *Subserosal leiomyomas* develop beneath the peritoneum that covers the external surface of the uterus, and are either sessile or pedunculated. The latter may undergo torsion, infection, and even separation from the uterus itself. When separation occurs, attachment to another

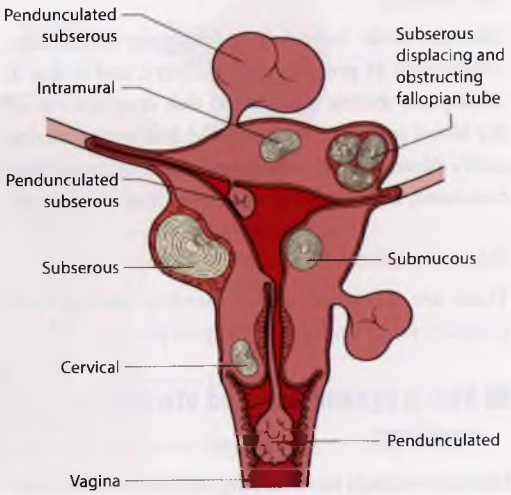

Figure 5 Diagram of the position of fibroids in the myometrium.

pelvic structure is possible, resulting in a 'parasitic leiomyoma'.

- *Intraligamentous leiomyomas* are so called because they develop between the anterior and posterior peritoneal leaves of the broad ligament. These myomas can compress adjacent organs, resulting in intestinal and urinary symptoms. Constipation up to and including bowel obstruction, urinary frequency, urge incontinence, urinary retention, and possibly ureteric obstruction may also occur.

All types of myomas can undergo degenerative change. Submucosal myomas are frequently ulcerated and haemorrhagic. Necrosis and haemorrhage can also be found in large fibroids during pregnancy or after administration of high-dose progestin therapy. Cystic degeneration occurs, and leiomyomas often become extensively calcified as identified on plain abdominal X-ray. Malignant change of fibroids is reported to occur in 0.1 per cent of cases but should be suspected in cases of rapid growth and acute abdominal pain. Adenomyomas (circumscribed nodular aggregates of smooth muscle, endometrial glands, and endometrial stroma located within the myometrium) can mimic uterine leiomyomas. Adenomyosis is a condition characterised by the presence of endometrial glands and stroma within the endometrium, and can result in a bulky uterus that is tender on bimanual examination. These conditions (adenomyosis and adenomyomas) may be difficult to distinguish from leiomyomas clinically, but ultrasound and MRI are useful in making the diagnosis pre-operatively. The final diagnosis is made on histology following hysterectomy.

Other benign causes

Among the infective causes of uterine swelling, tuberculous endometritis deserves mention. It is secondary to a systemic infection by *Mycobacterium tuberculosis*, generally presenting in women of reproductive age. The endometrium is the second most commonly infected site in the female genital tract, after the Fallopian tubes. Infection develops by haematogenous spread from a primary focus in the lungs or gastrointestinal tract, and uterine infection is usually by direct transmission from the Fallopian tubes. Presentation is usually with lower abdominal pain and an associated uterine mass. However, this infection may mimic ovarian malignancy.

In older women, cervical stenosis secondary to atrophy may occur. This is usually asymptomatic but may result in a distended uterine cavity on imaging. In this age group, the presence of a haematometra (cavity containing blood) or pyometra (cavity containing pus) requires further investigation (usually dilatation of the cervix, drainage, and cervical/endometrial biopsy), as the presence of a malignancy must be excluded. In these cases, the distended uterus may present with pain and may be palpable on physical examination.

Cervical stenosis may occur in younger patients. Causes include cervical scarring secondary to trauma (lacerations following parturition or abortion), surgery (cone biopsy, cryotherapy, cervical cauterisation), and radiotherapy for primary cervical cancer.

Benign endometrial polyps may also result in an enlarged uterus and should be included in this section (Fig. 6).

Approximately 90 per cent of women diagnosed with endometrial cancer present with postmenopausal bleeding, and up to 10 per cent of women with this symptom will be diagnosed with the disease. The recommended initial investigation is a transvaginal ultrasound scan for measurement of endometrial thickness and identification of ovarian masses. The most commonly used threshold for further investigation is an endometrial thickness of over 5 mm. Outpatient endometrial biopsy correctly diagnoses cancer in over 80 per cent of women and can be preceded by outpatient hysteroscopy if necessary, for example where endometrial polyps are suspected on ultrasound. Hysteroscopically directed biopsy is also useful in the evaluation of women with bleeding while taking tamoxifen. Magnetic resonance imaging (MRI) is used in the preoperative imaging of women with endometrial cancer to assess the depth of myometrial invasion and also assess pelvic and para-aortic nodal status. Computed tomography (CT) may be helpful in assessment of the upper abdomen if distant metastases are suspected in high-risk disease.

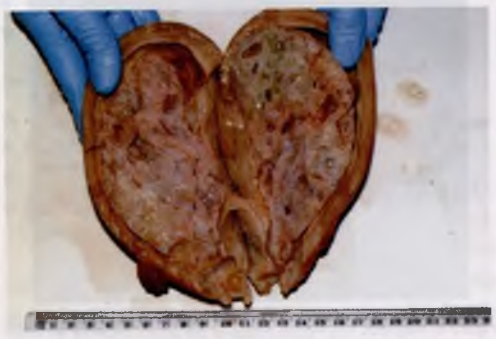

Figure 6 Benign asymptomatic polyp presenting as a pelvic mass.

Malignant (primary and secondary)

Uterine cancers are the most common gynaecological malignancies in the UK, with more than 8000 new cases occurring each year. The overall 5-year survival rate is high, reflecting early presentation in most cases, but outcomes for advanced disease remain poor. Most arise in the endometrium, and the majority are diagnosed in women aged over 50 years, although 20–25 per cent of women are premenopausal and approximately 5 per cent are women below 40 years of age. Over 80 per cent of primary endometrial cancers are endometrioid adenocarcinomas which are usually presented early and carry a very good prognosis (Figs 7 and 8). Serous, clear cell, and squamous carcinomas, and uterine sarcomas, including leiomyosarcomas, endometrial stromal sarcomas, and carcinosarcomas (previously known as mixed Müllerian tumours) are less common and more aggressive malignancies.

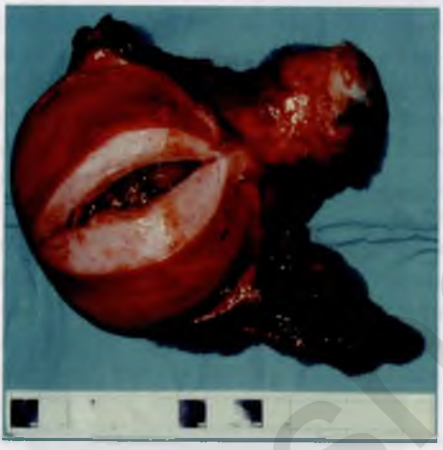

Figure 7 Hysterectomy specimen showing an endometrial cancer.

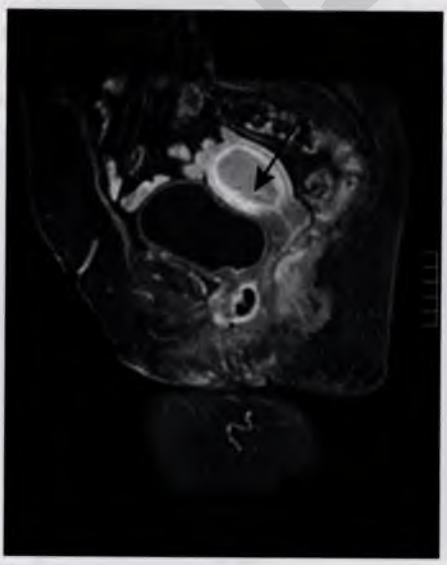

Figure 8 Magnetic resonance image of the pelvis showing an endometrial cancer infiltrating the myometrium (arrow).

The cornerstone of treatment is total hysterectomy and bilateral salpingoophorectomy, and laparoscopic surgery is recommended as a means of reducing morbidity. Systematic lymphadenectomy in all cases is unjustified. Adjuvant radiotherapy is given to selected patients at high risk of recurrence, and chemotherapy is increasingly used in high-risk and advanced disease.

Secondary malignancies of the uterus are less common than primary uterine tumours. The commonest sources of metastatic disease at this site include direct extension from cervical malignancies and, less commonly, other genital tract cancer primaries. Haematogenous spread from the breast and involvement due to lymphoma are also high on the list.

VAGINAL DISCHARGE

Rekha Wuntakal

Discharge from the vagina can be classified as:

- Physiological
  - common, and usually a diagnosis of exclusion;
  - varies with age and the time of menstrual cycle.
- Pathological
  - pre-pubertal;
  - during the reproductive age;
  - postmenopausal age.

Physiological discharge

The normal discharge from the vagina is a mixture of secretions from the uterine body, the cervix, and the vaginal wall, the bulk of which originates from the columnar epithelial cells in the cervix. There are no mucous glands in the vagina and, as such, it is not mucosa but a skin (non-keratinised stratified squamous epithelium).

The secretions vary throughout the menstrual cycle, being abundant, clear, and almost free from leucocytes at the time of ovulation. At this time, the elasticity of the secretions is at its greatest (*spinnbarkeit*), which allows easier penetration by the spermatozoa. At other times of the month, the cervical mucus is scanty, opaque, and tenacious. The secretion from Bartholin's gland, which is thin and mucoid, may be copious under sexual excitement,

but under normal conditions it is scanty, and so does not contribute significantly to vaginal discharge.

The vaginal mixed secretion is acidic in reaction, owing to the presence of lactic acid produced by the action of Doderlein's bacillus on the glycogen in the basal cells of the vaginal epithelium. This bacillus is normally found in the vagina from puberty to the menopause. The pH of the vagina is 4.5, the vaginal acidity being a bar to vaginal infection; unmixed uterine secretion is alkaline.

Normally, the amount of mixed vaginal discharge should do no more than just moisten the vaginal orifice; however, it may be increased with the presence of an ectropion, where there is eversion of the columnar epithelium towards the vagina (Fig. 1). Ectropion is more common in the reproductive age group, with oral contraceptive usage, and after delivery. If excessive, the ectropion may require cautery or cryotherapy. Girls before puberty and women after menopause do not have the protection of an acid secretion in the vagina.

In pregnancy, the physiological white discharge usually increases owing to the increased shedding of epithelial cells and an increased vascularity of the cervix, which in turn leads to an increase in secretion production.

Pathological discharge

Pre-pubertal

The causes of vaginal discharge in this age group can be classified as:

- Non-infective
  - foreign body;
  - poor hygiene;
  - sarcoma botryoides.
- Infective
  - threadworms;
  - sexual abuse.

Figure 1 Cervical ectropion.

In young girls presenting with vaginal discharge, the most common diagnosis is a foreign body that may necessitate imaging by either ultrasound scanning or occasionally X-ray of the pelvis, and sometimes may require an examination under anaesthetic (EUA).

At the time of EUA, a small hysteroscope can be inserted into the vagina, and the irrigating fluid used may flush the foreign body out and so treat the problem. Poor hygiene again is not uncommon and appropriate advice should be given to the mother. Threadworms may cause intense itching, especially at night. One needs to be cautious if sexual abuse is suspected, in which case the paediatric lead for child protection should be consulted. Each hospital in the UK should now have a named professional for child protection following the Climbié report.[1] Sarcoma botryoides is a rare tumour that may present with discharge or bleeding in young girls and would need referral to a cancer centre for further management.

Reproductive age

Vaginal discharge in women of reproductive age is most likely to be caused by infection. However, cervical polyps and malignancy may present with excess discharge or mucus production; these conditions are covered in the relevant chapters. The causes of vaginal discharge in this age group can be classified as:

Non-infective

- Cervical ectopy.
- Cervical polyps.
- Malignancies.
- foreign bodies (rarely), e.g. retained tampon.
- Genital dermatitis.
- Allergies.

Infective

Not sexually transmitted:

- *Candida.*
- Bacterial vaginosis.

Sexually transmitted:

- *Chlamydia.*
- Gonorrhoea.
- *Trichomonas vaginalis.*
- Pelvic inflammatory disease.

In all cases, a relevant history should be obtained, followed by any appropriate physical examination plus a vaginal speculum examination in order to take the relevant swabs, as discussed below.

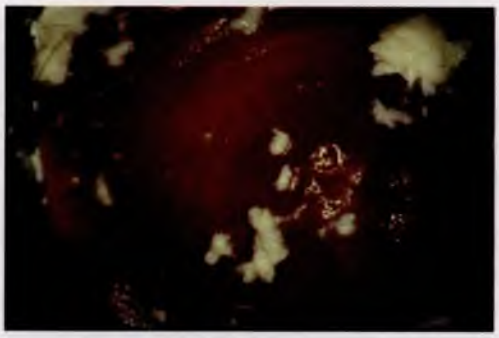

Figure 2 Vaginal *Candida*.

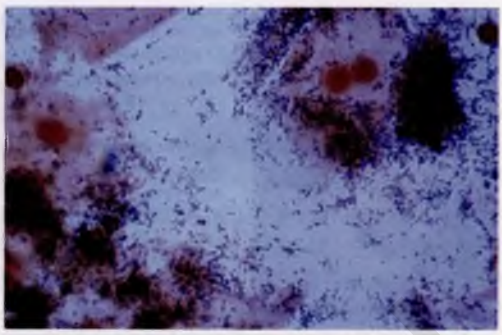

Figure 3 Slide showing 'clue cells' diagnostic of bacterial vaginosis.

Candida

This is a common infection in women and is often over-diagnosed and treated. It gives rise to characteristic white patches of thrush on the vagina walls and cervix (Fig. 2). It causes itching, discomfort, redness, external dysuria, and superficial dyspareunia. Vaginal and vulval examination may be normal or show non-malodorous discharge, mild inflammation of the vagina or vulva with fissuring, redness, and oedema. Vaginal pH is less than or equal to 4.5. It can occur as a complication of diabetes, immunosuppression, during pregnancy, following the use of antibiotics, and also in women using the combined oral contraceptive pill. A swab may be taken for recognition of the mycelium and spores of *Candida albicans* in stained smears and for culture. Treatment may be topical or systemic azoles, e.g. clotrimazole 500 mg PV (vaginal) stat dose or econazole or fluconazole (150 mg oral stat dose) in uncomplicated cases.[2]

Bacterial vaginosis (BV)

This is the commonest cause of abnormal vaginal discharge in women of reproductive age. It can arise and resolve spontaneously in sexually active and inactive women. The factors linked to BV include recent new partner, smokers, black heritage, vaginal douching, bubble baths, receptive oral sex, and alkaline vaginal pH due to, for example, semen and menstruation. It is associated with an increased risk of female-to-male transmission of human immunodeficiency virus (HIV), concurrent sexually transmitted infections (STIs), as well as being more common in women with pelvic inflammatory disease (PID) and those with a copper intrauterine device (IUCD) in situ. BV is associated with late miscarriage, premature rupture of the membranes, preterm birth, postpartum endometritis, and post-op endometritis (e.g. following termination of pregnancy [TOP], post-hysterectomy vault infections).[2]

BV is caused by *Gardnerella*, *Mycoplasma*, and overgrowth of anaerobes in the vagina. Women typically present with vaginal discharge which is homogenous, grey/white, thin, watery, copious, and with an offensive fishy smell (Fig. 3). Unless associated with another infection such as *Candida*, it usually does not have other symptoms as itch and soreness. Examination shows discharge coating the vagina and the vestibule and the absence of vaginal inflammation. Amsel's criteria can be used for diagnosis, the presence of 3 out of 4 criteria confirming the diagnosis: 1) vagina pH is >4.5; 2) thin, white homogenous discharge; 3) 'clue cells' (epithelial cells covered in bacteria) seen on wet microscopy; 4) release of fishy odour on adding alkali (10% potassium hydroxide) to drop of discharge on wet mount microscopy. The treatment for BV is metronidazole 400 mg twice daily orally for 5–7 days, or 2 g stat oral dose, or local clindamycin cream.[2]

Trichomonas vaginalis

This flagellate parasite produces a frothy purulent discharge (causing local pain, itch, and soreness that are extremely irritating to the external genitalia (Fig. 4). It also causes dysuria (urethral infection is seen in 90 per cent of cases) and lower abdominal pain (symptoms are absent in 50 per cent of women). The discharge is green or greenish yellow with small bubbles of gas and has a characteristic odour. Genital examination may be normal or show evidence of vulvitis, vaginitis, or cervicitis (<15 per cent of women do not show signs of inflammation or vaginal discharge). Rarely (only in <2 per cent of cases), the so-called strawberry cervix (typical red-stippled appearance) can be seen.[2] The vaginal pH is >4.5 and the vagina is inflamed. The motile protozoon can be identified on wet mount microscopy. *Trichomonas* (a gram-negative organism) lives in the vagina in symbiosis with *Micrococcus aerogenes*, which forms the froth or

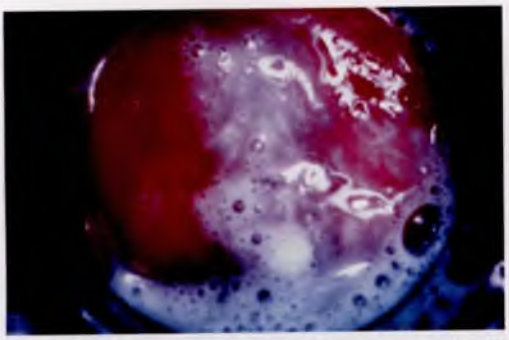

Figure 4 Trichomonal infection of the cervix.

bubbles so characteristic of the discharge. Systemic treatment is recommended with metronidazole 400 mg twice daily orally for 5–7 days, or metronidazole 2 g stat oral dose (avoid during pregnancy and breast-feeding) and should also include treatment for the partner. Both patient and partner should be advised to avoid sex until treatment is completed.

Neisseria gonorrhoeae

Gonorrhoea is caused by gram-negative diplococcus *Neisseria gonorrhoeae*. It usually infects the mucous membranes of the endocervix, urethra, rectum, pharynx, and conjunctiva. It presents with an abnormal vaginal discharge (the incubation period is 3–5 days) but is asymptomatic in 50 per cent of women. Transmission of HIV infection is facilitated in association with gonorrhoea.[2] Examination reveals a red, swollen, and oedematous cervix bathed in pus (Fig. 5). There is nothing characteristic of gonorrhoeal discharge visible to the naked eye. The detection of the gonococcus can alone confirm the diagnosis. This is often a matter of difficulty because it is only in the few days immediately after infection that the organism can be found in the discharge. In chronic cases, the gonococcus must be looked for in three places: in the endocervical canal, in the urethra, and in discharge squeezed from the orifices of Bartholin's glands. Gram's method stains the discharge, since the organisms are gram-negative diplococci. Endocervical swab sample can be taken for nucleic acid amplification techniques (NAAT). Appropriate treatment may be given in the form of spectinomycin (ceftriaxone 500 mg IM stat dose) depending on the organism's sensitivity, which may vary from one locality to the next. One should also be treated for *Chlamydia* irrespective of swab results. Contact tracing via the local sexually transmitted diseases service is essential.

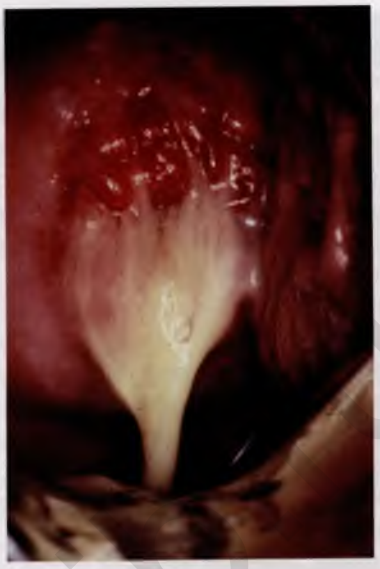

Figure 5 Gonorrhoea of the cervix. (Reproduced with kind permission from Peter Greenhouse.)

Chlamydia trachomatis

Chlamydia is the commonest STI in the UK (3–7 per cent of sexually active women under the age of 24 have chlamydia) and the highest incidence is seen among young adults. It is caused by an intracellular obligate pathogen which usually affects the mucous membranes of the endocervix, urethra, rectum, pharynx, and conjunctive (Fig. 6). The risk factors for chlamydia include women below the age of 25, more

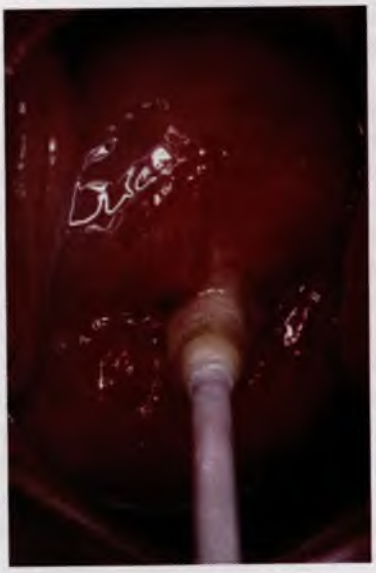

Figure 6 *Chlamydia trachomatis* infection of the cervix. (Reproduced with kind permission from Peter Greenhouse.)

than one partner in the last year or a recent sexual partner, and lack of consistent use of condoms. It can present with vaginal discharge, post-coital or intermenstrual bleeding, dysuria, lower abdominal pain, deep dyspareunia, and cervicitis, or can be asymptomatic (70 per cent of women) and only detected on screening for fertility problems or prior to a termination of pregnancy. Speculum examination reveals an oedematous, congested friable cervix which bleeds on touch. An endocervical swab is needed for culture or for NAAT to identify DNA. Treatment involves doxycycline (100 mg oral twice daily for 14 days) or azithromycin 1 g oral stat (can be used if compliance is the issue). Erythromycin is used during pregnancy. The treatment should include the partner, and a referral should be made to a genito-urinary medicine (GUM) clinic.[2]

Untreated, chlamydia may cause serious complications, including PID (10–40 per cent of women will develop PID without treatment), sexually acquired reactive arthritis (SARA), adult conjunctivitis, neonatal conjunctivitis (30–50 per cent of neonates may develop infection of the lungs, eyes, nasopharynx, and genitalia), perihepatitis (Fitz-Hugh–Curtis syndrome), increased risk of preterm rupture of membranes, preterm delivery, intrapartum pyrexia, late postpartum endometritis, and postabortal endometritis.

Pelvic inflammatory disease

Pelvic inflammatory disease (PID) is an infection ascending from the cervix that causes cervicitis, salpingitis, oophoritis, and tubo-ovarian abscess. It can also cause peritonitis, perihepatitis and periappendicitis. The risk factors for PID include young women, multiple partners, recent new partner, past PID or STI, and recent uterine instrumentation. Women with this condition may be asymptomatic or present with bilateral lower abdominal pain, abnormal vaginal discharge, abnormal vaginal bleeding (intermenstrual, post-coital, and menorrhagia), low-grade pyrexia, tachycardia, and deep dyspareunia. Examination may reveal raised temperature (>38°C), bilateral adnexal tenderness and/or swelling, cervicitis, and cervical excitation. The differential diagnosis of abdominal pain in such women in the reproductive age includes ectopic pregnancy, endometriosis, acute appendicitis, complication of ovarian cyst (rupture or torsion), urinary tract infection, and irritable bowel syndrome, and it can be functional. The organisms which cause PID include *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma hominis*, and anaerobes. However, the absence of an STI does not exclude a diagnosis of PID. Endocervical and/or vuvovaginal NAAT samples for gonorrhoea and chlamydia are recommended. Effective treatment on the first occasion is important, as successive bouts of PID may lead to infertility, tubal pregnancy, chronic lower abdominal or pelvic pain, and menstrual problems, as well as psychological morbidity. PID is treated with broad-spectrum antibiotics. The first-line antibiotics include doxycycline (100 mg oral twice daily for 14 days) and metronidazole (400 mg oral twice daily for 15 days) plus ceftriaxone (500 mg intramuscular stat dose) or ofloxacin (or levofloxacin) plus metronidazole. Moxifloxacin (400 mg oral once daily for 14 days) is used as second line (the addition of metronidazole is not needed). Erythromycin (500 mg oral twice daily for 14 days) should be used during pregnancy instead of doxycycline (contraindicated during pregnancy).[2] Local protocols should be available that will take into account the severity of the symptoms, local antibiotic sensitivities, need for hospital admission, and parenteral antibiotic therapy.

It is important to emphasise, once again, that contact tracing and treatment of the partner should be undertaken for chlamydia, gonorrhoea, and PID.

Retained tampons/foreign bodies

Any retained foreign body will start to cause discharge, which may become offensive after 24 hours. Removal will result in the discharge settling very quickly. A ring pessary inserted for prolapse should be changed regularly; otherwise, discharge may develop.

Postmenopausal

The causes of vaginal discharge in this age group are:

- atrophic changes;
- pyometra;
- malignancy e.g. uterine, cervical, vaginal and vulval cancer;
- complication of treatment of prolapse with vaginal pessaries;
- fistulae: arising mainly due to genital malignancy and consequences of its treatment.

In postmenopausal women, unless they are receiving hormone replacement therapy the amount of vaginal discharge produced is reduced and the squamocolumnar junction retreats along the endocervical canal. If the woman develops a vaginal discharge, especially if it is offensive in nature, it is necessary to exclude malignancy, including endometrial, cervical,

vaginal, or vulval lesions, by performing an abdominal, genital, and pelvic examination and organising appropriate imaging (ultrasound or Magnetic resonance imaging [MRI] scan) if necessary. A postmenopausal woman is extremely unlikely to have the infections that occur during reproductive age, the exception being candida.

In elderly women, a foul discharge may originate from the uterine cavity – a *pyometra*. The pus can be released by dilating the cervical os, which will usually require a general anaesthetic. It is usually due to senile endometritis, although it can be associated with carcinoma of the uterine body or cervix. Therefore such women would require a hysteroscopy and endometrial biopsy to rule out malignancy once the pus is drained.

Vaginal pessaries used for treatment of prolapse can cause vaginal discharge. These women are often referred with postmenopausal bleeding, as the discharge may be blood stained due to excoriation of the vagina by the vaginal pessary. A thorough examination of the vagina and pelvis following removal of the vaginal pessary is necessary to ascertain the cause of this blood-stained discharge to avoid unnecessary investigations such as hysteroscopy and endometrial biopsy. Examination usually reveals a circumferential, excoriated area at the level of the vaginal pessary. The treatment of excoriation is removal of the vaginal pessary followed by application of local oestrogen cream before reinsertion of the pessary, which should then be changed every 4 to 6 months.

Fistulae may develop as a late manifestation of malignant disease, although this is not common. They can also occur in bowel tumours, Crohn's disease, or after radiotherapy.

The majority of the postmenopausal women will have atrophic changes but they usually present with postmenopausal bleeding rather than discharge.

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StratOG: The RCOG online learning resource. http://www.rcog.org.uk/stratog

VAGINAL SWELLINGS

Rekha Wuntakal

Vaginal swelling is not uncommon, and most women will experience it at some point in their lifetime. Depending on the cause, it can be painful or associated with burning sensation, itching, or discomfort in the vagina.[1] The swelling may be generalised or localised. Allergens and irritants (soaps, creams, douches, perfumes, clothing materials) are common causes of generalised vaginal swelling and inflammation not related to a medical condition. Some women may also develop vaginal swelling in response to the use of latex condoms and lubrication gels. Generalised swelling and oedema within the vagina may occur as a result of infection, which may be primary (e.g. candida) or secondary (e.g. infected herpetic lesions). Fournier's gangrene[2] is a less common cause of generalised vaginal swelling but is potentially a serious or life-threatening bacterial infection of the genital area. Condylomata (warts) are common benign lumps that may occur with a frond-like surface. Biopsy may be useful before instituting treatment.

There are few other structures that present as localised swellings within the vagina (vaginal cysts and abscesses). Cysts in the vaginal wall may occur in the remnants of Gartner's ducts (embryological ducts that form during fetal development); they can result from trauma at birth or occur in the Bartholin's gland. They may be incidental findings during pregnancy or when taking a cervical smear. They may cause discomfort during intercourse or tampon insertion, and may be found on self-examination.

Patients may present with a lump in the vagina. In the vast majority of cases this will be due to some form of prolapse (see Prolapse of the uterus and vagina).

Identifying the cause is the first step before treating any vaginal swelling. Avoiding irritants and allergens can reduce vaginal and vulval inflammation. Antifungals and antivirals can be given to treat candida and genital herpes, respectively. Genital warts can be treated medically (local creams) or surgically by excision or destruction. Cysts and abscesses may need to be drained or removed depending on the cause. If the swelling is caused by a Bartholin's abscess, marsupialisation of the cyst should be performed to prevent recurrence and a course of antibiotics given to treat infection. Vaginal prolapse can be treated conservatively or surgically.

Benign swellings

The hymen is a membrane that partially covers the external vaginal opening in girls. When the membranous fold completely blocks the external vaginal orifice, it is called *imperforate hymen*.[3] As a result of this occlusion, the secretions or the blood accumulate in the vagina instead of escaping out during menstrual periods. Often it is not diagnosed until puberty, as children are asymptomatic with this condition. They then typically present with cyclical lower abdominal pain and amenorrhoea (absence of periods) with or without urinary retention. Examination of the genitalia reveals a bluish bulging membrane (see Fig. 3 in Menstrual periods, absent) at the external vaginal orifice owing to collection of blood behind the membrane (haematocolpos). The treatment involves minor surgery (cruciate incision on the hymen or hymenotomy) to create an opening to facilitate the flow of menstrual blood externally.

Simple *mesonephric* (Gartner's) or *paramesonephric cysts* may be seen high up in the vagina in the fornices or along the lateral wall of the vagina. They are embryological remnants, which have failed to be obliterated. They may be small and asymptomatic, and found incidentally on vaginal examination. Occasionally, they can grow and cause some degree of dyspareunia. Rarely, they can get substantially bigger and can be mistaken for urethral diverticum. The characteristic position and cystic 'feel' serve to distinguish them from the various types of vaginal prolapse (Fig. 1). They can be treated by excision or marsupialisation, if necessary.

Small implantation cysts may be seen at the vaginal orifice posteriorly. They are small and may follow operations on the perineum or lacerations at childbirth. They may cause dyspareunia, and occasionally the scarring from removal will result in no improvement of the symptoms.

Occasionally, an *endometrioma* may burrow through into the posterior vaginal fornix from the floor of the pouch of Douglas into the recto-vaginal septum, forming nodular growths, which tend to bleed at the time of menstruation. It can also cause dyspareunia. This condition may be confused with a primary carcinoma of the vagina, although it is not friable. Biopsy for histological examination will confirm the diagnosis and may require surgery to resolve it, in some cases involving a general surgeon.

Benign tumours could be sessile and pedunculated swellings arising in the vaginal wall, which on histology are found to be papilloma, fibroma, or lipoma. They are uncommon and excision may be necessary if they interfere with intercourse. Prolapsed fibroids from the uterine cavity may present with vaginal discharge and vaginal swelling, requiring examination under anaesthesia and removal.

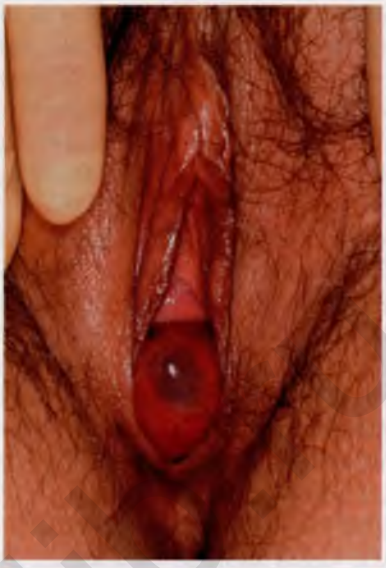

Figure 1 Posterior vaginal wall cyst.

Malignant swellings

As with any type of malignancy, there is always the possibility of primary or secondary tumours. Primary tumours of the vagina are rare, and management needs to be undertaken at a gynaecological cancer centre. By and large the prognosis for these tumours is poor despite radical surgery, radiotherapy and chemotherapy. The types of tumour are:

- *Squamous cell carcinomas*: the vast majority; usually occur in the upper vagina and usually treated by radiotherapy
- *Clear cell carcinomas*: these were thought at one time to be related to exposure to diethylstilboestrol while in utero. Often they are aggressive tumours with high recurrence rate.
- *Malignant melanomas*: these may present with bleeding rather than swelling. The prognosis is very poor.
- *Endodermal sinus tumour*:[4] this is a very rare type of malignant germ cell tumour which is exclusively seen in children under the age of 3 years.
- *Rhabdomyosarcoma* (sarcoma botryoides):[5] this is a rare tumour in girls under 5 years, which usually presents as vaginal bleeding. It has a characteristic appearance, like a bunch of grapes, and microscopic section proves its nature.

- *Secondary tumours* usually originate from the local organs, namely the cervix and uterus, although there have been reports of secondaries from primary tumours in the ovary, colon, choriocarcinoma, and hypernephroma.

Diagnosis is made by biopsy or excision biopsy, depending on the size of the lesion, followed by magnetic resonance imaging of the pelvis and referral to a gynaecological cancer centre.

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VOMITING IN PREGNANCY

Nandita Deo and Mala Arora

Vomiting and nausea are caused by physiological changes during pregnancy, and are nearly the most common symptoms of early pregnancy, second only to amenorrhoea. It affects up to 50–90 per cent of pregnant women. It usually begins in the first trimester at 6–8 weeks, typically peaking at approximately 9 weeks, and starts fading by about 12 weeks. In most women, the symptoms are gone by 20 weeks' gestation.

Hyperemesis gravidarum (HG) is a severe form of vomiting in pregnancy and effects 1 per cent of pregnant women.[1] The features of HG include intractable vomiting associated with weight loss of more than 5 per cent of pre-pregnancy weight, ptyalism (inability to swallow saliva) and associated spitting, dehydration, electrolyte imbalances, ketosis, and the need for admission to hospital. It is a diagnosis of exclusion by carefully eliminating other causes of severe nausea and vomiting.

Physiological vomiting

There are several explanations proposed for physiological vomiting in the first trimester of pregnancy:

- Rising progesterone and beta-human chorionic gonadotrophin (β-HCG) levels cause delayed intestinal motility and gastric stasis. Physiological vomiting is exaggerated in cases of multiple pregnancy and hydatidiform mole owing to higher β-HCG levels.
- High levels of oestrogen and progesterone, which accompany pregnancy, are potential mediators of gastric slow-wave dysrhythmias in nausea of pregnancy.[2]
- Vitamin B6 deficiency is caused by a change in protein metabolism in pregnancy; hence, vitamin B6 is used in its treatment.
- Relaxation of the gastro-oesophageal sphincter and hyperacidity also contribute to the condition.
- A few studies find a correlation between female fetal sex and hyperemesis gravidarum.[3]
- During the third trimester of pregnancy, the gravid uterus can mechanically reduce the distensibility of the stomach and change the contour of the cardiac sphincter, leading to an increased incidence of vomiting and a return of the first-trimester symptoms.

Differential diagnosis of nausea and vomiting in pregnancy

Gastrointestinal causes

The most frequently encountered causes in clinical practice are gastrointestinal in nature (Box 1). Exclusion of *Helicobacter pylori* infection is important.[4,5] In this infection, vomiting may be spontaneous or self-induced for relief of symptoms, as in peptic ulcer.

Gastroenteritis and food poisoning are common causes of vomiting in pregnancy. A variety of pathogens can be involved. The onset of vomiting is abrupt and related to the ingestion of food. Other cases may also be reported after ingestion of the same food. Pre-existing allergies to food products, such as eggs or nuts, can cause intractable vomiting after inadvertent ingestion.

Gallstones may be commonly associated with pregnancy, and can cause both hyperacidity and vomiting. They are easily diagnosed on upper abdominal ultrasound scan. If complicated with cholecystitis, the vomiting will be accompanied with right upper quadrant pain and/or fever.

Inflammation of any part of the gastrointestinal tract will manifest with vomiting. The most common example is acute appendicitis, when vomiting is

Box 1 Gastrointestinal causes

Oesophageal
- Gastro-oesophageal reflux disease
- Hiatus hernia

Gastric
- Gastritis
- Peptic ulcers due to *Helicobacter pylori*
- Disordered gastrointestinal motility seen in diabetes or idiopathic gastroparesis
- Fundoplication for obesity
- Gastric carcinoma

Intestinal
- Appendicitis
- Enteritis
- Intestinal inflammation as in ulcerative colitis or Crohn's disease
- Intestinal obstruction
- Food poisoning
- Bacterial due to *Shigella, Salmonella, Staphylococcus, Clostridium*
- Viral due to rotavirus
- Toxins, such as *Clostridium botulinum*
- Allergy to foods, such as eggs, nuts, or mushrooms
- Intestinal ischaemia, as in mesenteric vein thrombosis, Henoch–Schönlein purpura
- Hepatitis viral hepatitis A, B, C, D, and E, Epstein–Barr virus, cytomegalovirus, leptospirosis
- Pancreatitis due to a calculus in the common bile duct, viral or alcohol induced
- Cholecystitis

accompanied with right iliac fossa pain. Diverticulitis and cholecystitis will also present with vomiting. Acute pancreatitis can be precipitated by alcohol or may be a complication of underlying gallstones.

Vomiting may be the first symptom in hepatitis and can precede the appearance of jaundice by a few days. Liver function tests will show elevated liver enzymes, and hepatitis markers will clinch the diagnosis.

Gastrointestinal reflux disease is characterised by reflux of gastric contents during gastric peristalsis owing to incompetence of the oesophageal sphincter. In the first trimester, this is due to impaired forward gastric peristalsis, while in the third trimester, the cause could be purely mechanical owing to the gravid uterus pushing up on the stomach. If this becomes a chronic condition, this type of regurgitation will cause damage to the oesophageal lining because of the acidic nature of the contents. In the long term, there is a risk of stricture formation.

Pregnancy-related causes
- Multifetal pregnancy – twins, triplets, and higher-order births.
- Gestational trophoblastic disease – including hydatidiform mole.
- Pre-eclampsia.

Multifetal pregnancy (Fig. 1) and hydatidiform mole cause hyperemesis in the first trimester and are easily diagnosed on a first trimester scan. Degeneration of coexistent fibroids (Fig. 2) with pregnancy will present with vomiting and lower abdominal pain. Management is conservative with rest and analgesics.

Pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, and low platelets) syndrome occur in the third trimester of pregnancy and are accompanied by raised blood pressure and albuminuria. Vomiting may occur in patients with severe pre-eclampsia and HELLP.

Acute systemic infections

Examples of these are chorioamnionitis and viral infections, including influenza, encephalitis, meningitis, hepatitis, pancreatitis, and generalised peritonitis. As part of a generalised viraemia or bacteraemia, all acute systemic infections can be accompanied by

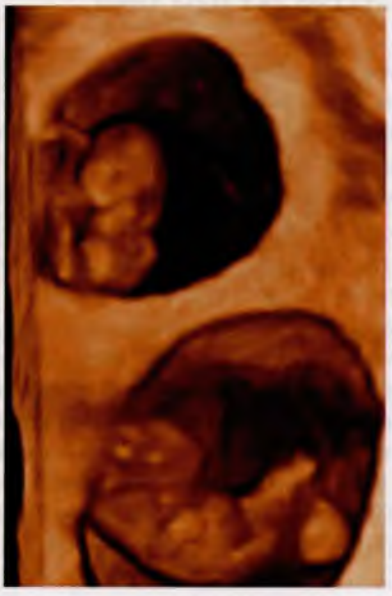

Figure 1 Twin pregnancy on 3-D ultrasound scan.

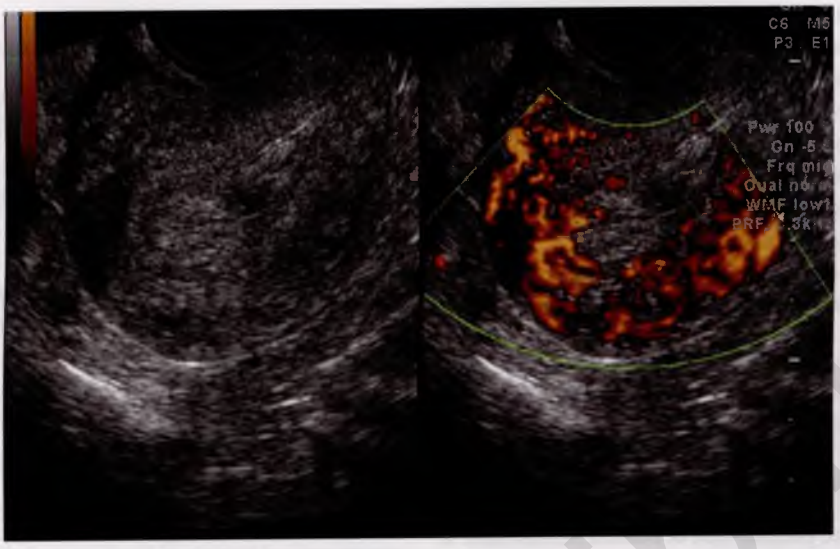

Figure 2 Degenerating fibroid. No vascular signals are present at the centre.

vomiting. In these cases there are coexistent symptoms of infection, such as fever, body ache, malaise, and a raised white cell count.

Urinary tract infections and pyelonephritis are common causes of vomiting in pregnancy.

Central nervous system

Raised intracranial tension can be accompanied by vomiting, and may be associated with benign intracranial hypertension, neoplasms, meningitis, and encephalitis. Raised intracranial pressure can sometimes occur with pre-eclampsia and eclampsia owing to cerebral oedema, which can also cause vomiting in the third trimester.

Benign intracranial hypertension is common in obese young women. It can present for the first time in pregnancy (in the second trimester) or may worsen if existing prior to pregnancy. Headache and papilloedema are present without computerised tomography evidence of a space-occupying lesion.

Cerebral neoplasms can occur, though rarely, in association with pregnancy.

Middle ear

- Ménière's disease.
- Acute viral labyrinthitis.
- Migraine.
- Motion sickness.

Middle ear disease can cause vomiting owing to stimulation of the labyrinth. There is often a past history, which is then aggravated in pregnancy. Motion sickness is common in pregnancy, while Ménière's disease generally presents in the fourth decade of life and so will rarely coexist with pregnancy. Migraine is often aggravated in pregnancy.

Cardiological

- Congestive cardiac failure.
- Acute myocardial infarction, especially posterior wall and transmural.

Congestive cardiac failure will cause congestion of the liver and hence lead to nausea. In patients with hyperhomocysteinaemia, myocardial infarction may occur at a younger age. If the ischaemia/infarct involves the posterior wall, it will irritates the oesophagus and can cause vomiting.

Endocrinal

- Diabetic ketoacidosis.
- Uraemia.
- Hyperthyroidism and thyrotoxicosis.[6,7]
- Hyperparathyroidism.
- Adrenal insufficiency or Addison's disease.
- Zollinger–Ellison syndrome.

Diabetic ketoacidosis may present for the first time in pregnancy with intractable hyperemesis. Blood sugar and urine ketone estimation will clinch the diagnosis. Uraemia, hyperthyroidism, and hyperparathyroidism have all been reported. Addison's disease will cause infertility in the first instance, but de novo deficiency can develop during pregnancy in cases of tuberculosis of the adrenal gland.

Zollinger–Ellison syndrome leads to increased gastric acid production and vomiting.

There is evidence of transient hyperthyroidism in 60 per cent of women with hyperemesis gravidarum.[6] This may be due to a similar structure of the HCG and thyroid-stimulating-hormone molecules, plus the fact that their receptors facilitate cross-reactivity between the two hormones. The degree of hyperthyroidism and HCG concentrations correlate with the severity of vomiting, and most often the thyroid dysfunction is self-limiting.[7]

Psychological

- Anorexia nervosa.
- Bulimia.
- Psychological or emotional disturbance.

Women with purging-type of bulimia nervosa have a significantly higher odds ratio of having nausea and vomiting in pregnancy than women without eating disorders.[8] Weight loss in women with anorexia nervosa is usually significant, as are nutritional deficiencies. Treatment is by psychological counselling.

Iatrogenic, medication- or drug-induced

Some drugs prescribed in pregnancy can cause gastric irritation, such as low-dose aspirin prescribed for patients with antiphospholipid syndrome.

Surgical

- Ovarian torsion, degenerating fibroids.
- Inflammations, such as appendicitis, diverticulitis, cholecystitis.
- Renal and biliary colic.
- Intestinal obstruction (see Abdominal pain).

Ovarian torsion (Fig. 3) can occur with the presence of ovarian cysts of the ovary that can coexist with pregnancy. There is accompanying lower abdominal pain and tenderness. Ultrasound scan will show the cyst, while Doppler signals of the ovarian vessels will show impaired flow.

The most common surgical emergency in pregnancy is acute appendicitis; however, both diverticulitis and cholecystitis will present with vomiting. Patients with acute renal or biliary colic vomit as a general response to pain. Intestinal obstruction from any cause will present with vomiting.

Types of vomiting

The most important clues to diagnosis lie in the history of vomiting and its accompanying symptoms. Hyperemesis tends to recur in subsequent pregnancies, and hence an absence of its history in previous pregnancies makes the diagnosis less likely.[9]

- Vomiting only in the early morning occurs in pregnancy, hyperacidity, and uraemia.
- Vomiting after eating is more likely to point to peptic ulcer.
- Projectile vomiting without nausea occurs in raised intracranial tension. Silent regurgitation of food occurs in oesophageal diverticuli.
- Vomiting accompanied by tinnitus and/or giddiness is seen in middle ear disease.
- Vomiting with diarrhoea occurs in enteritis and food poisoning.

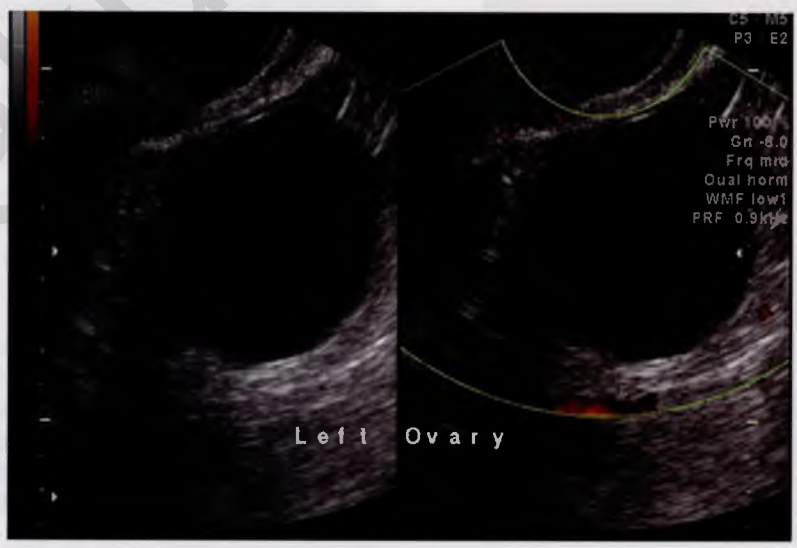

Figure 3 Ovarian torsion. Reduced ovarian perfusion is seen on power Doppler.

- Vomiting accompanied by lower abdominal pain could signify appendicitis.

Examination

A full clinical examination needs to be performed to assess for clinical signs of dehydration. Monitor vital signs, including pulse rate, BP (lying down and standing), and temperature. A chart recording the weekly weight should be maintained. Assess for signs of hypokalaemia (muscle weakness), hypercalcaemia, hypocalcaemia (Chvostek's or Trousseau's sign), and thyrotoxicosis.

Investigations

Investigations should include:

- *Urine analysis*: urine should be checked for the presence of glucose and ketones and urinary infection.
- *Complete blood count*: this may show a rise in haematocrit. There may be slight leucocytosis.
- *Serum electrolytes, such as sodium and potassium*: this may show hyponatraemia, hypokalaemia and, in severe cases, hypokalaemic metabolic acidosis.
- *Blood sugar*: hyperglycaemia may be present in diabetes, while hypoglycaemia may be present in persistent vomiting, which requires correction with intravenous fluids.
- *Liver function tests*: 20–30 per cent of women show mild elevation of liver enzymes in hyperemesis. In cases of hepatitis, the enzymes are markedly raised, and it may be of value to check the hepatitis markers. Serum amylase and/or lipase will be raised in pancreatitis. Liver function tests also provide an opportunity to look at serum protein levels, an indication of the nutritional status of the mother.
- *Renal function tests*: as renal failure is a complication of severe dehydration.
- *Thyroid function tests*: 50–70 per cent of women have transient hyperthyroidism. This is usually a self-limiting condition and does not require antithyroid therapy.[10]
- *Parathyroid hormone, if clinically indicated*: hyperparathyroidism is a rare cause of hyperemesis, which may be intractable. High serum calcium levels will point to the diagnosis. Both maternal and fetal morbidity is high, and surgery is the definitive cure.[11]
- An *electrocardiogram* will show widened QRS complexes and U waves in hypokalaemia.
- An *ultrasound scan* to confirm intrauterine pregnancy, to exclude multiple pregnancy and hydatidiform mole.

Complications of vomiting

The most obvious complications are dehydration, malnutrition, and weight loss. Loss of gastric fluid leads to dehydration, metabolic alkalosis, and hypokalaemia.

In cases of weight loss and muscle wasting, total parenteral nutrition may be necessary. Poor fetal outcomes have been reported if maternal weight loss is >5 per cent in pregnancy,[12] which include fetal intrauterine growth restriction.[13,14]

Other complications of vomiting include:

- Patients may complain of muscular aches and pains in the intercostal and upper abdominal region due to the accompanying retching.
- Thrombosis can be precipitated in susceptible patients through dehydration.
- Vomiting may cause tears in the oesophageal epithelium, known as the Mallory–Weiss syndrome, which may result in haematemesis. (See Haematemesis in pregnancy.)
- Rarely, forceful vomiting will lead to pressure rupture of the oesophagus, termed Boerhaave's syndrome, where the patient will complain of acute severe retrosternal chest pain.
- Vomiting during childbirth or under anaesthesia may result in regurgitation of stomach contents into the respiratory passages, leading to Mendelson's syndrome, which requires management in an intensive care unit. Subconjunctival haemorrhages may occur, which are inconsequential, but retinal detachment can be a serious complication.
- Wernicke's encephalopathy has also been reported in continued vomiting and dehydration.[15] This is due to thiamine (vitamin B1) deficiency, and is characterised by diplopia, nystagmus, ataxia, and confusion. It can be precipitated by infusion of dextrose-containing fluids. In the presence of Wernicke's encephalopathy, the incidence of fetal loss is higher.
- Erosion of the dental enamel is seen in the repeated vomiting of bulimia. B12 and B6 deficiency may occur leading to anaemia and peripheral neuropathies.

Management

Psychological support and reassurance that the vomiting will settle as the pregnancy advances is helpful. Non-drug-based treatments include dietary modification and alternative treatments such as ginger, acupuncture, and behavioural interventions. The mainstay of treatment of patients with hyperemesis gravidarum is IV hydration and antiemetics.

Correct dehydration and electrolyte imbalance

The patient will need fluid replacement to treat the dehydration. A general examination will give some idea of the severity of dehydration. Fluid and electrolyte balance needs to be titrated carefully in women with hyperemesis gravidarum. The presence of ketones in the urine and a raised haematocrit will

confirm the severity of dehydration, in which case the patient needs to be admitted to hospital.[16]

The fluid replacement regimen should include fluids such as normal saline or Hartmann's solution. Three litres of fluid could be infused over 24 hours. Potassium chloride (KCl) should be added to the intravenous infusion according to serum potassium levels. Add 20 mmol KCl to each litre of the fluid to a maximum of 60 mmol/24 hours in order to replace the potassium.

Fluid and electrolyte requirements should be adapted daily based on daily measurements of Na and K levels and the fluid balance charts.

Nutritional deficiency should be corrected in consultation with a dietician. Vitamin B1, B6 and B12 deficiency is common and may require supplementation. Other issues include:

- Oral intake of food could be withheld for 24 hours until the woman is able to tolerate oral feeds.
- Avoid dextrose-containing fluids: they do not contain sufficient sodium to correct hyponatraemia, and they can precipitate Wernicke's encephalopathy.
- Double-strength sodium should not be used, as central pontine myelinolysis can occur with rapid correction of hyponatraemia.
- Folic acid (400 µg od orally) and thiamine supplements (oral 25–50 mg tds daily; or IV thiamine 100 mg in 100 mL NaCl infused over 30–60 minutes once a week; or Pabrinex, which contains 250 mg thiamine per pair of ampoules, taken weekly).
- There is increased risk of venous thromboembolism (VTE) due to pregnancy, severe dehydration, and reduced mobility. Hence thrombo-embolic deterrent stockings and low-molecular-weight heparin must be prescribed as prophylaxis during inpatient stay.[17]
- Antacids (ranitidine, omeprazole) could be prescribed for symptom relief. For antiemetics, see Table 1.
- Extrapyramidal side effects and oculogyric crises have been reported with metoclopramide and phenothiazines. Oculogyric crises caused by metoclopramide is treated with benzatropine 1–2 mg IM/IV.
- Headache, tremors, and myalgia have been reported with prednisolone, prochlorperazine, promethazine, dimenhydrinate, doxylamine, and metoclopramide.
- Ondansetron (4–8 mg bd or tds iv/po/im) is a 5-HT3 receptor antagonist and a potent antiemetic. Several case reports show no adverse fetal effects reported. Its use is recommended in severe intractable HG.[18]
- Steroids are reserved for intractable HG when conventional treatment has failed (IV hydrocortisone 100 mg bd followed by prednisolone 40 mg once a day, gradually reduced by half every 3 days provided symptoms are controlled).[19]

Table 1 Routine antiemetics: there is no evidence that any one antiemetic is superior to another

Generic Name	Strength / Route of administration
Cyclizine	50 mg tds (im/iv/po)
Metoclopramide	10 mg tds (im/iv/po)
Promethazine	25 mg/po q 4–6 h (prn)
Domperidone	10 mg po qds; 30–60 mg rectally tds
Prochlorperazine	5 mg tds (po) or 12 im/iv tds or 25 mg daily PR followed if necessary 6 h later by an oral dose
Promethazine	25 mg po nocte

Conclusion

Emotional support and frequent reassurance is required. Multidisciplinary support from medical, nursing and dietician staff is vital in patients with severe HG. Outpatient management of HG has been tried with good success in patients with moderate dehydration, with patients receiving fluids and antiemetics in the outpatient setting.[20]

HG is common in pregnancy; it subsides as pregnancy progresses and is unlikely to adversely harm the baby when appropriately treated.

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VULVAL INVESTIGATIONS

Karen Gibbon

A useful algorithm when assessing a woman presenting with vulval symptoms is shown in Figure 1.

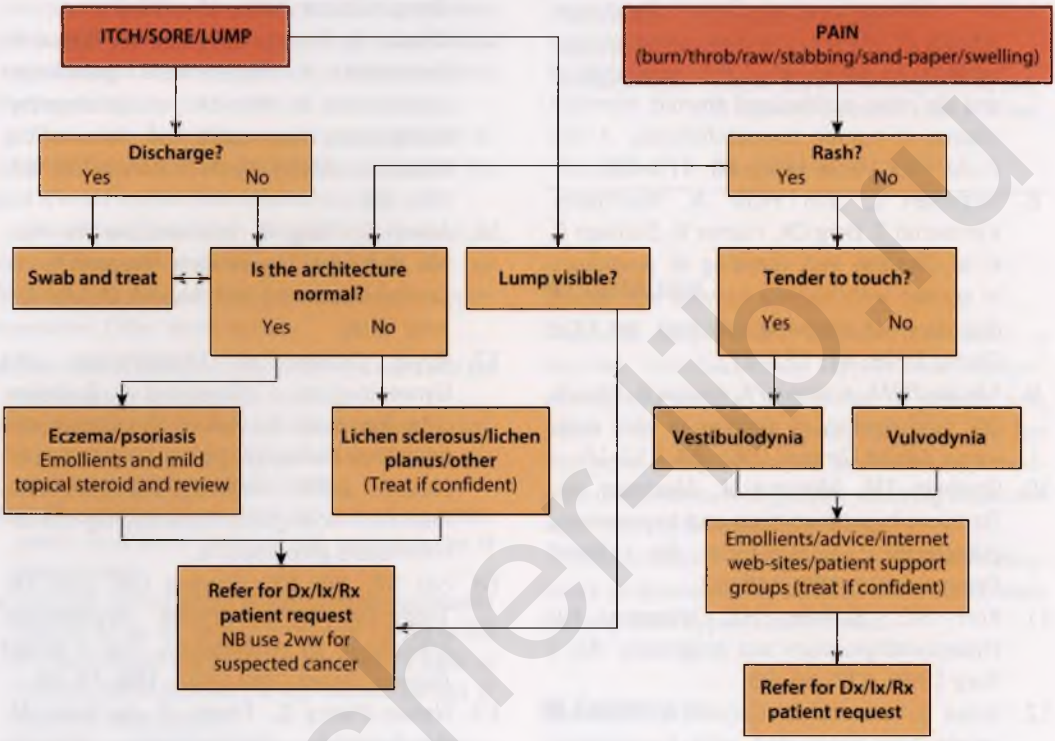

Figure 1 Assessment of vulval symptoms.

VULVAL ITCHING

Karen Gibbon and Sian Evans

Vulval itching (*pruritus vulvae*) may be caused by local or systemic disease processes (Box 1). The sensation of itch is generated by unmyelinated C-nerve fibres, distinct from but similar to pain nerve fibres. Consequently, it may be difficult for some patients to distinguish between sensations of itch, burning, tingling, and pain, which may be used to describe the same symptoms. Vulval itch is an unpleasant, intense, and embarrassing sensation that must not be underestimated.

The following information is based on the RCOG's Green-top Guideline No. 58: The Management of Vulval Skin Disorders (www.rcog.org.uk).

Box 1 Causes of vulval itching

Generalised pruritis

- Generalised dermatoses
  - inflammatory skin disease
  - atopic eczema
  - other eczema (e.g. contact, seborrhoeic)
  - psoriasis
  - lichen planus
  - urticaria
- Infection
  - scabies
  - HIV-related skin disease[a]
  - tinea (fungal skin disease)
  - body and pubic lice

- Other causes[b]
  - xerosis (dry skin)
  - hyper/hypothyroid disease
  - liver disease
  - chronic renal failure
  - haematological malignancy
  - drug rashes
  - occult malignancy
  - iron deficiency
  - psychogenic causes

Localised pruritis

- Localised (vulval) dermatoses
  - inflammatory skin disease
  - lichen sclerosus
  - lichen planus
  - lichen simplex chronicus
  - eczema
  - psoriasis
  - plasma-cell (Zoon's) vulvitis
- Infection
  - genital warts
  - molluscum contagiosum
  - candidiasis
  - trichomoniasis vaginalis
  - bacterial vaginosis
  - public lice
- Other causes
  - irritant or allergic contact vulval dermatitis
  - atrophic vulvitis
  - psychogenic
  - vulval intraepithelial neoplasia
  - extra mammary Paget's disease
  - vulvodynia

[a] See Itching in pregnancy
[b] See HIV (human immunodeficiency virus)

Assessment of vulval itch

A full history should be taken, which in addition to assessing the patient's symptoms should consider the impact of these on the patients functioning and well-being. Associated conditions such as dermatological disorders, atopy, autoimmune disease, and incontinence should be specifically enquired about, as should extra-vulval symptoms.

Physical examination should include not only the anogenital skin, but also any other epithelial or mucosal surfaces which the patient may identify as being abnormal, or are commonly affected by the suspected causative disease, such as the mouth in lichen planus.

The use of biopsy is indicated when a diagnosis cannot be reached solely on clinical findings, the response to treatment is poor, or malignant or pre-malignant changes are suspected. Co-existing autoimmune disease should be investigated only where clinically indicated. Appropriate investigation or referral to sexual health services should be done to rule out sexually transmitted infections.

Patients with vulval itch, irrespective of aetiology, may benefit from the following conservative measures:

- avoidance of irritants, including detergents, fragrances, and colourings found in products such as soaps and shower gels;
- voidance of synthetic or tight-fitting underwear or sanitary towels which increase friction and humidity;
- use of soap substitutes and emollients;
- treatment of any co-existing faecal or urinary incontinence;
- self examination which allows monitoring of disease progression.

Generalised disease (see also Itching in pregnancy)

Dermatological conditions can affect the vulval skin either in isolation or as part of a generalised skin disease. Inflammatory dermatoses are common and often affect the vulva; however, patients may not disclose vulval disease unless specifically asked (usually through fear of having a sexually transmitted disease or because of embarrassment).

Dermatoses

Irritant vulval dermatitis

Vulval pruritis is most commonly caused by irritant vulval dermatitis. Soaps, shampoos, and shower gels often contain detergents, which can deplete the skin's natural oily barrier. Irritant vulval dermatitis causes localised eczematous changes, such as erythema, excoriation, fissuring, scaling, or weeping (Figs 1 and 2), with no changes to the vulval architecture. Soap substitutes and emollients are essential in the management of irritant vulval dermatitis. Short courses of moderately potent steroid ointment may be necessary (e.g. clobetasone butyrate 0.05%). Patch testing to identify potential allergens may be considered.

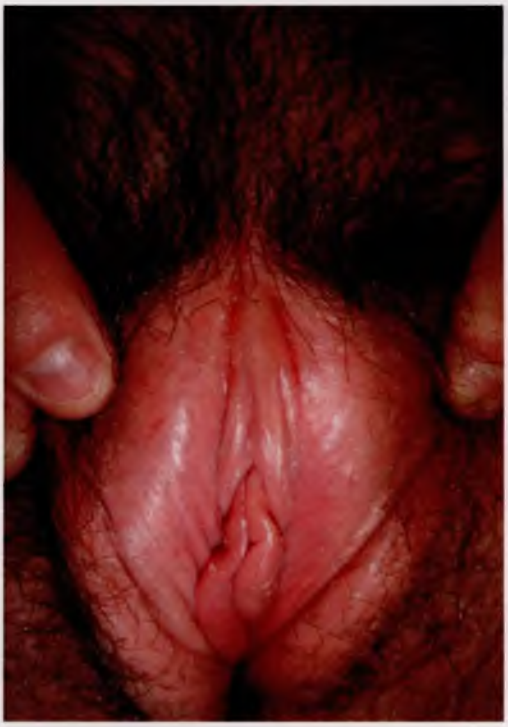

Figure 1 Fissuring in sulcus between labia minora and majora.

Atopic and seborrhoeic eczema

Atopic and seborrhoeic vulval eczema (dermatitis) are commonly associated with generalised eczematous disease. Personal or family history of atopy or seborrheic dermatitis is present in the majority of women with vulval dermatitis. Excoriation, lichenification (skin thickening), scaling, weeping, and pigmentation change are also commonly encountered. Treatment with emollients and soap substitutes is often sufficient, but judicious use of mild to moderate topical steroid ointments (e.g. hydrocortisone 1% or clobetasone butyrate 0.05%) may also be considered. Infected eczema may require treatment with topical or systemic antibiotics. Persistent eczema may be driven by specific contact allergens, and patch testing should be considered to identify causative chemicals.

Lichen sclerosus

Lichen sclerosus (Figs 3 and 4) is a well-recognised vulval dermatosis which is thought to have an underlying autoimmune basis, with co-existing autoimmune disease seen in many women. It may affect any age group, but is predominantly seen in middle-aged and older women. Vulval examination initially reveals erythema, later progressing to

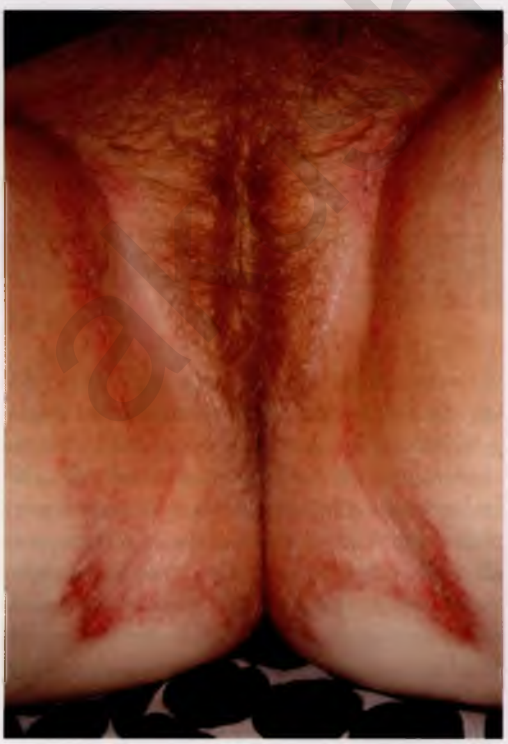

Figure 2 Acute irritant dermatitis.

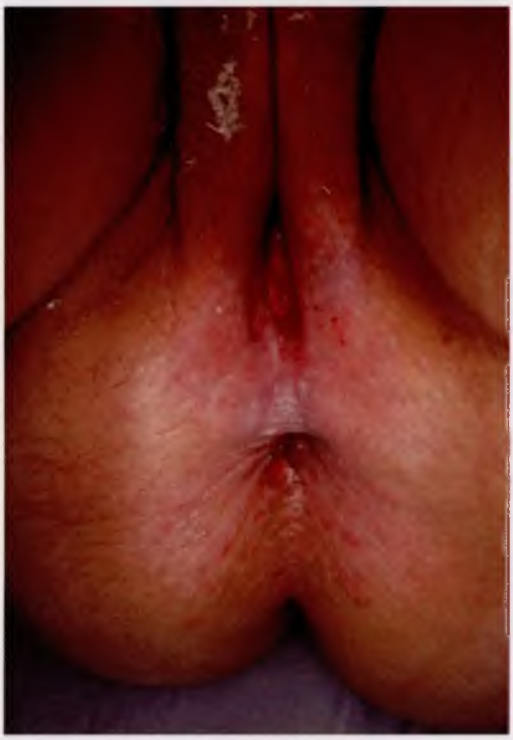

Figure 3 Lichen sclerosus.

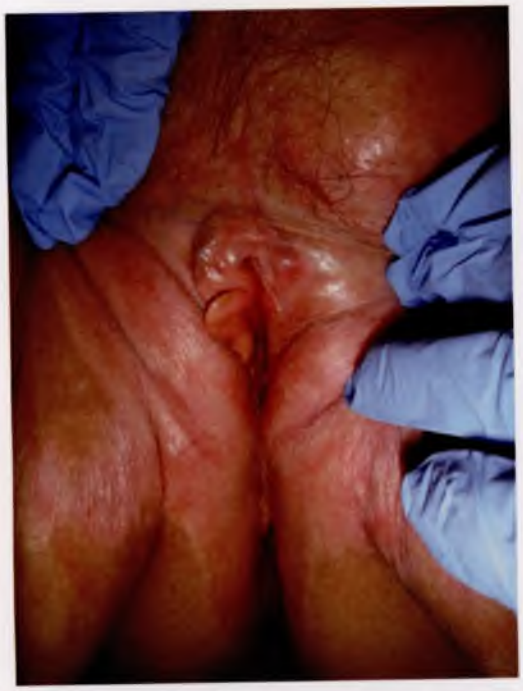

Figure 4 Lichen sclerosus.

Box 2 Reducing regime of topical steroids for lichen sclerosus and lichen planus

(Adapted from see RCOG's Green-top Guideline No. 58: The Management of Vulval Skin Disorders, appendix 6)

Half to one fingertip of clobetasol proprionate 0.05% may be applied to the affected areas:

- Once daily for the first month
- Alternate days for the following month
- Twice weekly for the following month
- Gradually decreasing to occasionally or not at all

If a flare up occurs following completion of the four-month reducing regime, clobetasol may be used daily for 2 weeks, then reduced as above.

porcelain-white scarring (hyperkeratosis), purpurae, atrophy, and eventually architectural changes. Late presentation is common, and therefore signs are often easily recognisable. Treatment with a reducing regime of topical potent steroid ointment (clobetasol proprionate) (Box 2) often leads to symptom resolution, although relapse is common. In steroid-resistant lichen sclerosus, topical calcineurin inhibitors may be trialled, usually under specialist supervision. Emollients and soap substitutes are also important. Lichen sclerosus may progress to squamous cell carcinoma in 1–4 per cent of women; however, this is less likely with prompt diagnosis and treatment. Therefore, lichen sclerosus should treated early and monitored carefully.

Lichen planus

Lichen planus (Figs 5 and 6) is a common dermatosis of unknown aetiology which may affect the vulva in isolation or in conjunction with other epithelial surfaces. Distinguishing lichen planus from lichen sclerosus can be difficult, as both may be destructive and are intensely pruritic. Lichen planus on the vulva may present as a lacy (reticular), white hyperkeratosis known as Wickham's striae. This may be similar to oral lichen planus, which is also seen in 30 per cent of patients, and may help in distinguishing between the two disease processes. Inflammation of the skin may result in a purplish (violaceous) colour. Classical lichen planus does not result in changes to the vulval architecture, while erosive lichen planus may result in erosions and architectural changes; however, the late signs of lichen sclerosus (porcelain-white cigarette-paper scarring) are not seen. Vulval biopsy

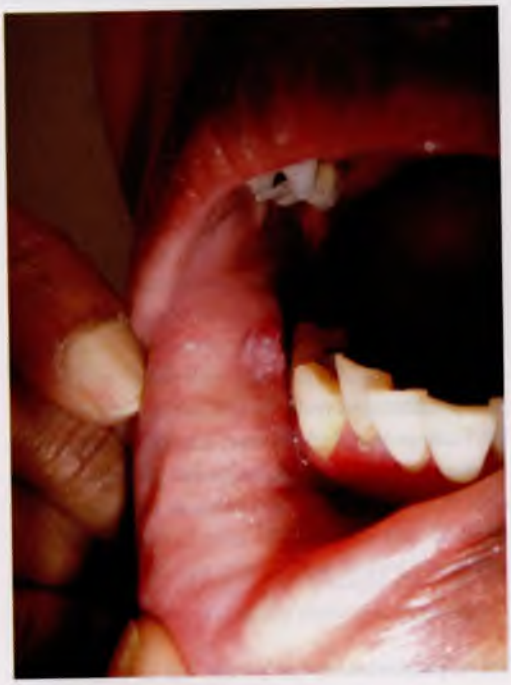

Figure 5 Oral manifestation of lichen planus.

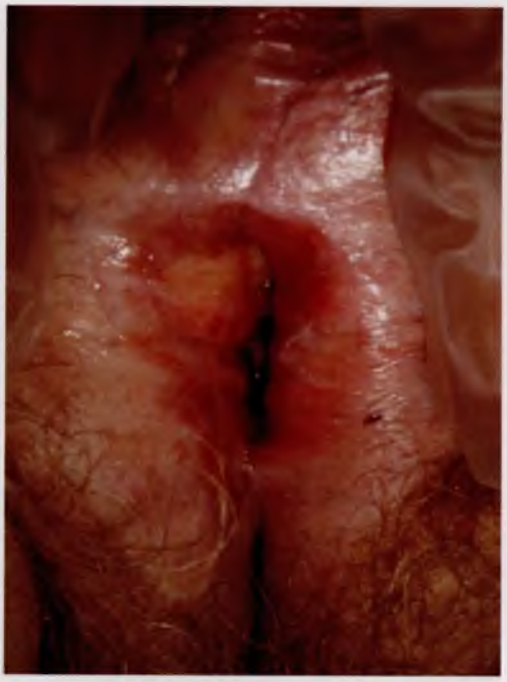

Figure 6 Erosive lichen planus.

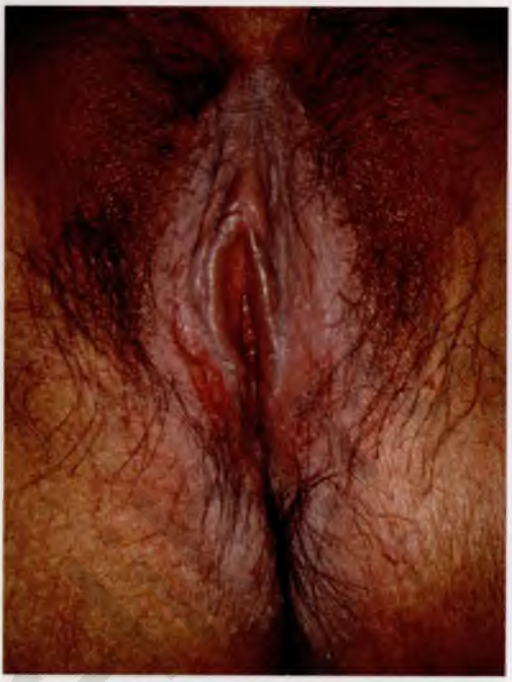

Figure 7 Lichenification of the vulval skin plus fissuring due to chronic itch/scratch problem – lichen simplex chronicus.

may be needed to histologically distinguish between lichen planus and lichen sclerosis when this cannot be achieved clinically. Classical lichen planus is usually self-limiting, while persistent erosive vulval lichen planus may require treatment with a reducing regime of potent topical steroids similar to that used in lichen sclerosus (see Box 2). Neoplastic change in lichen planus is thought to be less common than in lichen sclerosus; therefore, self-surveillance is usually sufficient with a long-term follow-up.

Lichen simplex chronicus

Repeated scratching of the vulval skin due to contact irritants, or even stress or habit in the case of resolved eczema, can lead to lichen simplex chronicus, or LSC (Fig. 7). Vulval LSC presents with severe and persistent pruritus, and vulval examination reveals similar findings to vulval eczema. Advice regarding not scratching and strategies to enable this, and avoidance of irritants, soap substitutes, and emollients are often all that is needed to treat LSC, but antihistamines and topical steroids may also be required.

Psoriasis

Vulval psoriasis is not only itchy, but also tender. On the mons it appears as scaly, red, and well-demarcated lesions similar to psoriasis at other sites on the body, while on the vulval mucosae it has a beefy red appearance similar to that of flexural psoriasis. Treatment with moderately potent topical steroids, calcipotriene and emollients is helpful. Second-line treatments involve phototherapy, methotrexate, and ciclosporin. These should be reserved for refractory cases and administered under specialist supervision, especially if the patient is pregnant or is trying to conceive.

Plasma cell (Zoon's) vulvitis

Plasma cell vulvitis is less common than but analogous to Zoon's balanitis in men. Chronic inflammation results in multiple red patches, pruritus, and superficial dyspareunia. Treatment with emollients and topical steroids may be of benefit.

Infections

A number of sexually transmitted and non-sexually transmitted infections may cause pruritus.

Candidiasis

Vulvovaginal candidiasis (thrush) is a common infection caused by an overgrowth of *Candida* species, most

commonly *C. albicans*. Vulvovaginal candidiasis is characterised by a curdy white discharge which leads to pruritus and soreness. It may be associated with diabetes, antibiotic use, or pregnancy. Treatment with topical and/or systemic imidazoles is usually curative; recurrence is common, however. Some advocate complementary medicine, probiotics, and yeast-free diets. However, there is no evidence as to their effectiveness.

Scabies and pubic lice

Scabies and pubic lice may be acquired through close contact, including sexual activity. Treatment involves the use of topical delousing agents.

Abnormal vaginal discharge

Other causes of vaginal discharge (see Vaginal discharge), such as bacterial vaginosis, trichomoniasis and urinary tract infections may cause pruritus vulvae and irritation.

Neoplastic disease

Vulval intraepithelial neoplasia (VIN) typically presents with leucoplakia, persistent erosions, and plaques, which may be itchy and uncomfortable. VIN can be divided into two main types:

- Usual type VIN: more common in younger women and associated with human papilloma virus (HPV) types 16, 18, and 31.
- Differentiated type VIN: less common and not associated with HPV infection. Biopsy is essential for diagnosis and classification.

Lesions should be biopsied to make a definitive diagnosis and to rule out underlying invasive malignancy. Local surgical excision of the lesions is the recommended management of VIN; however, topical treatment with imquimod may be preferred due to its reduced impact on sexual activity and psychological well-being. Long-term specialist follow-up is needed, as there is a risk of progression to invasive malignant disease.

Extramammary Paget's disease

Vulval extramammary Paget's disease is characterised by pruritic eczematous lesions. Surgical excision of the lesion is both therapeutic and diagnostic, allowing the identification and treatment of associated adenocarcinoma. If invasive malignancy is ruled out, alternative non-surgical treatments, such as photodynamic therapy and imiquimod, may be considered. Ongoing follow-up is important.

Vulvodynia

Vulvodynia is the persistent discomfort of the vulva that cannot be attributed to any clinical or pathological diagnosis. It is most frequently described as a burning sensation, although itch, stinging, pain, or discomfort may be reported (see Vulval pain).

Patient advocate groups

Candidiasis: www.candida-society.org.uk
Eczema: www.eczema.org
Herpes: www.herpes.org.uk
HIV: www.tht.org.uk
Lichen sclerosus: www.lichensclerosus.org.uk
Psoriasis: www.psoriasis-association.org.uk
Vulvodynia: www.vulvalpainsociety.org
VIN: www.macmillan.org.uk

Further reading

Royal College of Obstetricians and Gynaecologists. Green-top Guidelines 58: The Management of Vulval Skin Disorders. 2011. Available online at www.rcog.org.uk

VULVAL PAIN

Karen Gibbon and Sian Evans

Vulval pain affects a significant number of women and can negatively impact quality of life and sexual function. Management should therefore take a holistic approach. Vulval pain may be due to a number of specific disorders or pain syndromes, such as vulvodynia or vestibulodynia (see Box 1). Previously used terms such as vestibulitis should be avoided.

Assessment

Women may present with vulval pain alone or in conjunction with other symptoms such as vulval skin changes, itching, or vaginal discharge. In addition to assessing the nature of the pain, one should also determine:

- any triggers (e.g. sexual contact or tampon use);
- precipitating events (including physical or psychological trauma);
- the impact of the pain on the patient's function and well-being.

Box 1 International Society for the Study of Vulvovaginal Diseases (ISSVD) classification of vulval pain (adapted from Moyal-Barracco 2004)

Vulval pain related to a specific disorder

Infectious (see Vulval itching and Vulval ulceration)

- Sexually transmitted
  - herpes simplex virus
  - lymphogranuloma venereum
  - granuloma inguinale
  - chancroid
  - syphilis
- Non-sexually transmitted
  - candidiasis
  - tuberculosis
  - fununculosis
  - diphtheria
  - apthous ulcers

Inflammatory

- Lichen planus
- Lichen sclerosus
- Immunobullous disorders
- Crohn's disease
- Lipschütz ulcers
- Behçet's disease

Neoplastic (see Vulval swellings)

- Squamous cell carcinoma
- Basal cell carcinoma
- Melanoma
- Sarcoma
- Bartholin's glands adenocarcinomas
- Vulval intraepithelial neoplasia
- Extramammary Paget's disease
- Undifferentiated tumours
- Possible secondary tumours

Neurological

- Herpes neuralgia
- Spinal nerve compression
- Pudendal nerve entrapment
- Pudendal neuralgia

Vulvodynia

Generalised

- Provoked (sexual, nonsexual, or both)
- Unprovoked
- Mixed (provoked and unprovoked)

Localised (vestibulodynia: previously known as vulval vestibulitis, clitorodynia, hemivulvodynia, etc.

- Provoked (sexual, nonsexual, or both)
- Unprovoked
- Mixed (provoked and unprovoked)

Examination should include inspection of the vulval skin, speculum and bi-manual examination, and inguinal lymph node palpation (Fig. 1).

Vulvodynia

Vulvodynia is pain or discomfort of the vulva in the absence of any pathological cause. It is most frequently characterised as a burning sensation, but may be described as pain, stinging, or irritation over a prolonged period of time (months or years). It can be classified based on the area of the vulva affected and factors provoking the pain (Box 1). Alternatively women may repeatedly report developing and treating thrush or a urinary tract infection, with no or partial response to therapy. Examination of the vulva does not usually reveal any architectural or skin changes, but does allow the site of pain to be elicited and the pelvic floor muscle tone to be assessed. Application of gentle pressure with a cotton bud may allow the exact site of pain to be determined. The diagnosis is clinical in nature. Management usually requires a combination of conservative and pharmacological measures. All patients are likely to benefit from education, support groups (e.g. www.vulvalpainsociety.org) and self care. Other conservative measures include counselling, pelvic floor physiotherapy, and chiropractic. Topical anaesthetics, such as 5% lidocaine ointment and gel can offer temporary pain relief. Pharmacological treatments include tricyclic antidepressants (typically amitriptyline) and gabapentin.

Infection

A number of infections, both sexually and non-sexually transmitted (Box 1), may result in pain, usually from ulceration or suppuration. These are discussed in detail elsewhere (see Vulval ulceration).

Inflammatory disease

Inflammatory skin disease and systemic disease can both cause vulval pain, often through ulceration (see Vulval ulceration) and excoriation (see Vulval itching).

Neoplasia

Neoplastic lesions of the vulva can give rise to pain (Box 1). These are discussed in detail elsewhere (see Vulval swellings).

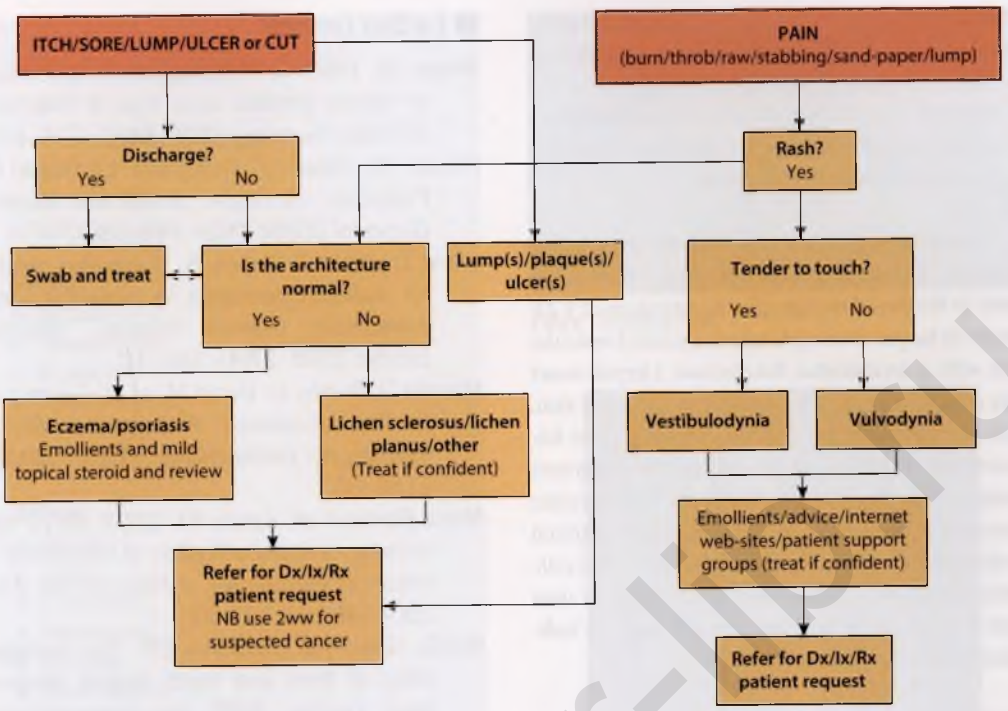

Figure 1 Algorithm for vulval pain investigation.

Neurological conditions

Pudendal nerve entrapment and pudendal neuralgia

Pudendal neuralgia is pain in the distribution of the pudendal nerve (the anogenital area including the vulva, Fig. 2), typically described as superficial, burning, or paraesthesia. It can be unilateral or bilateral and radiate deep or into the thighs. Pudendal neuralgia most commonly results from pudendal nerve entrapment or damage, but can be caused by herpes neuralgia, stretch neuropathy, and radiotherapy. Diagnosis may be clinical or involve electrophysiological studies or magnetic resonance neurography. Treatment may involve a combination of conservative measures, such as physiotherapy, chiropractic, and acupuncture, and pharmacological treatments, including tricyclic antidepressants and gabapentin. Pudendal nerve blocks may also be used both therapeutically and diagnostically.

Herpes neuralgia

Herpes simplex virus (HSV) commonly causes pain when it is active through ulceration (see Vulval ulceration). HSV lies dormant in the dorsal root ganglia and can cause symptoms of neuralgia in between

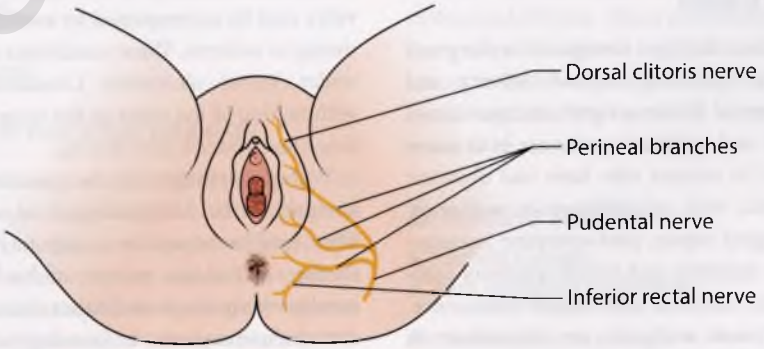

Figure 2 The distribution of the pudendal nerve.

recurrent episodes of genital herpes. Additionally, cases of HSV radiculopathy have been reported, causing both sensory and motor symptoms in the distribution of the affected nerve. Episodes of both neuralgia and radiculopathy are usually self-limiting; however, antivirals may decrease duration of the episode.

Shortly after primary infection, varicella zoster virus (VZV) causes chickenpox, after which it lies latent in the dorsal root ganglia. Reactivation of VZV results in herpes zoster (shingles), a painful vesicular rash with a dermatomal distribution. Herpes zoster may affect any dermatome, including the vulval skin. Post-herpetic neuralgia describes persistent pain following the resolution of the rash and is a common complication. The risk of developing post-herpetic neuralgia is thought to be decreased with antiviral treatment (e.g. aciclovir) of herpes zoster. Tricyclic antidepressants or gabapentin may be used to treat post-herpetic neuralgia, and opioids may be indicated if these do not help.

Spinal nerve compression

Compression or irritation of the second to fourth sacral nerve roots (S2-4) which form the pudendal nerve can cause lower back pain radiating to the anogenital (including vulval) area. The pain may be described as burning, numbness, and tingling. The sacral nerve roots may be compressed by herniated intervertebral discs, spinal stenosis, malignancy, and metastatic growths, among other causes. Diagnosis is clinical, and magnetic resonance imaging (MRI) of the lumbosacral spine may be helpful in severe and persistent disease. Treatment depends on the cause of the sacral nerve root irritation or compression and is usually undertaken by the patient's general practitioner or an orthopaedic surgeon.

Obstetric trauma

Perineal pain is a common complaint in the postpartum period following vaginal delivery and may persist beyond this in a significant number of women. Acute and persistent pains are both more likely to occur in women who have had obstetric perineal trauma, such as episiotomies and tears. Following surgical repair, post-operative management includes laxatives and broad-spectrum antibiotics to avoid infection and wound dehiscence. Physiotherapy and analgesia are important in restoring function and pain management.

Further reading

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VULVAL SWELLINGS

Tony Hollingworth

The differential diagnosis of vulval swellings includes not only tumours of the vulva itself, but also swellings that appear at the vulva as a result of the displacement of other structures, as in cases of uterine prolapse and cystocoele (see Prolapse of uterus and vagina). Hernias into this region can occur. Inflammatory lesions and ulceration of the vulva may be accompanied by swelling of the vulva owing to oedema. These conditions are considered under Vulval ulceration. Conditions presenting with itching of the vulva as the main complaint are described under Vulval itching.

Vulval swellings may be specific to the vulva anatomy or be dermatological in origin (Box 1). They may be benign or malignant, which can be further divided into primary and secondary. These conditions are diagnosed either clinically, related to their anatomical site, or histologically by excision biopsy.

Box 1 Classification of vulval swellings

Infective
- Bartholin's abscess
- Warts (condyloma acuminatum)

Cystic
- Bartholin's cyst
- Sebaceous cyst
- Mucous cyst
- Implantation cyst
- Dermoid cyst
- Hydrocoele of the canal of Nuck vestigial cyst

Benign
- Fibroma
- Lipoma
- Fibromyoma
- Hidradenoma
- Papilloma
- Lymphangioma
- Myxoma
- Angioma
- Melanoma benign
- Neuroma
- Caruncle

Malignant
- Squamous cell carcinoma
- Rodent ulcer – basal cell carcinoma
- Adenocarcinoma
- Sarcoma
- Melanoma – malignant
- Choriocarcinoma

Cystic swellings

- Bartholin's cyst.
- Sebaceous cyst.
- Mucous cyst.
- Implantation cyst.
- Dermoid cyst.
- Hydrocoele of the canal of Nuck vestigial cyst.

The commonest one is a Bartholin's cyst (Fig. 1). This is caused by the duct opening of the Bartholin's gland becoming blocked, thus producing a swelling in the posterior third of the labium majus. This projects medially so as to encroach on the vaginal entrance and may cause dyspareunia. It is not particularly tender unless it becomes infected and forms an abscess.

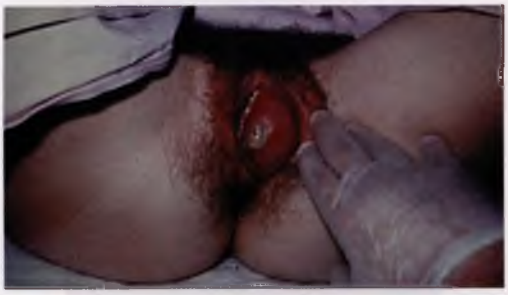

Figure 1 Bartholin's cyst.

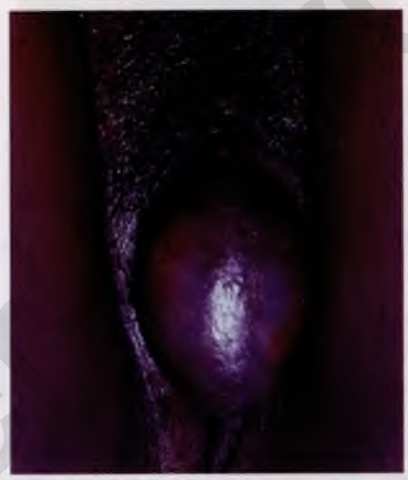

Figure 2 Vulval cyst following female circumcision; the content was old blood.

The cyst tends gradually to increase in size, causing local discomfort, until marsupialisation is performed. This results in a new duct being formed.

Sebaceous cysts are fairly common, affecting the labia majora as a rule. They may occur in groups. Mucous, inclusion, implantation (Fig. 2), and dermoid cysts also occur. The true nature of these cysts is usually known only through histological examination. A very uncommon swelling in the vulva is a cyst in the canal of Nuck. This is a peritoneal diverticulum that passes through the inguinal canal, and swelling occurs in the labium major owing to a persistent processus vaginalis. It is essentially a type of hernia and needs to be treated accordingly.

Infective swellings

- Bartholin's abscess.
- Warts (condyloma acuminatum).

Bartholin's abscess presents as an extremely painful swelling in the region of Bartholin's gland, which

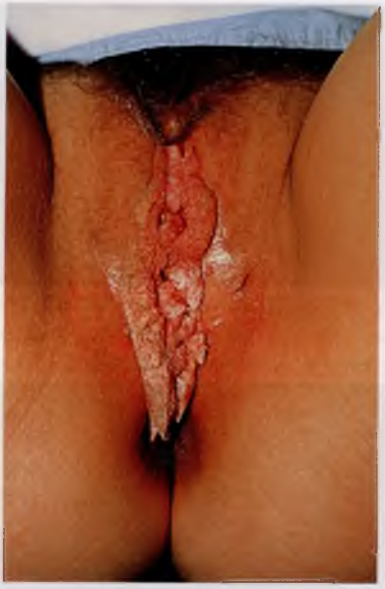

Figure 3 Vulval warts.

occurs at the entrance to the vagina. Pressure on the gland causes much pain, and the area appears reddened. The duct of the gland has become blocked and the secretions within the gland infected. It may discharge by itself; if not, treatment is surgical in the form of marsupialisation to create a new duct. Recurrence may occur.

Warts on the vulva are usually multiple (Fig. 3). They are caused by the human papillomavirus types 6 and 11, and are almost invariably transmitted sexually. They may spread throughout the lower genital tract and anal region. They have been associated with premalignant disease of the cervix. Vulval warts may proliferate and coalesce, in which case they are referred to as condyloma acuminata. This situation can be problematic in pregnancy and in patients who are immunocompromised (e.g. human immunodeficiency virus or patients with systemic lupus erythematosus on long-term steroids).

Blood cysts

- Varicocoele.
- Traumatic haematoma.
- Endometrioma.

Varicocoele of the vulva occurs mainly in pregnancy and can become worse with successive pregnancies. They give a typical varicose appearance in the labia majora, and the patient can become conscious of an uncomfortable swelling on standing. The veins seldom rupture during delivery. Varicocoele must be distinguished from an inguinal hernia extending into the labium majus and from a cyst of the canal of Nuck (the processus vaginalis, which has failed to become completely obliterated). Both of the latter tend to involve only the anterior parts of the labium majus, but all these conditions extend to the groin. Whereas a hernia is reducible as a rule, a cyst of the canal of Nuck is not. Inguinal hernias usually disappear as pregnancy progresses, but varicocoeles become worse. If a hernia contains bowel, it is resonant to percussion. A strangulated hernia will not be reducible, but the accompanying acute symptoms and the history should make the diagnosis clear.

A haematoma of the vulva may follow delivery or occur as the result of direct trauma. It is recognised as a bluish swelling, which is painful and tender, and spreads up into the pelvis by the side of the vagina. The appearance is characteristic, and the diagnosis is made on the history. An endometrioma is a rare cause of a blood-containing cyst on the vulva and is seldom seen as an isolated finding.

Benign new growths

- Fibroma.
- Fibromyoma.
- Lipoma.
- Hidradenoma.
- Papilloma.
- Lymphangioma.
- Myxoma.
- Angioma.
- Melanoma.
- Neuroma.
- Caruncle.

As the vulva comprises skin, any swelling that can occur in a skin appendage can be found in the vulval region. Both fibroma and lipoma are seen in the vulva, and may become pedunculated. They may occur at any age, are soft and oval or rounded, and are covered by vulval skin. They may grow slowly to reach the size of a fist. A lipoma is usually broader based than a fibroma.

Several other benign swellings are found on the vulva. They are usually solitary and small (about 1 cm in diameter) and their nature is confirmed by histology. A papilloma is a sessile benign tumour of the skin of the labia in women of middle or old age. A hidradenoma is a tumour of sweat gland origin, which may be solid or cystic, and which may ulcerate

to allow a red papillomatous growth to be extruded. When ulcerated, it may suggest the diagnosis of carcinoma clinically. Biopsy resolves the problem. Less commonly, fibromyoma, myxoma, angioma, lymphangioma, benign melanoma, and neuroma are found, each distinguished by microscopic examination of the excised lesions.

Tumours at the urethral meatus

Urethral caruncles are frequent, especially in older women. A caruncle appears as a small, reddish, sessile growth arising from the posterior wall of the urethral meatus, causing bleeding and painful micturition. It is often very tender but may be symptomless. It is usually granulomatous, but may be polypoidal and papillomatous. It has to be distinguished from prolapse of the urethral mucosa, in which there is a ring of protruding red tissue all round the urethral opening.

Malignant new growths

- Squamous cell carcinoma.
- Rodent ulcer – basal cell carcinoma.
- Adenocarcinoma.
- Sarcoma.
- Melanoma.
- Choriocarcinoma.

It must be emphasised that cancer within the vulva is a very uncommon condition and any tumour that occurs in the skin can occur in the vulval region. The commonest type is squamous cell carcinoma, which may have been preceded by pruritus but may be completely asymptomatic (Fig. 4). It occurs mainly in postmenopausal women, usually as a single tumour, although on occasions may present as kissing ulcers. The commonest site is on the labia; it spreads locally in the first instance and then to the inguinal lymph nodes. Squamous lesions account for 85 per cent of vulval cancers, the remainder comprising tumours of the skin and vulval appendages. Other malignant tumours found in the vulva include:

- rodent ulcer (basal-cell carcinoma), forming a flat plaque with its characteristic rolled edge;
- malignant melanoma (pigmented and non-pigmented);
- adenocarcinoma arising in Bartholin's gland or in the urethra;
- sarcoma;
- undifferentiated tumours;

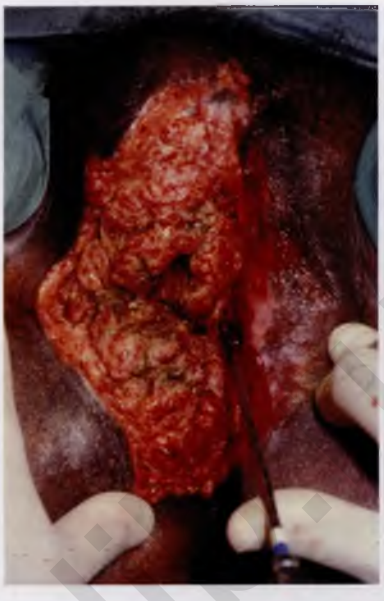

Figure 4 Extensive vulval carcinoma.

- rarely, metastatic tumours from primaries in the cervix, uterine body and ovary can occur;
- choriocarcinoma has also been described.

The diagnosis is dependent on either a biopsy or an excision biopsy. For details of the staging of tumours together with the prognosis for each tumour, see the Appendix.

VULVAL ULCERATION

Karen Gibbon and Sian Evans

Ulceration can be defined as a persistent breach in any epithelial surface, in other words, a break in any surface lining. Vulval ulceration may result from a number of causes (Box 1), including physical, infective, and neoplastic. Diagnosis will usually be made from taking a history and examining the patient. The investigations that may be necessary include appropriate microbiology and ultimately biopsy.

Infective – sexually transmitted

Up to one third of patients diagnosed with a sexually transmitted infection (STI) may have further concomitant STIs. Therefore referral to sexual health services for screening, treatment, and contact tracing should be considered in patients diagnosed with or

Box 1 Causes of vulval ulceration

- Physical
  - pressure – secondary to sensory loss
  - chemicals including urine
  - irradiation (radiotherapy injury)
  - excoriation – due to a wide range of underlying causes (see Vulval itching)
- Infective – sexually transmitted
  - herpes simplex virus
  - syphilis
  - lymphogranuloma venereum
  - chancroid
  - granuloma inguinale
  - yaws
- Infective – non-sexually transmitted
  - tuberculosis
  - diphtheria
  - candidiasis
- Systemic
  - vascular insufficiency
  - Crohn's disease
  - Lipschütz ulcers
  - Behçet's disease
- Malignancy – may produce swellings that subsequently become ulcerated
  - squamous cell carcinoma
  - basal cell carcinoma
  - melanoma
  - sarcoma
  - Bartholin's glands adenocarcinomas
  - vulval intraepithelial neoplasia
  - extramammary Paget's disease
  - undifferentiated tumours
  - possible secondary tumours

at risk of STIs. Patients should be advised to practice abstinence until both they and their partner(s) have been screened and completed treatment.

The following takes reference from national guidance produced by the British Association for Sexual Health and HIV (www.bash.org).

Genital herpes

Genital herpes manifests as vesicular eruptions, which rapidly erode, resulting in painful shallow ulcers anywhere on the vulva or vagina. A primary episode of herpes may occur 2–12 (average 4) days following primary infection with herpes simplex virus (HSV) (Fig. 1); however, 80 per cent of infections are asymptomatic. Following infection,

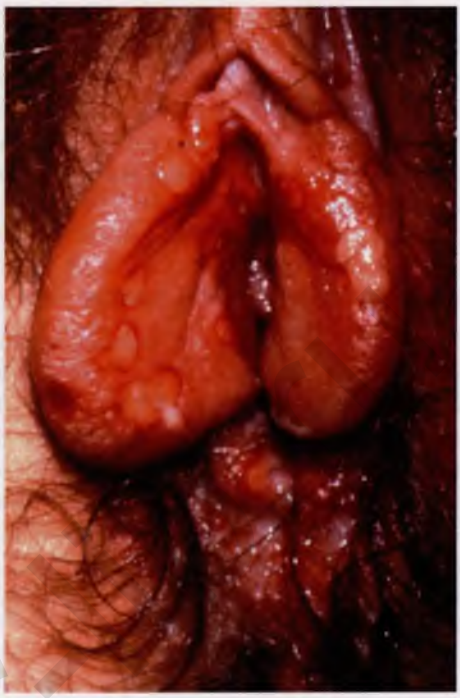

Figure 1 Genital herpes.

HSV lies latent in the sensory ganglia and reactivates periodically to cause symptomatic recurrent episodes or asymptomatic viral shedding. Primary infections are more likely to be bilateral and have systemic symptoms of inguinal lymphadenopathy, fever, and general malaise, lasting between 10–20 days, while recurrent episodes are usually shorter (7–10 days), unilateral, and without systemic symptoms. Recurrences occur on average every 3 months in HSV-2 and annually in HSV-1. Diagnosis is usually by taking a swab from the lesion and using a polymerase chain reaction (PCR) method to look for herpes DNA. Genital infection with HSV-1 or HSV-2 is equally commonly. Transmission most commonly occurs from direct sexual contact. Vertical transmission may occur if primary infection occurs or lesions are present at the time of delivery; this is avoided by the use of antivirals and caesarean section where appropriate.

Treatment with a 5-day course of antivirals, such as aciclovir, decreases the severity and duration of episodes and helps avoid complications such as urinary retention due to autonomic neuropathy and aseptic meningitis. Symptomatic relief with analgesia and topical lidocaine is also important. Prophylactic antivirals may be used if a patient experiences more than 6 recurrent episodes in a year.

Syphilis

Primary syphilis typically gives rise to a single, painless indurated ulcer with a clear serous discharge, known as a chancre. It appears between 10 and 90 (average 21) days following infection. Less commonly, chancres may be painful, multiple, and destructive; therefore, any anogenital ulcer should be considered to be due to syphilis until proven otherwise. Genital lesions in women often escape notice because they are hidden inside the vagina or on the cervix. A chancre must be distinguished from an epithelioma. If an epithelioma is suspected, both the ulcer and swelling should be excised and examined histologically. The serous fluid from a chancre contains the spirochete *Treponema pallidum*, which can be seen under a microscope with the aid of dark ground illumination. Serological testing with treponemal enzyme immunoassay (EIA) is recommended if primary syphilis is suspected. Antitreponemal EIA for IgM is usually positive 2 weeks following infection and IgG by 4–5 weeks. The currently recommended serological tests to confirm diagnosis include the Venereal Disease Research Laboratory/rapid plasma reagin test (VDRL/RPR), *Treponema pallidum* particle agglutination assay (TPPA), or *Treponema pallidum* particle haemagglutination assay (TPPHA). To exclude primary syphilis in the sexual contacts of those infected with syphilis, or in patients with dark-ground negative ulcerative lesions, serological tests should be performed at 6 weeks and 3 months post presentation.

Two weeks to 6 months after the chancre has healed, the generalised cutaneous eruption of secondary syphilis appears. Numerous moist, flat-topped papules, known as condylomata latum, occur on the vulva and around the anus. In one-third of untreated cases tertiary syphilis occurs 10–30 years after the primary lesion. Treatment is with benzathine penicillin G. Pregnant women should be reviewed by fetal medicine specialists.

Lymphogranuloma venereum

Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by *Chlamydia trachomatis* serovars L1, L2, and L3. This condition is usually found in the tropical and subtropical regions of Africa, Asia, and southeastern USA. However, since 2003 there have been outbreaks in Europe, usually occurring in men who have sex with men and their female partners.

LGV occurs in 3 stages:

- Following an incubation period of 3–30 days, the initial lesion of a painless papule, pustule, or shallow erosion appears on the vulva, vagina, or cervix in females.
- Thrombolymphangitis and perilymphangitis lead to (usually unilateral) inflammation and swelling of the inguinal and femoral lymph nodes and surrounding tissues. Buboes (swellings of the lymph nodes) may be formed, subsequently ulcerating and discharging pus, creating fistulae.
- Tertiary LGV is uncommon. Progressive spread of *C. trachomatis* leads to anogenital tissue destruction, causing proctitis and proctocolitis, granulomatis disfigurement of the vulva, strictures, fistulae, and lymph node destruction causing lymphoedema.

Diagnosis is made by positive serological testing with either complement fixation or microimmunofluorescence; culture and isolation of chlamydial organisms; and nucleic acid amplification testing (NAAT) identification of chlamydial DNA in the infected tissue. Treatment is with a 3-week course of doxycycline.

Granuloma inguinale (donovanosis)

This is a chronic STI caused by the organism *Klebsiella granulomatis* (previously known as *Calymmatobacterium granulomatis*). It is almost non-existent in the UK, but is seen in India, Brazil, Africa, and the Caribbean. Once infection is established it may resolve spontaneously or persist, causing a raised papilloma, which soon erodes into an ulcer with a friable, serpiginous outline. There is subsequent formation of granulation tissue in the groin, which rarely suppurates, but may lead to abscess formation and overlying skin ulceration. Complications include haemorrhage, scarring, squamous cell carcinoma, inguinal lymph node enlargement, and spread of infection to local tissues.

Diagnosis may be made from identifying Donovan bodies in a smear/scraping or biopsy from the ulcer. Donavan bodies are gram-negative pleomorphic *K. granulomatis* bacteria with bipolar densities in large histiocytes. Recommended treatment regimes include ciprofloxacin and azithromycin for at least 3 weeks. Other options include ceftriaxone and doxycycline.

Chancroid

This is a very common cause of genital ulceration in tropical parts of the world and usually occurs 3–10 days after infection. It begins as single or multiple

vesicopustules, which become tender punched-out ulcers or saucer-shaped ragged ulcers with a necrotic base which bleeds easily on contact and has purulent discharge. It is most commonly seen on the fourchette of the vagina. There may be associated painful inguinal adenitis, which may form buboes that break down and discharge pus. The purulent discharge from both the ulcer and buboes contain the causative organism, Ducrey's bacillus (*Haemophilus ducreyi*), a gram-negative coccobacillus. Diagnosis may be made by culture, microscopy, or PCR. Appropriate antibiotics include a one-off dose of azithromycin or ceftriaxone or courses of ciprofloxacin or erythromycin. Co-infection with HIV, HSV, and/or syphilis is common. Lymph nodes may need to be biopsied to exclude neoplasia.

Yaws

Yaws is endemic in several tropical countries, where over 75 per cent of those affected are under 15 years old. Transmission is by direct contact and is often non-sexual. A single painless ulcer or papilloma develops 9–90 (average 21 days) after infection and subsequently produces lesions similar in appearance to the condyloma latum of secondary syphilis. If left untreated, one in ten develop bone, joint, and soft tissue deformities. It is caused by a spriochaetal organism, *Treponema pertenue*. The diagnosis can be confirmed with the serological tests for venereal syphilis. First-line treatment is with a benzathine penicillin or azithromycin.

Infection – non-sexual

Aphthous ulcers

These are analogous to the small painful ulcers, which can be found in the mouth. The exact cause is not clearly defined but is thought to be a disturbance in the immune system by some external factor. Treatment is symptomatic.

Tuberculosis

This is a rare cause of vulval ulceration and may be associated with inguinal lymphadenopathy. It usually arises from haematogenous spread from primary tuberculosis in other organs, such as the lungs. Primary vulval lesions are very rare, as are ascending infection or vertical spread. The ulcers are indolent and can be diagnosed with certainty only on microscopic section of a biopsied part of the lesion.

Furunculosis

These are boils caused by staphylococcal infection of hair follicles. They are common and affect the labia majora in particular. Shaving the area may predispose to this problem.

Diphtheria

This condition is an upper respiratory tract infection from *Corynebacterium diphtheriae*. It causes a low-grade fever and produces ulceration with membranous exudates. It is highly contagious, but vaccination has reduced the incidence dramatically. It can cause vulval ulceration. The diagnosis is on identifying the organism, and treatment is with either erythromycin or procaine penicillin.

Candidiasis

Mycotic and diabetic vulvitis due to *Candida* species can cause soreness and pruritis of the vulva with erythema, excoriation, and oedema of the skin and a characteristic white, curd-like discharge containing the mycelium of *C. albicans* (see Vulval itching).

Systemic disease

Behçet's syndrome

Behçet's syndrome is a rare, chronic, multisystem disorder resulting in blood vessel damage (Fig. 2). It is characterised by painful recurrent oral and vulval ulceration; skin and eye lesions such as uveitis, retinitis, and iritis may also develop. It is difficult to diagnose, as there are no specific confirmatory tests. It can be treated with corticosteroids. More information can be obtained from www.behcets.com.

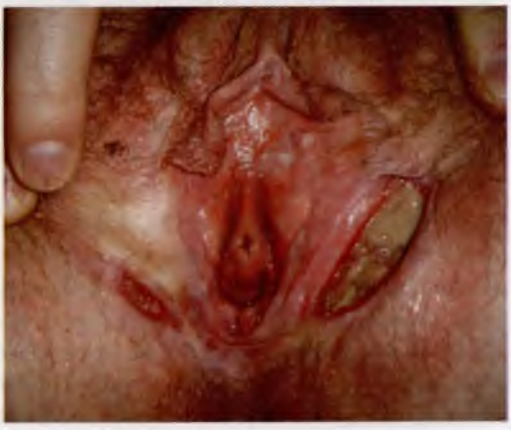

Figure 2 Behçet's syndrome.

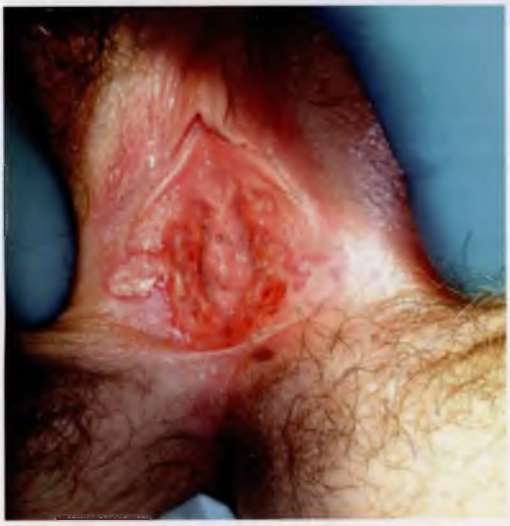

Figure 3 Lipschütz ulcer.

Crohn's disease

The vulva and perineum may be affected in up to 30 per cent of patients, and this may pre-date gastrointestinal symptoms. The vulval skin is oedematous with ulcers which appear like knife cuts in the skin; however, discharging sinuses and irregular ulcers are more common. Treatment is usually with metronidazole and immunomodulators; surgery should be avoided. This problem is rarely seen by gynaecologists. Access www.crohns.org.uk for further information.

Lipschütz ulcers

These mainly occur on the labia minora and are of acute onset with an associated fever and lymphadenopathy (Fig. 3). It is a very rare cause of genital ulceration and has been reported as associated with typhoid and paratyphoid fever, with salmonella being the causative organism.

Malignancy

There are a number of types of tumours that arise on the vulva and may subsequently ulcerate (see Box 1; see Vulval swellings).

Further reading

British Association for Sexual Health and HIV. National Guideline for the Management of Genital Herpes, 2007. Available online at www.bashh.org.uk

British Association for Sexual Health and HIV. National Guidelines for the Management of Syphilis, 2008. Available online at www.bashh.org.uk

British Association for Sexual Health and HIV. National Guideline for the Management of Lymphogranuloma Venereum (LGV), 2006. Available online at www.bashh.org.uk

British Association for Sexual Health and HIV. National Guideline for the Management of Donovanosis (Granuloma Inguinale), 2011. Available online at www.bashh.org.uk

British Association for Sexual Health and HIV. National Guideline for the Management of Chancroid, 2007. Available online at www.bashh.org.uk

Royal College of Gynaecologists. Green-top Guideline 58: The Management of Vulval Skin Disorders. 2011. Available online at www.rcog.org.uk

World Health Organisation. Fact Sheet 316: Yaws. 2012. Available online at www.who.int

Appendix: Definitions and Tumour Staging

Definitions

Abduction Movement of an extremity (e.g. arm) on a transverse plane away from the axis or midline, where the axis lies on the frontal or sagittal plane.

AC The *abdominal circumference* is the perimeter of the fetal abdomen at the level of the stomach, the intrahepatic umbilical vein, and the confluence of the right and left portal veins. At 20 weeks' gestation, the average AC is 150 mm, and there is usually an increase of 10–12 mm per week.

Adduction Movement of a limb or body part towards the midline.

AFI The *amniotic fluid index* is the sum of the maximum vertical amniotic depth measure in each quadrant (see Amniotic fluid abnormalities for details and values).

AFP *Alpha-fetoprotein* is a glycoprotein produced by the fetal yolk sac, fetal gastrointestinal tract, and eventually the fetal liver. It is measured in the quadruple test for Down's syndrome, where the serum level is usually low, and is used as a marker for hepatocellular carcinoma, endodermal sinus tumours and, more rarely, mixed Müllerian tumours. The maternal serum AFP level rises with gestational age. It is elevated in multiple pregnancies and in a number of fetal abnormalities, including neural tube defects (spina bifida and anencephaly) and abdominal wall defects.

Alloimmunisation An immune response to foreign antigens from members of the same species. e.g. transplant rejection reaction.

Aneuploidy The chromosome number not being an exact multiple of the number characteristic to that species, e.g. extra (Down's syndrome) or fewer (Turner's syndrome).

Aplastic The inability of stem or precursor cells to generate mature blood cells.

Asynclitism The posture of the baby's head in which one parietal bone is at a lower level than the other, owing to lateral inclination of the head.

Atopy Any allergy involving an inherited immunoglobulin of the IgE type that predisposes a person to certain allergic responses.

Attitude The relationship of the parts of the baby to itself, e.g. flexed or extended head.

Azotaemia Abnormally high levels of nitrogen-containing compounds in the blood (e.g. urea and creatinine).

BPD The *biparietal diameter* is an ultrasound measurement of the fetal head from the outer edge of the cranium nearest the transducer to the inner aspect of the cranium furthest away. At 12 weeks' gestation, it measures 20 mm, and there is an increase of 3–4 mm every subsequent week.

CA-125 The abbreviation for cancer antigen 125, which is a mucinous glycoprotein produced by the *MUC16* gene. It is used as a tumour marker for ovarian cancer; though sensitive, it is not specific for this type of tumour, as it is elevated in only 80 per cent of cases. It may also be raised in tumours arising from the endometrium, Fallopian tubes, lungs, breast, and gastrointestinal tract. It may also be elevated in benign conditions that cause peritoneal irritation, e.g. endometriosis, tuberculosis of the pelvis, pelvic inflammatory disease, appendicitis, and pregnancy. It is especially useful in monitoring response to treatment. The normal range is 0–35 U/mL.

Caput Oedema of the fetal scalp (see Fig. 3 in Labour, prolonged).

Chloasma A patchy brown or dark brown discoloration of the skin occurring on the face and usually related to the hormonal changes of pregnancy.

Contralateral On the opposite side of the body.

CRL *Crown–rump length* is an ultrasound measurement from the apex of the skull to the base of the torso not including the limbs. It is used as an early pregnancy dating measurement; at 6 weeks' gestation it will be 3–4 mm and 9–10 mm by 7 weeks.

Denominator The bony landmark on the presenting part of the fetus used to define the position. It is usually a midline structure, e.g. occiput for a cephalic presentation, mentum or chin when it is a face presenting, or the sacrum if a breech.

Diastasis Separation of parts of the body that are normally joined together (e.g. symphysis pubis joint).

Diathesis A predisposition to a specific problem.

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Diastasis Separation of parts of the body that are normally joined together (e.g. symphysis pubis joint).

Diathesis A predisposition to a specific problem.

Diplopia The perception of two images of a single object.

Dysgenesis Abnormal development of tissue, especially an epithelium.

Dystocia An abnormal labour.

Effacement The thinning or taking up of the cervix, which in primips usually occurs before dilatation.

Embryo A conceptus between the time of fertilisation up to 10 weeks' gestation.

Engagement When the widest diameter of the presenting part of the fetus is through the pelvic brim. In the case of a vertex presentation, this is the biparietal diameter; for a breech, it is the bitrochanteric diameter.

Fetal weight The weight of a fetus at birth. The expected 50th centile fetal weights per week of gestation are as follows:

28 weeks	1200 g
30 weeks	1500 g
32 weeks	1900 g
34 weeks	2300 g
36 weeks	2800 g
38 weeks	3200 g
40 weeks	3500 g

Fetus The embryo is termed fetus from 10 weeks' gestation until the time of birth.

Gestation sac The cavity of fluid within the uterus with an embryo present, identifiable by utrasound. At 5 weeks' gestation the diameter measures 2 mm and then increases 8–9 mm over the subsequent few weeks.

Gravidity The number of pregnancies the woman has had, including the current one, irrespective of the outcome (e.g. miscarriage, live birth, etc.).

Hamartoma A benign tumour-like nodule composed of an overgrowth of mature cells and tissues normally present in the affected part but with disorganisation and often with one element predominating.

HC The *head circumference* is an ultrasound measurement of the outer perimeter of the cranium at the level of the thalami and the cavum septum pellucidum. It measures 90 mm at 14 weeks' gestation and then increases by approximately 15 mm per week for the remainder of the pregnancy.

HCG (or **hCG**) *Human chorionic gonadotrophin* is a peptide hormone made by the embryo and subsequently the syncytiotrophoblast. Its role is to support the corpus luteum, thereby maintaining progesterone production, which in turn maintains the pregnancy. It is used in early pregnancy testing and can be detected before a menstrual period has been missed. It usually measures 1000 mIU/mL by day 32 (28-day cycle) and should reach at least 10,000 mIU/mL by day 40, when the fetal head may be visible. The quantification of HCG is useful during pregnancy as the level should double every 36–48 hours, and lack of this doubling may point to either a failing pregnancy or possibly an ectopic pregnancy. It can also be used as a tumour marker for trophoblastic disease, including hydatidiform mole and choriocarcinoma, as well as islet cell tumours.

Infant A child from birth until 1 year of age.

Intrapartum This is synonymous with labour.

Ipsilateral On the same side of the body.

Labour The process by which a baby is born. Labour can be defined as the onset of regular painful contractions with dilatation of the cervix and descent of the presenting part. The mechanism of labour in a cephalic presentation involves descent, flexion of the head, internal rotation of the presenting part, extension or crowning, restitution or external rotation of the head, and internal rotation of the shoulders.

LFTs The *liver function tests* largely remain unaltered during pregnancy except for the alkaline phosphatase level; this is raised owing to an isoenzyme produced by the placenta, which may account for half of that level.

Lie The relationship of the longitudinal axis of the fetus to the longitudinal axis of the mother, e.g. longitudinal, oblique, transverse, and unstable.

Maternal mortality The number of deaths of women while pregnant or within 42 days of termination of pregnancy irrespective of duration and site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management (but not from accidental or incidental causes) per 100,000 births (see www.CEMACH.org.uk). They are usually divided into:

- **Direct obstetric deaths** Deaths resulting from obstetric complications of the pregnant state, e.g. amniotic fluid embolism.

- **Indirect obstetric deaths** Deaths resulting from previously existing conditions or those developing during the pregnancy which were not due to direct obstetric causes but were aggravated by the physiological effects of the pregnancy. An example would be maternal cardiac disease.
- **Late obstetric deaths** Deaths which occur between 42 days and 1 year after delivery owing to direct or indirect maternal causes.
- **Incidental or accidental deaths** Deaths from a cause completely unrelated to pregnancy in women who happened to be pregnant at the time. Examples are road traffic accidents and accidental overdoses.

Microangiopathy Disease affecting small blood vessels.

Miscarriage The spontaneous loss of a pregnancy prior to 24 weeks' gestation or expulsion/extraction of a fetus weighing 500 g or less.

Moro reflex An infantile reflex normally present in all newborns and infants up to the age of about 5 months. It is used to assess neurological development: during a sudden loss of support, the infant, feeling as though it is falling, spreads out its arms (abduction), unspreads them (adduction), and cries.

Moulding The bones of the fetal skull sliding over one another (see Fig. 3, Prolonged labour). The skull bones do not usually fuse until some time after delivery, the only exception being craniosynostosis.

Multigravida A woman with a history of previous pregnancies, usually with live children; also called a multip.

Neonatal death rate The number of deaths within 28 days of birth of all live-born infants (regardless of gestation) per 1000 live births.

NICE National Institute for Health and Care Excellence.

Nuchal translucency The thickness of the cystic area posterior to the occiput, measured excluding the skin surface and the occiput. An increase in this measurement is suggestive of a chromosomal disorder, especially trisomy 21. The level usually used is below 3 mm.

Odonophagia Painful or difficult swallowing.

Parametrium The fibrous tissue that separates the supravaginal portion of the cervix from the bladder and extends on to its sides and laterally between the layers of the broad ligament, and contains the uterine artery.

Parity The number of pregnancies with a birth beyond 20 weeks' gestation or an infant weighing more than 500 g.

Perinatal death rate The number of stillbirths and first-week neonatal deaths per 1000 total deliveries.

Pinopod(e) Apical epithelial cellular protrusions of the endometrium of the uterus.

Placenta A temporary organ existing during pregnancy that allows fetomaternal exchange; also known as the afterbirth. Implantation can be low in the uterus, resulting in a placenta praevia, in which it is below the presenting part. The placenta can become morbidly adherent:

- **Accreta** Abnormal attachment of the placenta to the myometrium.
- **Increta** The placenta having invaded the myometrium.
- **Percreta** The placenta having penetrated through the myometrium.

Position The location of the denominator relative to fixed points within the maternal pelvis, e.g. occipitoanterior. It is also a term used to describe the relation of the fetal back to the right or left side of the mother.

Postmature The infant delivered after 41 completed weeks of pregnancy. It is associated with an increase in the perinatal mortality rate.

Premature The infant delivered before 37 completed weeks of pregnancy.

Presentation The part of the fetal body which is in or over the pelvic brim, e.g. cephalic or breech.

Preterm The infant delivered between 24 and 37 weeks' gestation.

Previable The infant delivered before 24 weeks' gestation.

Primigravida A woman in her first pregnancy; also called a primip.

Prognosis A forecast for the outcome of a condition.

Puerperium The time from immediately after delivery and extending for 6 weeks. It is also known as the postnatal or postpartum period.

Quadruple test The measurement of serum AFP, HCG, oestriol, and inhibin. It is used to screen for Down's syndrome. The levels change throughout gestation.

RCOG Royal College of Obstetricians and Gynaecologists.

Sclerosis Abnormal hardening of a tissue.

Semen analysis See Infertility/Subfertility for values and comments.

Station The descent of the presenting part into the pelvis measured in relation to the ischial spines in centimetres, with minus being used if above the spines and plus if below.

Stillbirth rate The number of infants born with no signs of life after 24 completed weeks' gestation per 1000 total births.

Term From 37 to 41 completed weeks of pregnancy, assuming a 28-day cycle. Term may vary between racial groups (see Prolonged pregnancy). The average time of a human pregnancy is 280 days.

TORCH Toxoplasmosis, rubella cytomegalovirus, herpes.

Trimesters The antenatal period is traditionally divided into trimesters. Each trimester is associated with particular problems:

- **First trimester** The interval from the first day of the last period to 12 weeks' gestation, assuming a 28-day cycle. It is during this period that most organogenesis occurs.
- **Second trimester** The interval between the 13th and 27th week of pregnancy.
- **Third trimester** This extends from the 28th week of pregnancy until the time of delivery.

Tumour marker A substance produced by a particular tumour, which can be measured in the serum to aid diagnosis and response to treatment of that tumour.

U&E *Urea and electrolytes* are measures of renal function. In pregnancy, there is an increase in the glomerular filtration rate and, as a consequence, the serum urea usually falls. The serum sodium, potassium, and chloride remain essentially unchanged.

Urate The serum urate level decreases during the early part of the pregnancy owing to the increase in glomerular filtration rate; however, it rises during the later stages of the pregnancy and can reach levels at term that are higher than non-pregnant values. It is useful in monitoring a woman with pre-eclampsia.

Vertex A diamond-shaped area between the anterior and posterior fontanelles and the biparietal eminences. This is the area that presents to the pelvis when the head is flexed.

Tumour staging

Staging is the means by which the extent of the cancer or tumour is assessed at the time of presentation. The following are the FIGO classifications for the four main gynaecological cancers.

Vulval cancer

Stage 0 Carcinoma *in situ*, VIN3, or severe vulval dysplasia. This would be classed as premalignant.

Stage I Tumour <2 cm and confined to the vulva or perineum

Stage IA <1 mm stromal invasion, negative lymph nodes

Stage IB >1 mm stromal invasion, negative lymph nodes

Stage II Tumour of any size with adjacent spread (lower third of urethra or vagina), negative lymph nodes

Stage IIIA Tumour of any size with positive inguino-femoral lymph nodes
- (i) 1 lymph node metastasis greater than or equal to 5 mm
- (ii) 1–2 lymph node metastases of less than 5 mm

Stage IIIB
- (i) 2 or more lymph node metastases greater than or equal to 5 mm
- (iii) 3 or more lymph nodes less than 5 mm

Stage IIIC Positive nodes with extracapsular spread

Stage IVA
- (i) Tumour invades other regional structures (upper two thirds of urethra and/or vagina), bladder mucosa, rectal mucosa, or is fixed to pelvic bone
- (ii) Fixed or ulcerated inguino-femoral lymph nodes

Stage IVB Tumour spread to the pelvic lymph nodes and/or more distant sites

Endometrial cancer

This staging is a surgically based system.

Stage I

Stage IA Tumour is confined to the uterus with no or less than half myometrial invasion

Stage IB Tumour confined to the uterus with invasion more than halfway through the myometrium

Stage II

Stage II Cervical stromal invasion but not beyond the uterus

Stage III

Stage IIIA Tumour invades the serosa or adnexa

Stage IIIB Vaginal and/or parametrial involvement

Stage IIIC1 Pelvic lymph node involvement

Stage IIIC2 Para-aortic lymph node involvement

Stage IV

Stage IVA Invasion of the bladder or the bowel mucosa

Stage IVB Distant metastases, including abdominal metastases and/or inguinal lymph nodes

Cervical cancer

This staging is based on clinical examination rather than surgical findings. It does not include lymph node involvement.

Stage 0 Full thickness of the epithelium but no invasion of the stroma – CIN3

Stage I Confined to the cervix

Stage IA Diagnosed microscopically, no visible lesions

Stage IA1 Stromal invasion <3 mm in depth and up to 7 mm horizontal spread

Stage IA2 Stromal invasion between 3 and 5 mm in depth and up to 7 mm horizontal spread

Stage IB Visible lesion or a microscopic lesion with >5 mm of depth or >7 mm horizontal spread

Stage IB1 Visible lesion 4 cm or less in greatest dimension

Stage IB2 Visible lesion >4 cm

Stage II Invasion beyond the cervix

Stage IIA1 Without parametrial invasion but involves the upper two-thirds of the vagina, <4 cm in greatest dimension

Stage IIA2 As above, but >4 cm in greatest dimension

Stage IIB With parametrial involvement

Stage III Extends to the pelvic side wall or the lower third of the vagina

Stage IIIA Involves the lower third of the vagina

Stage IIIB Extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney

Stage IV Spread has extended beyond the true pelvis or has involved the mucosa of the rectum or bladder

Stage IVA Invasion of the mucosa of the bladder or rectum and/or beyond the true pelvis

Stage IVB Distant metastases

Ovarian cancer

Stage I Limited to one or both ovaries

Stage IA Involves one ovary; capsule intact; no tumour on the ovarian surface; no malignant cells in ascites or peritoneal washings

Stage IB Involves both ovaries; capsule intact; no tumour on the ovarian surface; negative washings

Stage IC Tumour limited to both ovaries with any of the following: ruptured capsule, tumour on the ovarian surface, positive washings

Stage II One or both ovaries with pelvic extension or implants

Stage IIA Extension or implants of tumour onto the uterus, or Fallopian tumour; negative washings; no ascites

Stage IIB Extension or implants of tumour onto other pelvic structures; negative washings

Stage IIC Pelvic extensions or implants with positive peritoneal washings

Stage III Cancer spread outside the pelvis to the abdominal area, including the liver surface

Stage IIIA Grossly confined to the pelvis with microscopic peritoneal metastases beyond the pelvis

Stage IIIB Macroscopic peritoneal metastases beyond the pelvis <2 cm in size

Stage IIIC Peritoneal metastases beyond the pelvis >2 cm or regional lymph node metastases includes inguinal, pelvic, and para-aortic

Stage IV Distant metastases – in the liver parenchyma or outside the peritoneal cavity

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