

Nutrition and Health

Series Editors: Adrienne Bendich · Connie W. Bales

Carol J. Lammi-Keefe · Sarah C. Couch
John P. Kirwan *Editors*

Handbook of Nutrition and Pregnancy

Second Edition



Humana Press

Nutrition and Health

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The Nutrition and Health series has an overriding mission in providing health professionals with texts that are considered essential since each is edited by the leading researchers in their respective fields. Each volume includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data driven answers to patient/health professionals questions which are based upon the totality of evidence rather than the findings of a single study.

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To Patrick, and our sons, Liam and Christopher, for the love, support, and encouragement provided and for embracing our family mantra, "We do the best we can."

— Carol J. Lammi-Keefe

To my wife April; kids—Jennifer, Brent, Lani, and Aran; and grandkids—Hannah, Charlotte, and Addie. You are the constants, the purpose, and the inspiration of my life.

— John P. Kirwan

To my mother Sally Collins, whose caring nature, love of science and medicine, and zest for life are a daily inspiration to me.

— Sarah C. Couch

Foreword

This is not a typical handbook of nutrition and pregnancy that reviews the effect of pregnancy on nutrient requirements and how to meet those needs. Instead, it reviews the diverse nutritional *challenges* providers need to address when counseling pregnant women in developed and developing countries. The editors recognize that there is no “one-size-fits-all” approach for counseling all pregnant women about nutrition. Thus, they created a handbook that gives doctors, nurses, dietitians, and other health care professionals the information and tools they need to manage the wide range of pregnancy-related nutrition issues existing worldwide.

Unfortunately, today many women still enter pregnancy with underlying nutrition concerns that influence their metabolic adjustments to pregnancy and fetal nutrition. Fifty years ago, an insufficient nutrient intake was the primary concern. Pregnancy was thought to be a risk factor for iron-deficiency anemia, and iron supplementation was a common practice. Iron-deficiency anemia still exists, but the emphasis has shifted to the provision of *optimal* amounts without increasing adverse pregnancy outcomes due to elevated hemoglobin levels. Also, today nutritional concerns have expanded beyond iron. The unique iodine, vitamin D, and the one-carbon nutrient (folate, vitamin B12, vitamin B6, and choline) needs for maternal and fetal health are addressed in this edition. Plus, there is a new chapter on “epigenetics and diet in pregnancy” that describes the link between maternal nutrition and the long-term health of the child.

Maternal obesity is another theme throughout the handbook. Obesity, its metabolic consequences (gestational diabetes and preeclampsia), and the associated eating disorders or surgical treatment procedures all influence fetal health and subsequent growth and development of the child. Furthermore, the problem of obesity is exacerbated by the pregnancy metabolic changes that enhance maternal fat gain. In an ideal world, all women of reproductive age would receive counseling for achieving a healthy body weight prior to conception. But, given the prevalence of this problem worldwide, this is highly unlikely. For example, the World Health Association predicts that in 2030 nearly one-fifth of the women in lower income countries, such as sub-Saharan Africa, will be obese. A more feasible goal may be to use the pregnancy period as a teaching moment to improve the diet quality and

weight management of the whole family unit during and following pregnancy. The principles of nutrition described throughout this book could provide the basis for achieving that goal.

A third general theme of the handbook is the effects on pregnancy outcomes of a stressful lifestyle that many women of reproductive age are experiencing today. Depression, sleep disorders, domestic violence, and incarceration all fall into that category. Often health providers do not address these topics, even though they likely have a huge impact on diet quality and nutrient metabolism. The authors of these chapters not only review the effect of these conditions on maternal nutrition and health but, most importantly, they also suggest interventions or programs for improving the health of these women.

In summary, the 22 outstanding chapters in this book provide the latest evidence for managing the nutritional requirements of pregnant women in diverse settings worldwide. The authors recognized that one size does not fit all, and they clearly explain how to modify the dietary counseling for an individual woman's unique needs. The *Handbook of Nutrition and Pregnancy*, 2nd edition, is an excellent, easy-to-use resource for all health care providers.

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Preface

Handbook of Nutrition and Pregnancy, second edition, is written for clinicians and healthcare professionals who treat and counsel pregnant women and women of childbearing age. Reflecting new knowledge since the first edition was published in 2008, this second edition has updated recommendations, and it also includes coverage of topics that were not in the first edition, including body composition changes in pregnancy, US Hispanics and preterm births, epigenetics and diet in pregnancy, and safe food handling for successful pregnancy outcomes, as examples. This handbook is a resource for physicians, physician assistants, nurse practitioners, and dietitians, while students of nutrition and dietetics and medical and graduate students will also find this book a useful resource. Chapters provide historical perspectives and background supporting the recommendations made in each of the chapters. *Handbook of Nutrition and Pregnancy*, second edition, is a resource for practitioners and researchers all over the globe.

We live in an era of major scientific advances in which mining large data sets that include genes, metabolites, and proteins is yielding new insights into biological function as they relate to nutrition. Over the last decade, scientists have made giant steps toward individualizing nutrition in response to our growing knowledge of the human genome. It is now well recognized that prenatal and perinatal nutrition, along with environmental factors, is inextricably linked to childhood and adult obesity and chronic disease. In this new edition, we include the topic of diabetes in pregnancy and review the challenges of estimating the global prevalence of gestational diabetes, with its trends in at-risk groups. The overall objective for this new edition of the *Handbook of Nutrition and Pregnancy* is to provide current information and recommendations and to translate that information into clinically relevant practice recommendations.

This volume is arranged to address five major categories related to nutrition for successful pregnancy outcomes and also includes topics that have not heretofore been broadly written about or discussed, namely, incarcerated pregnant women, sleep during pregnancy, depression *in* pregnancy, and domestic violence during pregnancy.

Handbook of Nutrition and Pregnancy, second edition, is comprehensive with up-to-date information in twenty-two chapters written by leaders in the fields of nutrition and food science, environment, physiology, metabolism, and genetics and epigenetics while addressing the needs of women of childbearing ages and pregnant women. This volume contains information that brings the reader up to date on the state of the science and permits the reader to respond to practical queries from patients, family members, students, and researchers. It is the editors' vision that work contained in this edition will meet the needs of practitioners, researchers, and students who work with pregnant women and open the door to areas of new scientific investigation that will enhance the health and quality of life of mothers and their babies.

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Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, interchapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient as well as health professionals' questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editor(s), whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

"Handbook of Nutrition and Pregnancy, Second Edition," edited by Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan, is a very welcome and timely addition to the Nutrition and Health Series and fully exemplifies the series' goals. This volume represents a critical, in-depth review of the current life events that can adversely impact pregnancy outcomes for women across the globe. The increased risks associated with obesity during pregnancy as well as weight loss surgery are examined in detail. Ethnic dietary patterns of Hispanic women are detailed to better understand their potential effects on increasing preterm births. The medical conditions of anorexia, bulimia, and binge eating and their effects on pregnancy outcomes

are examined. Unique chapters look into the role of sleep patterns, depression, domestic violence, and pregnancy during incarceration on pregnancy outcomes. Of importance the volume also contains reference-rich chapters on the newest research concerning single as well as related nutrients including vitamin D, iodine, and iron and the B vitamins involved in one-carbon metabolism. New fields of research including epigenetics are also highlighted. Thus, the volume is designed as an important resource for physicians in many clinical fields, nutritionists and dietitians, research and public health scientists, and related health professionals who interact with women of childbearing potential as well as women who are planning pregnancy, are pregnant, and women who have given birth and are lactating. The volume provides objective and relevant information for professors and lecturers, advanced undergraduates and graduates, researchers, and clinical investigators who require extensive, up-to-date literature reviews, instructive tables and figures, and excellent references on all aspects of pregnancy, diet, and health as well as nutrition's role in enhancing the potential for optimal pregnancy outcomes. This volume is especially relevant as the number of research papers and meta-analyses in the clinical nutrition arena increases every year and clients and patients are very interested in dietary components such as vitamins and minerals, fatty acids, and protein needs during pregnancy. Certainly, the obesity epidemic remains a major concern especially as the comorbidities, such as the metabolic syndrome, gestational maternal diabetes, and type 2 diabetes prior to pregnancy, hypertension, and hyperlipidemia, are seen more frequently now than ever before in women during pregnancy. The adverse effects to both mother and child are reviewed in depth in related comprehensive chapters.

The editors of this comprehensive volume are experts in their respective fields of clinical research and practice. Carol J. Lammi-Keefe, Ph.D., is Alma Beth Clark Professor of Nutrition, School of Nutrition and Food Sciences, Louisiana State University, and Adjunct Professor at the Pennington Biomedical Research Center, Baton Rouge, Louisiana. Dr. Lammi-Keefe served as the primary editor of the first edition of the *Handbook of Nutrition and Pregnancy* that was published in 2008. For more than three decades, she has published critical studies in the areas of maternal and fetal nutrition, with an emphasis on lipids and especially omega-3 fatty acids. Her research findings include the benefit of docosahexaenoic acid (DHA) during pregnancy on infant functional outcomes, including sleep, visual acuity, problem solving, and decreased adiposity. Her research findings have been published in journals including the *American Journal of Clinical Nutrition*, the *Journal of the American Dietetic Association*, *Lipids*, the *British Journal of Nutrition*, and the *Journal of Pediatric Gastroenterology and Nutrition*. As principal investigator or co-investigator, her research support has come from the U.S. Department of Agriculture, the National Institutes of Health, and numerous foundations, boards, institutes, or industry. A current federally funded project will assess the benefit of omega-3 fatty acids in decreasing the inflammatory response in overweight pregnant women and the effect on infant adiposity.

Dr. Lammi-Keefe's professional activities include serving as Past Chair of the Health and Nutrition Division for the American Oil Chemists Society and

membership in the American Dietetic Association, American Society for Nutrition, International Society for the Study of Fatty Acids and Lipids, and International Society for Research on Human Milk and Lactation. She is a former member of the Governing Board for the American Oil Chemists Society. Prior to joining the faculty of Louisiana State University, she was a faculty member and Department Head at the University of Connecticut from 1981 to 2006 and she retains her Professor Emeritus status. In 2003 she was recognized by the university with the Chancellor's Research Excellence Award. For her research and scientific contributions, the American Dietetic Association Foundation presented her with its Ross Award in Women's Health and its Award for Excellence in Dietetic Research. In 2009, Louisiana State University cited her as a "Rainmaker."

Sarah Couch, Ph.D., R.D., is a professor and Director of the Graduate Program in Human Nutrition in the Department of Rehabilitation, Exercise and Nutrition Sciences at the University of Cincinnati. She has an M.S. and Ph.D. in nutritional sciences and is a registered dietitian specializing in evaluating dietary approaches in the prevention and management of cardiovascular disease risk factors. Dr. Couch has conducted human subject research for over 20 years, specifically examining dietary assessment approaches and dietary patterns related to cardiovascular disease risk reduction, and has authored over 65 peer-reviewed publications. She is a recipient of a grant award from the National Heart, Lung and Blood Institute to examine the efficacy of a DASH dietary pattern delivered as part of a clinic-based behavioral nutrition program for the management of elevated blood pressure in adolescents. Her studies have also involved assessment of the home food environment as a potential modifiable risk factor related to childhood obesity and CVD risk. Her particular interests related to the home environment are parenting style and child feeding practices and parent and adolescent food literacy in relation to diet quality and weight status.

John P. Kirwan, Ph.D., MSc, is Director of the Metabolic Translational Research Center and Professor of Molecular Medicine at the Cleveland Clinic in Cleveland, Ohio, USA. He is also a Professor of Nutrition, and of Physiology, at Case Western Reserve University School of Medicine in Cleveland. His professional expertise includes almost 30 years of research, teaching, and service in the obesity, diabetes, and nutrition fields. Dr. Kirwan received his clinical physiology training at Washington University School of Medicine in St. Louis, Missouri; his Ph.D. in human bioenergetics at Ball State University, Muncie, Indiana; and his MSc in exercise biochemistry from the University of Massachusetts, Amherst, Massachusetts; and his BA (Hons) from the University of Limerick, Ireland. Dr. Kirwan leads an internationally acclaimed biomedical research program focused on diabetes, obesity, nutrition, and exercise. To date, his research funding has been awarded from the US National Institutes of Health, and the food, pharmaceutical, and medical device industries. He has published over 200 scientific papers related to metabolism and nutrition in prestigious peer-reviewed journals including the *New England Journal of Medicine*, *JAMA*, *Diabetes*, and the *American Journal of Clinical Nutrition*. Among his most important research contributions is the discovery that, for a significant number of patients, diabetes can be cured by surgically altering the physiology of the intestine and stomach.

This volume, developed by three eminent editors, is organized into five parts: nutrient and health needs in pregnancy, metabolism during pregnancy, high-risk pregnancies, the postpartum period, and the developing world. The first part contains seven chapters and begins with the chapter that examines body composition in pregnancy. Chapter 1 reviews the physiologic and metabolic changes associated with pregnancy including all phases of gestational weight gain and examines the alterations in maternal body composition as well as embryonic and fetal growth. Numerous methodologies are described including anthropometry, whole body densitometry, underwater weighing, air displacement plethysmography, MRI, DXA stable isotope total body water measurement, and ultrasound. The importance of the measurement of gestational weight gain during the trimesters is discussed especially in view of the recent data linking increased weight gain with several adverse effects to both the mother and fetus.

The next three chapters review the importance of three essential nutrients for normal fetal growth as well as maternal health. Chapter 2 includes a risk/benefit analysis of the use of iron supplements during pregnancy. The chapter reviews the iron requirements of the fetus and emphasizes the significantly increased iron requirements of the fetus during the last trimester. Iron, as an essential micronutrient and as an element, must be consumed as it cannot be synthesized. However, it differs from most essential nutrients in that its excretion is very limited and thus absorption is under multiple controls that are affected further by pregnancy. The woman's optimal iron status prior to pregnancy helps to assure that both she and the newborn have adequate iron over the entire pregnancy. The chapter reviews the transport of iron including the hormones involved, genetic factors, and both heme and non-heme iron absorption during the pregnancy. Detailed discussions of iron deficiency and iron deficiency anemia as well as identification of risk groups are included. The practice of providing iron supplements to all pregnant women is examined in light of conflicting data from published studies and further research is suggested. Chapter 3 examines the developmental roles of iodine as this element is critical for the formation of thyroid hormones. Iodine requirements are increased during pregnancy as fetal growth is dependent upon sufficient synthesis of maternal thyroid hormones. Pregnant women have increased iodine requirements of 220–250 $\mu\text{g}/\text{day}$. Maternal iodine deficiency during pregnancy can have adverse obstetrical effects such as miscarriage, prematurity, and stillbirth, as well as adverse effects on offspring development including low birth weight and head circumference, and lower cognitive functions. Food sources of iodine are identified and the indirect determination of iodine status is reviewed. Iodine supplementation prior to pregnancy, during pregnancy and lactation is currently recommended in the USA. The adverse effects of both lower and higher recommended intakes of iodine during pregnancy are discussed. Chapter 4 reviews the recent findings on the importance of vitamin D during pregnancy and lactation and provides new data to support increases in daily supplementation levels during both pregnancy and lactation. These levels of supplementation remain controversial and thus this chapter is of particular value to health professionals who recommend vitamin D supplementation to the relevant women. We learn that the roles of vitamin D in the pregnant versus lactating woman

are different. In the pregnant woman, the primary role of vitamin D appears to be immunomodulatory while also retaining its calcium regulating function. During lactation, maternal vitamin D intake serves the primary role of supplying the nursing newborn infant with adequate vitamin D for its skeletal integrity function.

Chapter 5 examines the nutritional needs of women who consume vegetarian diets during pregnancy. The chapter provides information concerning the potential for a vegetarian or vegan diet to meet the nutritional requirements for all nutrients not provided by the vegetarian diet regardless of type (vegan, ovo-lacto, etc.) by adding fortified foods and/or supplements as needed. There are specially formulated vegetarian prenatal multivitamin-mineral supplements; however, these should be evaluated for adequacy for the individual woman during all trimesters as well as during lactation. Several of the at-risk nutrients for women who consume vegetarian diets include protein, iron, zinc, calcium, vitamin D, vitamin B12, iodine, and omega-3 fatty acids. The chapter includes tables that list the foods containing the at-risk nutrients and their contents in dietary supplements for pregnant vegetarians. As the prior chapters also include information on the increased requirements for iron, iodine, and vitamin D, these chapters should also be reviewed by health professionals who treat those consuming vegetarian diets.

Chapter 6 reviews the serious adverse effects of three major clinical sleep disorders and their consequences during pregnancy. The relationship of these disorders to dietary intakes is reviewed. The first condition discussed is insufficient sleep, also known as sleep restriction, and is known to negatively impact hormonal and metabolic function. We learn that short sleep duration is an independent risk factor for weight gain and obesity. Obstructive sleep apnea and restless legs syndrome are the two other common sleep disorders that are examined as both are influenced by diet and nutrition.

Chapter 7 reviews the importance of food safety for pregnant women. We are reminded that pregnancy is a time when a woman's immune system responses are reduced so that she does not reject her own fetus. Thus, pregnant women and their fetuses are at higher risk of food-borne illness than at other times during their adult lives. Moreover, during pregnancy, pathogenic microorganisms can cross the placenta, infecting the fetus because their immune system is not fully developed. These infestations can cause serious consequences including miscarriage, premature delivery, hearing loss, intellectual disabilities, blindness, and/or other serious sicknesses. Thus, safe food handling during pregnancy is critical for the health of the pregnancy. The safe food handling methods are reviewed in detail and the major pathogens and their sources are included in this informative and unique chapter.

Part II, containing two chapters, looks at the importance of one-carbon metabolism and certain consequences of deficiencies in the nutrients associated with normal one-carbon metabolism on the epigenetics of the fetus. Chapter 8 reminds us of the critical role of the essential vitamins (folic acid, vitamins B6 and B12) and the conditionally essential nutrient (choline) as methyl donors to genetic material and other key reactions in the development of the embryo and fetus and discusses the many adverse effects associated with deficiency in any one of these essential and conditionally essential nutrients. The chapter contains details pertaining to the

metabolic pathway that includes DNA methylation reactions, foods that contain these nutrients and their functions during pregnancy, and recommended intakes. Also, the frequency and effects of genetic factors that alter one-carbon metabolism are reviewed in depth, and consequences to the pregnancy are discussed separately from those effects on the fetus and neonate; the chapter includes over 150 relevant references. Epigenetics and diet in pregnancy is a relatively new area for investigation and Chap. 9 brings us up to date. Epigenetics is defined as modifications of offspring DNA that occur without changing their genetic sequences, but result in altered gene expression and function with subsequent changes in phenotype. The three main epigenetic mechanisms are DNA methylation, histone modification, and noncoding RNAs. As mentioned above, DNA methylation is the most widely studied evidence of epigenetic alterations in pregnancy. Maternal undernutrition, especially in the B vitamins discussed in Chap. 8, paternal undernutrition, and transgenerational effects of alterations in methylation of DNA and other epigenetic events are reviewed in detail and relevant consequences are outlined and tabulated.

Part III contains eight chapters that examine the most common as well as the most difficult pregnancies and the potential risks and benefits associated with dietary intakes during these pregnancies. Chapter 10 is of great importance as the number of women who enter pregnancy as either overweight or obese is increasing yearly around the globe. The chapter focuses on the most current and evidence-based clinical recommendations related to the U.S. Institute of Medicine's (IOM) gestational weight gain (GWG) guidelines from 2009 and the IOM updated 2015 practice paper, controversies related to these GWG guidelines, maternal and fetal outcomes associated with adherence and noncompliance to these GWG guidelines, a review of factors influencing GWG, and general and nutritional recommendations for the management of maternal obesity. The chapter reviews the serious adverse effects to both mother and infant during and following birth if a woman enters pregnancy obese and stresses the value of preconceptional weight loss. Chapter 11 reviews the risks and benefits of weight loss surgery, which is one option for reducing obesity prior to pregnancy. The chapter describes the different types of bariatric operations and the nutritional disturbances associated with each one. Additionally, the standard recommendations for supplementation and follow up are reviewed. Alterations to these regimens during pregnancy are discussed. Pregnancy outcomes after bariatric surgery are reviewed. The nutritional deficiencies in vitamins and other nutrients are common after bariatric surgery, and the differences between the types of surgeries are outlined and illustrated.

One of the most serious and devastating conditions affecting pregnancy is preeclampsia. Chapter 12 provides a comprehensive review and explains that preeclampsia is a multi-organ disease that occurs after 20 weeks gestation and is characterized by the development of hypertension and either proteinuria or other evidence of end-organ effects. Preeclampsia occurs in 5–7% of pregnancies. The exact etiology of the disorder continues to be poorly understood. Factors associated with preeclampsia include both poor placentation and placental hypoxia, resulting in a cascade of events that may culminate in increased maternal mortality and morbidity including placental abruption, acute renal failure, cerebrovascular and

cardiovascular complications, disseminated intravascular coagulation as well as fetal/neonatal morbidity and mortality caused by intrauterine growth restriction, abruption, and prematurity. There are no well-established methods of primary prevention or reliable and cost-effective screening. New research, described in the chapter, focuses on biomarkers that may be useful for screening in the future. With regard to nutritionally based interventions, calcium supplementation in high-risk women and in women with low dietary calcium intake has been shown to reduce the risk of hypertension and preeclampsia.

The next five chapters review population groups that are at higher than average risk of adverse pregnancy outcomes and provide options for risk reduction. Chapter 13 looks at the data linking Hispanic ethnicity in US women with increased risk of preterm birth. The chapter identifies critical factors associated with the increased risk including maternal socio-demographic characteristics, medical and pregnancy-related conditions, maternal lifestyle including dietary factors, and acculturation. Of note, vitamin D deficiency is a risk factor for preterm delivery and is more prevalent among Hispanic compared with non-Hispanic White women. The chapter discusses the increased prevalence of several known risk factors in Hispanic populations including Hispanic mothers who are 17 years old or younger and Hispanic women of childbearing age who have significantly higher rates of obesity, diabetes, and pregnancy-related diabetes and hypertension compared to non-Hispanic White women. Lower than recommended body weight before becoming pregnant also increased risk of preterm birth in Hispanic women. Chapter 14 looks at pregnancy risks in women who have serious eating disorders either before becoming pregnant or develop these conditions during pregnancy. The chapter reviews the adverse clinical effects of anorexia, bulimia, and binge eating and their nutritional consequences. These conditions are associated with inadequate or inconsistent energy and nutrient intakes, notably total energy; folate; vitamins B6, B12, and A; calcium; iron; and zinc. Electrolyte imbalances are also of concern. Inadequate or excessive weight gain, spontaneous abortion, intrauterine growth restriction, preterm delivery, and low birth weight, among other adverse outcomes, have been reported in pregnant women with eating disorders and their offspring. The chapter includes an important case study, six informative tables, and close to 100 relevant references.

Chapter 15 describes the risks associated with diabetes both before and during pregnancy. We learn that diabetes mellitus is the most common complication in pregnancy affecting nearly 8% of all pregnancies. Nearly 90% of women with diabetes develop the condition during pregnancy (gestational diabetes mellitus); the other 10% preceded the pregnancy. Perinatal mortality rates for women with diabetes have decreased with insulin use; however, infant morbidity remains higher than in the nondiabetic pregnant women. Although the dietary recommendations for diabetic women who become pregnant are the same as those for nondiabetic pregnant women, there are medical nutrition guidelines to help reduce maternal and fetal risks. The goals of medical nutrition therapy for pregnancy and diabetes are to provide adequate nutrients for maternal-fetal nutrition, to provide sufficient calories for appropriate weight gain, and to achieve and maintain optimal glycemic control.

Another unique topic included in this comprehensive volume examines the nutritional needs of incarcerated pregnant women. Chapter [16](#) reviews the data from the William & Mary Healthy Beginnings Project, a nutrition intervention program developed for pregnant incarcerated women in southeastern Virginia. Assessment of this program suggests that through the development of protocols and policies that consider the health-related needs of pregnant women, correctional facilities could play a pivotal role in helping incarcerated women develop healthier habits to better care for themselves and their newborns. Currently, there are about 100,000 women incarcerated in the USA or 10% of the incarcerated population. Of these women, about 10% are pregnant at any one time. Thus, in virtually all sites of incarceration policies and procedures are developed to meet the needs of the majority of prisoners who are male and not pregnant women prisoners. The chapter reviews the profile of many incarcerated women that includes drug abuse and sexually transmitted disease, lack of contraception, poor diet, and low educational level. Pregnancy is often unplanned and prepregnancy health status would suggest an at-risk pregnancy even if the woman was not incarcerated. The authors' Project is described: close to one-third of the participants in this program discovered they were pregnant upon entering the jail facility. This was a direct result of the pregnancy tests provided by the William & Mary Healthy Beginnings Project. Because these women were identified early, they were able to receive prenatal vitamins and timely prenatal care, as well as nutrition counseling and additional support to help them plan for their pregnancy. Moreover, results show participants' nutrition and pregnancy-related knowledge increased from pre- to post-counseling, and this increase in knowledge was associated with positive birth outcomes.

Chapter [17](#), the last chapter in Part III, looks at the effects of clinical depression during pregnancy and lactation and examines the potential for yoga to reduce the depressive episodes. In the USA, approximately 13% experience a major depressive disorder during pregnancy. There are numerous adverse outcomes associated with maternal depression for the infants, including preterm birth and low birth weight. Symptoms of depression or a clinical diagnosis of depression during pregnancy increase the risk for postpartum depression that can disrupt a mother's functioning and, in some cases, create significant difficulties with mother-infant bonding and interactions which may adversely affect the long-term cognitive and developmental outcomes during childhood and beyond. The chapter reviews the current literature and suggests that prenatal yoga classes can be of value to women who have depressive episodes during pregnancy.

Part IV contains two chapters that examine the nutritional needs during lactation and the nutritional risks associated with postpartum depression. The purpose of Chap. [18](#) is to provide an overview of the significant energy demands of lactation, as well as include a select list of nutrients known to be in short supply for a majority of reproductive-age women from developed countries. The specific nutrients examined include calcium, vitamin D, folate, vitamin B12, long-chain polyunsaturated fatty acids, and iron. Foods as well as supplemental sources of these key nutrients are enumerated. The chapter also reviews the literature concerning dieting and exercise during lactation. We learn that maternal deficiency of some nutrients can

adversely affect the concentration of these nutrients in breast milk. These nutrients include thiamin, riboflavin, vitamin B6, vitamin B12, choline, vitamin A, vitamin D, selenium, and iodine. In contrast, the content of folate, calcium, iron, copper, and zinc in breast milk is not directly linked to maternal status or intake and maternal sources are secreted into breast milk at the expense of maternal nutrient status. The chapter contains over 170 relevant references and 7 helpful tables. Chapter [19](#) examines the nutritional factors involved in postpartum depression. Postpartum depression is a major depressive episode, which has a duration of at least 2 weeks. Women experience either depressed mood or a loss of interest or pleasure in activities. For psychiatric diagnosis, women must experience at least four other symptoms including changes in appetite or weight, sleep and/or psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts. Although the onset of this disorder is usually within the first 4 weeks after delivery, clinicians and researchers both attest to this time criterion as being much too limited. Postpartum depression generally occurs during the first 12 months; however it has been identified as late as 18 months after the birth of an infant. The chapter reviews the roles of macro- and micronutrients that affect brain function and the requirements for these in women with postpartum depression.

The last part of the book, Part V, contains three chapters that look at issues of nutrition and pregnancy from a global perspective. Chapter [20](#) discusses the issue of diabetes in pregnant women as this disease is becoming one of the most common health complications of pregnancy globally. Diabetes in pregnancy is defined as pre-existing type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus (GDM). GDM involves carbohydrate intolerance of varying degree of severity with onset of first recognition that happens during pregnancy. In some cases, GDM may actually be identified as undiagnosed pre-existing type 2 diabetes. Determination of the global prevalence of diabetes in pregnancy is difficult as there are no standard definitions and diagnostic criteria; however it appears that prevalence is increasing globally which correlates with increases in female obesity. The specific problems seen in low- and middle-income countries that result in adverse pregnancy outcomes are reviewed in Chap. [21](#). Common themes across countries include teen pregnancy, preconceptional malnutrition—either undernutrition or overnutrition, lack of access to essential nutrient food sources and/or supplements, poor sanitation and other aspects of poverty, political instability resulting in high stress, and lack of medical care and/or consistent access to medical monitoring during the entire pregnancy. Maternal iron deficiency anemia is directly linked to maternal mortality in the countries examined in this chapter. Preeclampsia is linked to calcium deficiency and supplemental calcium decreases this risk but the provision of calcium to prevent preeclampsia is not universal. The final chapter, Chap. [22](#), examines the serious consequences of domestic violence to the pregnant woman and her fetus, neonate, and growing child and uses Nepal as an example. Domestic violence during pregnancy is documented as a significant public health issue linked with adverse health outcomes for the newborn including low birth weight and preterm birth. The prevalence of violence experienced by pregnant women ranges from 0.9% to 20.1% in

different societies. Violence during pregnancy accounts for approximately 15% of all gender-based violence cases in Nepal. The estimated incidence of low birth weight is 16% globally, 19% in the least developed and developing countries, and 7% in developed countries. The prevalence of low birth weight, mainly an outcome of maternal undernutrition, is relatively high in Nepal, ranging from 14% to 43%, and it is a major public health concern. Birth weight is a major predictor of infant growth and survival, and low birth weight is linked with early mortality and morbidity. It is documented that women who experienced any type of abuse—physical, sexual, or emotional—during pregnancy are more prone to give birth to a baby with lower birth weight than non-abused women. Domestic violence during pregnancy interferes with the nutritional status of women, leading to suboptimal baby weight gain. The adverse consequences of violence during pregnancy on birth outcomes are well documented. In Nepal 93% of women were exposed to mental and emotional torture, 82% were beaten, 30% were raped, 28% were forced into prostitution, and 64% reported polygamy. These terrible statistics are of great concern as it appears that mistreatment of women is an accepted part of the culture and that domestic violence continues during pregnancy resulting in serious adverse effects to both mother and unborn child. The cultural conditions linked to the continuation of domestic violence are thoughtfully discussed; however there is no simple, quick fix and thus this final chapter highlights some of the most complex factors involved in reducing the risks of adverse pregnancy outcomes in this twenty-first century.

Conclusions

Of importance to obstetricians, gynecologists, pediatricians and related physicians, nutritionists, dieticians, researchers, nurses, and allied health professionals who provide advice concerning diet, foods, nutrition, dietary supplements, and clinical management of women of reproductive age, those planning pregnancy, women who are pregnant and/or lactating, and especially women who are at risk for adverse pregnancy outcomes is the identification of objective and reputable sources of nutrition information. “Handbook of Nutrition and Pregnancy, Second Edition,” edited by Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan, provides 22 valuable chapters that review and integrate these relevant and objective resources. The volume examines the major dietary patterns that have been identified as containing the components of a healthy diet especially during the reproductive years and contrasts these with dietary patterns documented in many populations of women around the globe whose access to safe foods and clean water is seriously lacking. Moreover, the volume includes extensive reviews of the key nutrients associated with normal embryonic and fetal development as well as maintaining the nutritional status of the pregnant woman. Many chapters emphasize the critical importance of adequate dietary intakes in women who enter pregnancy with medically relevant physical and/or mental issues.

This comprehensive volume examines patient-related topics including chapters on vegan and other vegetarian-based diets, the major changes in physiology that occur during normal and medically challenged pregnancies, the importance of consuming clean foods and maintaining their safety during food preparation and storage, the potential for adverse pregnancy outcomes associated with certain lifestyle factors such as smoking, alcohol, and unlawful drug use, and teen as well as older age pregnancies. Topics included in this comprehensive volume include the epigenetic consequences of folate and related B vitamin deficiencies and the adverse outcomes seen with deficiencies of iron, iodine, and vitamin D. Weight management prior to pregnancy and the consequences of being overweight or obese during pregnancy with potential diabetes, heart, liver, and kidney diseases affecting both the mother and child as well as the risks and benefits of weight reduction surgery are reviewed in depth. Unique chapters look at the global consequences of nutritional deficiencies that may be the result of population-wide lack of healthy and safe food, the result of domestic violence, and/or the effects of pathological conditions such as anorexia that compromise the nutritional status prior to as well as during and following pregnancy.

The volume contains over 70 data-rich tables and figures and appendices as well as 1900 up-to-date and relevant references that give physicians and health providers important tools that can help to improve patient dietary habits that may be less than ideal. There are more than a dozen chapters that provide clinically relevant information on risk reduction of the major adverse effects associated with conditions such as diabetes, postpartum depression, and issues of lactation. The 22 chapters within this valuable volume provide a wealth of timely information for health providers, medical students, graduate students, nurses, dietitians, and other related health professionals. Hallmarks of all of the chapters include complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Useful features of this comprehensive volume include the informative Key Points and Key Words that are at the beginning of each chapter and relevant references at the end of each chapter and a comprehensive index.

In conclusion, "Handbook of Nutrition and Pregnancy, Second Edition," edited by Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan, provides health professionals in many areas of research and practice with the most up-to-date, organized volume on the clinically researched and documented healthy dietary patterns that are linked to reducing the risks of adverse pregnancy outcomes for both the mother and child. Of great importance, major topics such as prepregnancy obesity, diabetes, and less than optimal nutritional status are presented so that the health provider can communicate from a position of facts and data to help assure the patient of the value of their care. Thus, the data provided in this book enables the reader to answer their patient or client questions with the confidence that their answers are based upon the totality of the evidence from well-accepted, data-driven nutrition research. This volume serves the reader as the benchmark in this complex area of interrelationships between the major dietary patterns that have been associated with reducing pregnancy-related risks. Drs. Lammi-Keefe, Couch, and Kirwan are applauded for their

efforts to develop this volume with the firm conviction that nutrition research serves as an essential source of important data for all health professionals. This excellent text is a very welcome addition to the Nutrition and Health series.

Morristown, NJ, USA

Adrienne Bendich

akusher-lib.ru

About the Series Editors



Adrienne Bendich, PhD, FASN, FACN has served as the “**Nutrition and Health**” Series Editor for more than 20 years and has provided leadership and guidance to more than 200 editors who have developed the 80+ well-respected and highly recommended volumes in the Series. In addition to *Handbook of Nutrition and Pregnancy, Second Edition*, edited by **Carol J. Lammi-Keefe, Sarah C. Couch, and John P. Kirwan**, major new editions published in 2012–2018 include:

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Earlier books included *Vitamin D, Second Edition* edited by Dr. Michael Holick; *Dietary Components and Immune Function* edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi, and Dr. Victor R. Preedy; *Bioactive Compounds and Cancer* edited by Dr. John A. Milner and Dr. Donato F. Romagnolo; *Modern Dietary Fat Intakes in Disease Promotion* edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson; *Iron Deficiency and Overload* edited by Dr. Shlomo Yehuda and Dr. David Mostofsky; *Nutrition Guide for Physicians* edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble; *Nutrition and Metabolism* edited by Dr. Christos Mantzoros; and *Fluid and Electrolytes in Pediatrics* edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include *Handbook of Drug-Nutrient Interactions* edited by Dr. Joseph Boullata and Dr. Vincent Armenti; *Probiotics in Pediatric Medicine* edited by Dr. Sonia Michail and Dr. Philip Sherman; *Handbook of Nutrition and Pregnancy* edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson; *Nutrition and Rheumatic Disease* edited by Dr. Laura Coleman; *Nutrition and Kidney Disease* edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow; *Nutrition and Health in Developing Countries* edited by Dr. Richard Semba and Dr. Martin Bloem; *Calcium in Human Health* edited by Dr. Robert Heaney and Dr. Connie Weaver; and *Nutrition and Bone Health* edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.

Dr. Bendich is President of Consultants in Consumer Healthcare LLC and is the editor of ten books including *Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition* coedited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the *Journal of Nutrition in Gerontology and Geriatrics* and *Antioxidants* and has served as Associate Editor for *Nutrition* the international journal; served on the Editorial Board of the *Journal of Women's Health & Gender-based Medicine*; and served on the Board of Directors of the American College of Nutrition.

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is

recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in *Who's Who in American Women*.



Connie W. Bales, PhD, RD is a Professor of Medicine in the Division of Geriatrics, Department of Medicine, at the Duke School of Medicine and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University Medical Center. She is also Associate Director for Education/Evaluation of the Geriatrics Research, Education, and Clinical Center at the Durham VA Medical Center. Dr. Bales is a well-recognized expert in the field of nutrition, chronic disease, function, and aging. Over the past two decades, her laboratory at Duke has explored many different aspects of diet and activity as determinants of health

during the latter half of the adult life course. Her current research focuses primarily on enhanced protein as a means of benefiting muscle quality, function, and other health indicators during geriatric obesity reduction and for improving perioperative outcomes in older patients. Dr. Bales has served on NIH and USDA grant review panels and is Past-Chair of the Medical Nutrition Council of the American Society for Nutrition. She has edited three editions of the *Handbook of Clinical Nutrition and Aging*, is Editor-in-Chief of the *Journal of Nutrition in Gerontology and Geriatrics*, and is a Deputy Editor of *Current Developments in Nutrition*.

About the Editors



Sarah C. Couch, PhD, RD is a professor and Director of the Graduate Program in Human Nutrition in the Department of Rehabilitation, Exercise and Nutrition Sciences at the University of Cincinnati. She has an MS and PhD in nutritional sciences and is a registered dietitian specializing in evaluating dietary approaches in the prevention and management of cardiovascular disease risk factors. Dr. Couch has conducted human subject research for over 20 years, specifically examining dietary assessment approaches and dietary patterns related to cardiovascular disease risk reduction, and has authored over 65 peer-reviewed publications. She is a previous recipient of a grant award from the National Heart, Lung and Blood Institute to examine the effi-

cacy of a DASH dietary pattern delivered as part of a clinic-based behavioral nutrition program for the management of elevated blood pressure in adolescents. Her studies have also involved assessment of the home food environment as a potential modifiable risk factor related to childhood obesity and CVD risk. Her particular interests related to the home environment are parenting style and child feeding practices and parent and adolescent food literacy in relation to diet quality and weight status.



John P. Kirwan, PhD, MSc is Director of the Metabolic Translational Research Center and Professor of Molecular Medicine at the Cleveland Clinic in Cleveland, Ohio, USA. He is also a Professor of Nutrition, and of Physiology, at Case Western Reserve University School of Medicine in Cleveland. His professional expertise includes almost 30 years of research, teaching, and service in the obesity, diabetes, and nutrition fields. Dr. Kirwan received his clinical physiology training at Washington University School of Medicine in St. Louis, Missouri; his PhD in human bioenergetics at Ball State University, Muncie, Indiana; his MSc in

exercise biochemistry from the University of Massachusetts, Amherst, Massachusetts; and his BA (Hons) from the University of Limerick, Ireland.

Dr. Kirwan leads an internationally acclaimed biomedical research program focused on diabetes, obesity, nutrition, and exercise. To date he has generated over \$35 million in research funding, most of which has come from the US National Institutes of Health, and the food, pharmaceutical, and medical device industries. He has published over 200 scientific papers related to metabolism and nutrition in prestigious peer-reviewed journals including the *New England Journal of Medicine*, *JAMA*, *Diabetes*, and the *American Journal of Clinical Nutrition*. Among his most important research contributions is the discovery that, for a significant number of patients, diabetes can be cured by surgically altering the physiology of the intestine and stomach.

He is married to his wonderful, brilliant wife April, has 4 fantastic children, and plays “Dad” to a lovable mutt named Bailey!



Carol J. Lammi-Keefe, PhD is Alma Beth Clark Professor of Nutrition, School of Nutrition and Food Sciences, Louisiana State University, and Adjunct Professor at the Pennington Biomedical Research Center, Baton Rouge, Louisiana.

She has devoted more than three decades to research in maternal and fetal nutrition, with an emphasis on lipids and especially omega-3 fatty acids. Her research findings include the benefit of docosahexaenoic acid during pregnancy on infant functional outcomes, including sleep, visual acuity, problem solving, and decreased adiposity. A current federally funded project will assess the benefit of omega-3 fatty acids in decreasing the

inflammatory response in overweight pregnant women and the effect on infant adiposity.

Her research findings have been published in journals including the *American Journal of Clinical Nutrition*, the *Journal of the American Dietetic Association*,

Lipids, the British Journal of Nutrition, and the Journal of Pediatric Gastroenterology and Nutrition.

Dr. Lammi-Keefe's professional activities include serving as Past Chair of the Health and Nutrition Division, the American Oil Chemists Society, and membership in the American Dietetic Association, American Nutrition Society, International Society for the Study of Fatty Acids and Lipids, and International Society for Research on Human Milk and Lactation. She is a former member of the Governing Board for the American Oil Chemists Society.

A faculty member and Department Head at the University of Connecticut from 1981 to 2006, Dr. Lammi-Keefe currently is Professor Emeritus there. In 2003 she was recognized by the university with the Chancellor's Research Excellence Award. For her research and scientific contributions, the American Dietetic Association Foundation presented her with its Ross Award in Women's Health and its Award for Excellence in Dietetic Research. In 2009, Louisiana State University cited her as a "Rainmaker."

As PI or co-investigator, research support has come from the U.S. Department of Agriculture, the National Institutes of Health, and numerous foundations, boards, institutes, or industry.

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Abbreviations

1-C	One-carbon
1,25(OH) ₂ D	1,25-Dihydroxy-vitamin D
25(OH)D	25-Hydroxy-vitamin D
AAP	American Academy of Pediatrics
ACE	Angiotensin converting enzyme (inhibitor)
ACOG	American Congress of Obstetrics and Gynecology/American College of Obstetricians and Gynecologists
ADP	Air-displacement plethysmography
AGB	Adjustable gastric band
AHRQ	Agency for Healthcare Research and Quality
AI	Adequate intake
ALA	Alpha-linolenic acid
ALPL	Alkaline phosphatase
ALSPAC	Avon Longitudinal Study of Parents and Children
AN	Anorexia nervosa
ANC	Antenatal care
APNCU	Adequacy of Prenatal Care Utilization index
ARA	Arachadonic acid
ASD	Autism spectrum disorders
ATA	American Thyroid Association
BAC	Blood alcohol concentration
BED	Binge-eating disorder
BIA	Bioelectrical impedance
BN	Bulimia nervosa
BMI	Body mass index
BPA	Bisphenol-A
BPD-DS	Biliopancreatic diversion with duodenal switch
CAM	Complementary and alternative medicine
CCHS	Canadian Community Health Survey
CDC	Centers for Disease Control and Prevention
CDP	Cytidine diphosphophate

CI	Confidence interval
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CPD	Cephalopelvic disproportion
CRN	Council for Responsible Nutrition
CRP	C reactive protein
DASH	Dietary Approaches to Stop Hypertension (diet)
DFE	Dietary folate equivalents
DHA	Docosahexaenoic acid
DHS	Demographic and Health Surveys
DIP	Diabetes in pregnancy
DMG	Dimethylglycine
DMRs	Differentially methylated regions
DBP	Vitamin D binding protein
DRI	Dietary Reference Intakes
DV	Domestic violence
DXA	Dual-energy X-ray absorptiometry
EAR	Estimated average requirement
EERs	Estimated energy requirements
EPA	Eicosapentaenoic acid
EPDS	Edinburgh Postnatal Depression Scale
EPO	Erythropoietin
FDA	Food and Drug Administration
FDR	False discovery rate
Fe	Iron
FM	Fat mass
FFM	Fat-free mass
FSIS	Food Safety Inspection Service
FUT2	Fucosyltransferase
g	Gram
GABA	Gamma amino butyric acid
GCT	Glucose challenge test
GDM	Gestational diabetes mellitus
GWG	Gestational weight gain
HAPO	Hyperglycemia and Adverse Pregnancy Outcomes (study)
Hb	Hemoglobin
hCG	Human chorionic gonadotropin
Hct	Hematocrit
HIP	Hyperglycaemia in pregnancy
HPA	Hypothalamic-pituitary-adrenal
HPL	Human placental lactogen
HUS	Hemolytic-uremic syndrome
IADPSG	International Association of Diabetes and Pregnancy Study Groups
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
ICD	International Classification of Diseases

ICR(s)	Imprinting control region(s)
ID	Iron deficiency/iodine deficiency
IDA	Iron deficiency anemia
IDD	Iodine deficiency disorder(s)
IF	Intrinsic factor
IFSO	International Federation for the Surgery of Obesity and Metabolic Disorders
IGN	Iodine Global Network
IHD	Ischemic heart disease
IL-6	Interleukin 6
INR	International Normalized Ratio
IOM	Institute of Medicine
IPV	Intimate partner violence
IQ	Intelligence quotient
IUGR	Intrauterine growth retardation/restriction
KI	Potassium iodide
LBW	Low birth weight
LC-PUFAs	Polyunsaturated fatty acids
LGA	Large for gestational age
LMIC	Low- and middle-income countries
LSG	Laparoscopic sleeve gastrectomy
LTR	Long-terminal repeat
MAOI	Monoamine reuptake inhibitors
mcg	Microgram
MCM	Methylmalonyl-CoA mutase
MDG	Millennium Development Goal
mg	Milligram
MNT	Medical nutritional therapy
MRI	Magnetic resonance imaging
MS	Methionine synthase
MTHFR	Methylenetetrahydrofolate reductase
MTR	Methionine synthase
MTRR	Methionine synthase reductase
MUAC	Mid-upper arm circumference
NCCHC	National Commission on Correctional Health Care
NCHS	National Center for Health Statistics
NHANES	National Health and Nutrition Examination Survey
NICE	National Institute for Health and Clinical Excellence
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
NTD(s)	Neural tube defect(s)
OGTT	Oral glucose tolerance test
OSA	Obstructive sleep apnea
oz	Ounce
PC	Phosphatidylcholine

PEMT	Phosphatidylethanolamine <i>N</i> -methyltransferase
PDSS	Postpartum Depression Screening Scale
PIGF	Placental growth factor
PLP	Pyridoxal 5'-phosphate
PNC	Prenatal care
ppBMI	Pre-pregnancy body mass index
PPH	Postpartum hemorrhage
PPWR	Postpartum weight retention
PTB	Preterm birth
PTH	Parathyroid hormone
PVE	Plasma volume expansion
RBC(s)	Red blood cell(s)
RCOG	Royal College of Obstetricians and Gynaecologists
RCT(s)	Randomized controlled trial(s)
RDA(s)	Recommended daily allowance(s)
RLS	Restless legs syndrome
RMR	Resting metabolic rate
RR	Relative risk
RYGB	Roux-en-Y gastric bypass
SAC	School-age children
SAMe	<i>S</i> -adenosylmethionine
SCID	Structured Clinical Interview for DSM-IV Axis 1 Disorders
SF	Serum ferritin
sFLT1	Soluble fms-like tyrosine kinase
SG	Sleeve gastrectomy
SGA	Small for gestational age
SHMT	Serine hydroxymethyltransferase
SNAP	Supplemental Nutrition Assistance Program
SNP(s)	Single nucleotide polymorphism(s)
SOL	Sleep-onset latency
sTfR	Serum transferrin receptor
SWS	Slow-wave sleep
T	Tablespoon
T3	Triiodothyronine
T4	Thyroxine
TBG	Thyroxine-binding globulin
TBI	Total body iron
TBW	Total body water
TCN2	Transcobalamin
TEF	Thermic effect of food
TfR	Transferrin receptor
Tg	Thyroglobulin
TRF	Thrasher Research Fund
TSH	Thyroid-stimulating hormone

USDA	United States Department of Agriculture
UL	Upper intake level/limit
USI	Universal salt iodization
USPSTF	United States Preventive Services Task Force
UVB	Ultraviolet-B
VGB	Vertical banded gastroplasty
WHO	World Health Organization
WIC	Special Supplemental Nutrition Program for Women, Infants and Children

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Part I
Nutrient and Health Needs in Pregnancy

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Body Composition in Pregnancy

Nicholas T. Broskey, Kara L. Marlatt, and Leanne M. Redman

Keywords Body composition · Gestational weight gain · Fat mass · Fat-free mass
Total body water · Birth weight

Key Points

- Entering pregnancy at a healthy weight, and maintaining a healthy weight gain throughout pregnancy, has become increasingly important.
- Excessive gestational weight gain, particularly early in pregnancy, has negative consequences on both maternal and infant health outcomes.
- The variance in total gestational weight gain is the result of variable increases in fat mass.
- Given body composition during pregnancy is different compared to pre-gravid conditions, careful methodological considerations and adjustments are required.
- Magnetic resonance imaging and ultrasound imaging have emerged as promising new techniques to measure maternal body composition.
- The distribution of gestational weight gain into different adipose tissue depots is an important avenue of exploration in pregnancy research.

Assessment of Body Composition During Pregnancy

Pregnancy is a unique time when the female body is undergoing physiologic and metabolic changes that support fetal development. These physiologic and metabolic changes are recognized in gestational weight gain (GWG), which includes gains in

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maternal and fetal body mass, as well as growth of placental tissue and alterations in amniotic fluid. Indeed, increased medical attention is placed on optimizing maternal and fetal outcomes and as such, body composition is recognized as an important modulator of these outcomes in a pregnant woman and her offspring.

Common methods used to assess body composition in a pre-gravid female cannot be directly applied to the pregnant female without adequate adjustments or consideration of the drastic deviation in normal body composition. Additionally, while non-invasive and less cumbersome methods of assessing body composition, particularly fat mass (FM) and fat-free mass (FFM), are necessary in research and clinical settings, certain methods are clearly more superior to others. Herein many of the common methods to assess body composition are described, as well as their consideration for measurement in pregnant women. Finally, changes in body composition throughout pregnancy using these techniques are also discussed.

Methods of Assessment

Anthropometry

Anthropometry via skinfold thickness measurement is a non-invasive method of assessing body composition that is suitable for field research given its use of highly mobile, non-specialized equipment. Specifically, skinfold thickness measurements provide an estimated size of the subcutaneous fat depot directly under the skin. The summation of skinfold thickness measurements at particular areas of the body can be used to obtain an estimation of total subcutaneous body fat. Extensive training and expertise of the technician is necessary to accurately assess skinfold thickness and ensure a high level of reliability both within an individual over time (pregnancy) and also between individuals. Moreover, the appropriate use of necessary equipment such as anthropometry tape (Gullick), stadiometer, weight scale, skinfold calipers, anthropometer, and segmometer is critical to locate the anatomical site for measurement, and thereby obtain reliable and consistent results while minimizing measurement error.

Pregnancy presents a unique challenge for assessing skinfold thickness due to both tissue expansion and stretch. The increase in individual skinfold thickness during pregnancy is often greater in underweight women compared to overweight women, and greater at central sites compared to those located in the periphery. Taggart and colleagues demonstrated the absolute change (millimeters) in individual skinfold thickness at seven anatomical sites (i.e., suprailiac, scapular, costal, biceps, knee-cap, mid-thigh, triceps) occurs between 10 and 30 weeks gestation, yet all sites but thigh, showed little change or decreased thickness from 30 to 38 weeks [1]. Similar observations were reported by Pipe et al. using the summation of four anatomical sites (i.e., triceps, biceps, subscapular, suprailiac); however, slight increases were observed up to 36–38 weeks due to greater gains at the suprailiac site [2]. Additionally, the increase in skinfold thickness during pregnancy is often greater, on average, among primiparae than among multiparae women [1].

Few studies use skinfold thickness during pregnancy to estimate total fat mass. Equations to estimate body composition from skinfold thickness also use weight and body composition (FM, FFM). While some published models claim to explain a high percentage of the variability in predicting FM or percent body fat, these models cannot be extrapolated across pregnancy, and instead serve to estimate fat mass only at designated time periods [3, 4]. One important anthropometric study [2] detailed skinfold thickness measures at six different sites across multiple time points before and during pregnancy and related total body fat; however, others have reported that only mediocre multiple correlation coefficients were observed [5]. Similar results have been demonstrated [6, 7], and collectively conclude that use of equations to estimate total body fat from skinfold thickness may be useful in certain groups; however, they are inappropriate for most clinical and research purposes. With precision being maintained, repeated assessment of subcutaneous fat with skinfold thickness throughout pregnancy can be useful in research and clinical settings.

Bioelectrical Impedance

Bioelectrical Impedance (BIA) is a commonly used non-invasive method that is based on assumptions and relationships in the electrical properties of biological tissues. Typically, BIA is performed by placing electrodes on the ankle and wrist, allowing for the flow of low-amperage current to travel throughout the body. The conductivity of the electrical current is determined by the amount of water the biological tissue contains. Tissues with high water content (e.g., muscle) are more conductive than tissue with less water content (e.g., bone, fat) and, therefore, the volume of conductive tissue can be calculated from the resistance of the electrical signal throughout body parts. BIA, therefore, allows for an estimation of total body water and subsequently, estimations of FM and FFM. A similar principle to BIA is bioimpedance spectroscopy, which allows for estimation of intracellular and extracellular water and thus, total body water (TBW) by summing the two cellular water compartments.

In a validation study for pregnant women, Lof and Forsum [8] utilized wrist-to-ankle bioimpedance spectroscopy during various stages of pregnancy (14 and 32 weeks, 2 weeks postpartum) and reported similar estimates of TBW measured by BIA versus deuterium dilution (the gold standard) early in pregnancy, but the estimate of TBW by BIA was underestimated later in pregnancy.

The inherent problem with BIA is that this measurement of body composition is based on TBW, which changes during the course of pregnancy. Therefore, in addition to fluid shifts associated with pregnancy that have a wide degree of inter- and intra-individual variation, hydration status can also affect BIA measurement [9]. Standardization of time of day is therefore important, as well as understanding the hydration status of the individual. Changes in TBW also happen concomitantly with changes in overall composition, adding to the problem of precision and accuracy, bringing into question the feasibility of BIA to measure body composition throughout pregnancy. Otherwise, BIA is a rapid, non-invasive, and inexpensive

method to estimate body composition that is suitable in field settings. Unfortunately, it is unable to decipher between maternal and fetal contributions.

Densitometry

Whole-body densitometry is a non-invasive method to obtain body density of the maternal–fetal unit as a whole. Unfortunately, densitometry is currently unable to separate both the maternal and fetal contribution. Densitometry can be estimated in water (known as hydrodensitometry or underwater weighing), or it can be estimated in air (known as air-displacement plethysmography). Relying on the assumption that the density of FM is constant (0.900 g/cm^3) and that FFM density depends on relative contributions of bone, protein, and water, and is estimated as 1.100 g/cm^3 in men and women in the pre-gravid state [16], whole-body densitometry commonly applies the equation of Siri to estimate FM [15]:

$$\text{FM (kg)} = \left(\frac{\text{Body Mass}}{100} \right) \times \left[\frac{\frac{100}{\text{TBD}} - \frac{100}{D(\text{FFM})}}{1 - \frac{1}{D(\text{FM})}} \right] \rightarrow \left(\frac{\text{Body Mass}}{100} \right) \times \left[\frac{495}{\text{TBD}} - 450 \right]$$

where TBD = total body density, $D(\text{FM}) = \text{density fat mass}$ (or 0.90 g/cm^3), $D(\text{FFM}) = 1.10 \text{ g/cm}^3$

Moreover, densitometry is thereby based on a 2C model of body composition where body mass is assumed to be a function of FM and FFM (combined). Hence, FFM is derived by subtracting the calculated FM from the total body mass of the individual.

The estimation of FM and FFM during pregnancy with 2C models, though, is more complex because of the well-documented changes in FFM density. In the early stages of pregnancy, small changes in FFM are predominantly due to the expansion of maternal tissue; the growth of these maternal tissues minimally affects the density of FFM. In later stages of pregnancy, however, the density of FFM is reduced due to the increased growth of fetal tissues that have higher water content and subsequently a lower density [17]. The accumulation of water in pregnancy is gradual, non-linear, and highly variable in women, and may even plateau or decline in late pregnancy [18, 19]. While some scholars suggest that FFM density is the same at 10 weeks when compared to the pre-gravid state (or 1.100 g/cm^3) [4, 20], others suggest that FFM density decreases during the first trimester to approximately 1.099 g/cm^3 [10]. Table 1 documents the estimated FFM density throughout pregnancy. To provide more accurate estimates of FM and FFM by 2C models applied at the different stages of pregnancy, the appropriate density of FFM should be substituted into densitometry equations (i.e., Siri). Without adjusting

Table 1 Changes in fat-free mass density throughout pregnancy (g/cm³)

Study	Pre-Gravid	10–14 weeks	~20 weeks	30–32 weeks	35–40 weeks
Van Raaij et al. [10]	1.100	1.099	1.097	1.093	1.087
Fidanza [20]	1.100	1.100	1.097	1.092	1.087
Paxton et al. [4]	–	1.100	–	–	1.091
Hopkinson et al. [11]	–	–	–	–	1.086

densitometry equations for pregnancy-specific FFM density, FFM will be underestimated and result in an overestimation of FM.

Careful steps to enhance measurement accuracy through protocol standardization can indeed be implemented; however, estimating body composition via whole-body densitometry is unfortunately prone to high degrees of variability in pregnancy. Namely, van Raaij et al. demonstrated how the presence of clinical edema can impact hydration and thus, the density of FFM [10]. The temporal relationship of edema adds further complexity to the quantification of FFM density. And while the presence of clinical edema may not be visibly present, the existence of edema may indeed be physically present. Nonetheless, van Raaij et al. [10] and their application of the changes in body composition contributions of Hytten and Leitch to approximate FFM density has become widely recognized as the most well-established method to estimate FFM density during pregnancy [21]. Additionally, while the estimates for FFM density may appear to be relatively consistent throughout the literature, studies are needed to understand the degree to which these FFM densities might be impacted by maternal age, race, and body size as measured by body mass index (BMI).

Underwater Weighing

Underwater weighing is a technique that can apply standard densitometry equations to derive a 2C measure of body mass. With this technique, individuals are completely submerged in a small tank of warm water. The weight of the individual in the water is measured after the individual performs a complete exhalation, to void the lungs and airway of as much residual air volume as possible. Underwater weighing is based off a buoyancy principle formulated by Archimedes, which states that force exerted on an object immersed in water is equal to the weight of the fluid the object displaces [22]. It follows the basic equation:

$$\text{body volume} = (\text{weight}_{\text{air}} - \text{weight}_{\text{water}}) / \text{density}_{\text{water}}$$

Although on its own, underwater weighing provides a 2C estimate of body composition, underwater weighing has been incorporated into several 4-compartment (4C) models in pregnant women [11, 12]. Underwater weighing has also been modeled together with anthropometric measurements of body composition (skinfold thickness triceps, subscapular, suprailiac) during late gestation and shown to predict

91% of the variance in FM [3]. Altering the hydration constants for body density and TBW has been shown to have little impact on measurements of maternal body composition [18]. As pointed out in the previous discussion of densitometry, the major drawback of hydrostatic weighing lies in the estimate of FFM density. Some women may also find it difficult to maximally exhale and undertake complete submersion with occluded nostrils. Nonetheless, underwater weighing is non-invasive and can be performed longitudinally without undue risk.

Air-Displacement Plethysmography (ADP)

ADP is a safe and relatively fast method of quantifying total body density from estimated total body volume, and is therefore becoming a more widely adopted body composition assessment method in vulnerable populations (e.g., pregnant women, infants). ADP is especially applicable where dual-energy X-ray absorptiometry techniques are harmful or not recommended. The patented “BodPod” technology (COSMED, Concord, CA, USA) utilizes a dual-chamber model that is based on Boyle’s law, where small contrasts in volume and pressure in each chamber are measured [23]. With correction for thoracic gas and lung volumes by either measurement or estimation, total body volume is determined. Thoracic gas volume is measured via an estimation of both functional residual capacity and tidal volume. While seated inside the measurement chamber, the individual is required to place a plastic tube in the mouth, and with remote coaching from the technician, lightly blow air into a breathing tube connected to the system. Although less accurate, the BodPod software can also predict total lung volume if a direct measurement cannot be adequately obtained by the instrument [24]. An accurate measurement of body volume requires that individuals wear tight-fitting clothing (e.g., lycra swimsuit) to eliminate any residual air from body surface. Table 2 summarizes the relevant BodPod equations that are utilized to estimate FM and FFM.

Advantages of the ADP technique include the high level of safety, therefore allowing repeated measurements across pregnancy, as well as the relative ease and speed of estimating body composition. Disadvantages of the technique in pregnancy are indeed more profound. First, given well-described changes in TBW throughout pregnancy, there is a need to adjust coefficients applied to the estimated FFM density throughout pregnancy to accurately reflect the degree of increased FFM hydration; the manufacturer does not provide these adjustments in the current software. However, as pointed out earlier, the available FFM density adjustments are outdated and were derived from mostly women of normal weight and without evidence of clinical edema. Second, the ADP technique is not portable, and thus not suitable for field research, and is expensive to operate and maintain. A third disadvantage is the inability to assess body density of a pregnant woman independent of the growing fetus and supporting tissues, which limits the assumptions from BodPod to changes in maternal/fetal tissues. While body composition estimation via a 2C model is accepted, the derived estimate of FM and FFM is subpar compared to 3C or 4C models. It is also likely that measures of FM and FFM by ADP are affected by

Table 2 Calculations for total body density using air displacement plethysmography

Total body density (TBD) (kg/L)	$\frac{\text{Body Mass}}{\text{Body Volume}}$	<i>Body Mass (kg)</i> : scale weight derived by BodPod <i>Body Volume (L)</i> : Estimated by BodPod
Body volume (L)	$\frac{\text{Vol1} + \text{Vol2}}{2} + (0.4 \times \text{TGV}) - \text{SAA}$	<i>Vol1 and Vol2 (L)</i> : Lung volume estimated twice by BodPod via “Huff” Test <i>Thoracic Gas Volume (TGV) (L)</i> : Measured or Predicted by BodPod <i>SAA (L)</i> : Estimated surface area artifact
Thoracic gas volume (TGV) (L)	<i>Measured TGV</i> = FRC + (0.5 × TV) <i>Predicted TGV (females only)</i> = (0.0360 × Height (cm)) + (0.0031 × Age) – 3.182 + 0.35	<i>Functional Residual Capacity (FRC)</i> : Measured by BodPod via “Huff” test <i>Tidal Volume (TV)</i> : Measured by BodPod via “Huff” test Predicted TGV (gender-specific, age ≥ 18 years): (Crapo et al. [24])
Surface area artifact (SAA) (L)	<i>Subjects >110 cm</i> = [71.84 × Body Mass ^{0.425} × Height ^{0.725}] × k <i>Subjects ≤110 cm</i> = [242.65 × Body Mass ^{0.5378} × Height ^{0.725}] × k	Subjects >110 cm: (Dubois and Dubois [132]) Subjects ≤110 cm: (Haycock et al. [133]) Constant $k = -0.0000467$

variability in the estimation of thoracic gas volume. While seldom discussed in the literature, obtaining an actual measurement of thoracic gas volume by the BodPod is difficult for some individuals, and thus requires the use of predicted equations. Discrepancies between measured and predicted thoracic gas volume exist and cannot be ignored. For longitudinal measurements, it is important to apply either the measured or estimated thoracic gas volume throughout the assessments to limit this as a potential source of error in the FM and FFM estimations. Finally, residual air may also cause an overestimation of body volume, and adequate attention should be provided to minimize this artifact, especially in pregnant women when the size of the bust and abdomen is changing considerably and could contribute to increased residual air volume.

Imaging

Magnetic Resonance Imaging (MRI)

MRI is an *in vivo* imaging technique that uses a powerful magnetic field to measure adipose tissue, skeletal muscle, and organ mass. MRI acquisition protocols require that individuals must lie still in a small, enclosed space, often for lengthy periods, while the magnet is running. MRI has several advantages in that it allows for whole-body as well as regional estimates of body composition, and with no exposure to radiation in comparison to DXA. Sohlström and Forsum were one of the first groups

to conduct a well-controlled study using MRI in a cohort of 15 Swedish women throughout pregnancy [25]. The MRI showed that of the 7.4 kg gained in pregnancy (to 7 days postpartum), the majority was gained in whole-body subcutaneous adipose tissue. Modi et al. also reported a positive correlation between maternal BMI and total adipose tissue gain [26]. A recent cross-sectional analysis of normal weight and overweight/obese pregnant women using MRI to assess body composition at the third trimester [27] found that overweight/obese women had almost two times the amount of total body FM as well as subcutaneous abdominal fat compared to normal-weight women, with no differences in visceral fat between the two groups.

A recent methodological study was performed in obese women during the early second trimester of pregnancy (15–18 weeks) in order to develop a consistent method for calculating subcutaneous and visceral fat area ratios. By varying the thickness and distance of abdominal slices, the group concluded to produce reliable measurements of subcutaneous and visceral fat using MRI between women, the region of interest and acquisition of abdominal slices should be centered above the uterine fundus [28].

MRI research is highly promising in regard to body composition analyses in pregnant women, and will be critical to advance the understanding of the changes in regional fat distribution, particularly fat accumulation within the abdominal compartment. However, MRI is not without limitations. The most obvious limitation is discomfort attributed to being confined in a small space and position for the scanning protocols. Abdominal protocols, while short, can be very difficult and uncomfortable for pregnant women, especially in the later stages of pregnancy; some protocols require a 15-s breath hold to minimize movement of the chest cavity. In addition, limitations to the field of view will limit accurate abdominal scanning in some women. The MRI scanners can also be noisy; however, newer 3.0 tesla magnets are equipped with sound dampeners that reduce noise, and individuals are provided ear protection and plugs as well. The obvious limitation is cost. Many clinical centers charge approximately \$600 USD per 30-min of scanning time (sufficient for an abdominal scan), then the cost for analysis of the images is an additional expense. Manufacturer differences between scanners can introduce problems in standardizing hardware and software among clinical centers. To date, there are no current publications reporting the use of MRI to assess changes in body composition throughout pregnancy; however, two studies employing a whole-body scanning protocol are currently ongoing (MomEE: NCT#01954342; LIFT: NCT#01616147). Finally, it should be noted that safety of using MRI during the first trimester is questionable and, therefore, estimates of changes in body composition across pregnancy with MRI is only possible from the second trimester onward.

Dual-Energy X-Ray Absorptiometry (DXA)

DXA scans are used to measure total body composition by emitting X-ray beams overhead and throughout the entire body while lying supine. While designed to measure bone mineral density, DXA can also provide measurements of total and

region-specific FM and FFM. Since DXA scans emit radiation considered harmful to a developing fetus, DXA scans can only be conducted before and/or after pregnancy. A pre-gravid assessment of body composition with DXA, which provides measurements of bone mineral content as well as FM and FFM, can be used in conjunction with other measures performed during pregnancy to compute body composition from equations for either 3C or 4C body composition models. For example, an elegant study by Butte and colleagues used 4C modeling to compute change in maternal body composition throughout pregnancy and postpartum [29]. With the aid of DXA prior to pregnancy to estimate bone mineral content, Butte showed that accretion of TBW, FM, and FFM related linearly to gestational weight gain and that gestational weight gain above Institute of Medicine (IOM) guidelines led to excess postpartum fat retention. Similarly, Kopp-Hoolihan et al. used a 4C model with a DXA estimation of bone mineral content and observed 4.1 kg of body fat was deposited by 36 weeks of gestation [14]. Estimates of the changes in FM and FFM by DXA are primarily hindered by radiation exposure, and secondarily by the rapid changes occurring in all these tissues and changes in body water. Therefore, estimates of body composition in pregnancy by DXA should be interpreted with caution.

Total Body Water (i.e., Hydrometry)

Total body water (TBW) of the combined maternal–fetal unit can be measured by stable isotope deuterium (^2H) dilution methods. The basic principle of the labeled water technique is that after an ingested deuterium oxide ($^2\text{H}_2\text{O}$, or D_2O) quantity equilibrates within the TBW pool above the level naturally present (i.e., enrichment), it is eliminated from the body as urine and/or saliva. As such, saliva and/or urine measurements are taken just before $^2\text{H}_2\text{O}$ consumption and repeated up to several hours post-dose delivery (normal equilibration takes 3 to 5 h). An increased level of $^2\text{H}_2\text{O}$ appears in saliva and urine. Pre-dose samples are compared to post-dose samples to calculate TBW, FFM, and ultimately FM.

In a normal weight, pre-gravid female, FM can be derived by (body weight–(TBW/HC)), where HC is the hydration constant of FFM (or TBW:FFM ratio, i.e., 72.3–72.4%) [30]. The true HC proportion, however, can range anywhere from 67% to 80% [15, 31], with the HC proportion likely increasing with adiposity [32, 33]. As was previously described of whole-body densitometry adjustments by van Raaij and others (Table 1) with regard to decreases in total body density resulting from variable increases in FFM hydration throughout pregnancy [32], similar HCs have been quantified throughout pregnancy in different populations, as shown in Table 3. As a precaution, these adjustments should not be utilized as definitive HCs for all populations, as HCs likely vary depending on ethnicity and racial backgrounds, as well as in obese pregnancies. Overconfidence in such adjustments may lead to errors in the estimation of body composition. Adjusted HCs developed by both the van Raaij and Hopkinson groups may improve estimations of FM and FFM during pregnancy [10, 11].

Table 3 Hydration constants throughout pregnancy reported in the literature

Study	Pre-Gravid	10–14 weeks	~20 weeks	30–32 weeks	35–40 weeks
Van Raaij et al. [10]	–	0.725	0.736–0.743	0.740–0.750	0.746–0.765
Fidanza [20]	0.738	0.738	–	0.752	0.761
Catalano et al. [18]	–	–	–	0.762	–
Lof and Forsum [32]	0.718	0.723	0.747	0.747	–
Paxton et al. [4]	–	0.738	–	–	0.757
Kopp-Houlihan et al. [14]	0.724	0.725	–	–	0.740
Hopkinson et al. [11]	–	–	–	–	0.760 ± 0.02
Lederman et al. [134]	–	0.740	–	–	0.758
Prentice et al. [33]	–	–	–	–	0.768

Advantages of TBW measurements to estimate FFM in pregnancy is the use of the stable isotope. The isotopes are not harmful to the human body and highly portable, making this method suitable for field research. Disadvantages, like other 2C models in pregnancy, include the relative assumptions that need to be applied or corrections for these assumptions for pregnant women using relevant published literature. Unfortunately, derived hydration values are likely population specific and *cannot be easily applied* beyond the estimated population.

Ultrasound

Ultrasound is a simple technique available in most hospitals that involves the production of sound waves at varying frequencies to measure body composition during pregnancy. Ultrasound applied to measure subcutaneous fat thickness is highly correlated with measurements of caliper-based skinfold thickness, but it is considered to have a slight advantage over caliper-assessments in that it avoids the issue of skin extension that is problematic when using skinfold calipers in obese or pregnant populations [34, 35]. Ultrasound has been used in longitudinal studies to assess thickness of visceral as well as subcutaneous fat in both pregnant [36] and non-pregnant women [37]. The latter study demonstrated a correlation between intra-abdominal thickness from ultrasound and visceral adipose tissue estimated from computed tomography, whereas the former concluded that visceral adipose tissue increased over time during pregnancy. Visceral fat thickness measured with ultrasound in early pregnancy (11–14 weeks) was shown to correlate with several metabolic risk factors [38]. Although it is a safe, simple, and non-invasive technique, ultrasound is lacking because there is no standard protocol for pregnancy, and it has yet to be validated with any MRI measurements. Another limitation with ultrasound is the ability to derive only site-specific measurements of adipose tissue thickness and not measurements of whole-body composition. More research is needed to assess ultrasound validity throughout the course of pregnancy to more precisely measure body composition changes.

Comparison of Different Compartment Models (2C, 3C, and 4C)

Maternal body composition can be estimated by taking into account the tissue partitioned into 2-, 3-, or 4-body compartments. Referred to as the 2C, 3C, or 4C models, each model offers advantages over the other. In the 2C model, the body mass is simply partitioned into FM and FFM, where FFM encompasses TBW, bone, protein, and non-bone mineral mass and the remaining mass is estimated as FM. Changes in FFM hydration throughout pregnancy require FFM density adjustments when using 2C models like skinfold thickness, ADP, underwater weighing, and BIA. While equations predicting body composition from skinfold thickness are not ideal, skinfold thickness is easy and fast to administer and cost-effective if large sample size assessment is required. While more costly assessments like ADP, underwater weighing, and BIA can offer advantages over skinfold thickness, assumptions of FFM hydration make the 2C model in pregnancy flawed. Additionally, such assumptions are based on decades-old studies that are likely not applicable to all populations. However, if a 2C model is the only available model, adjustments using van Raaij and colleagues are recommended [10].

While a 4C model is the ideal model of body composition estimation, the 4C model is not possible in pregnant women due to the inability to derive bone mineral data from DXA during gestation. Several studies have applied the 4C model successfully by measuring bone in the pre-gravid and postpartum states [11, 12]. However, it should be noted that since more than 50% of pregnancies in the US are unplanned, some of these assessments have occurred more than 1 year prior to the index pregnancy [13], therefore limiting the use of the method in most cases. Research has demonstrated, however, that 3C models, which include the addition of TBW estimation, may indeed be adequate to estimate body composition during pregnancy [11, 14, 15]. Specifically, equations derived by Pipe et al. [2] and Siri [15] are likely the optimal method for deriving an improved 3C model.

Gestational Weight Gain

What Is Gestational Weight Gain?

Normal physiologic and metabolic changes occur during pregnancy and are related to variable growth rates of maternal, placental, and fetal components that contribute to increased gestational weight gain (GWG), or weight gain from conception to delivery. Usually, pre-gravid weight is self-reported. As pregnancy progresses, the accumulation of FM, FFM (i.e., protein accretion), TBW, and minerals is deposited in the fetus, placenta, and amniotic fluid, which contribute to the fetal component of GWG or ~35% of total GWG [39]. Conversely, the developing uterus and breast tissue, as well as extracellular fluid, blood, and adipose tissues, contribute to the maternal component, or ~65% of total GWG [39].

Table 4 Recommended total weight gain ranges by pre-gravid BMI during pregnancy

Pre-gravid BMI	BMI (kg/m ²)	Total weight gain range (lbs)	Rate of weight gain ^a during second and third trimester [Mean Range in lbs/week]
Underweight	<18.5	28–40	1 [1.0–1.3]
Normal weight	18.5–24.9	25–35	1 [0.8–1.0]
Overweight	25.0–29.9	15–25	0.6 [0.5–0.7]
Obese (<i>includes all classes</i>)	≥30.0	11–20	0.5 [0.4–0.6]

^aCalculations assume a 1- to 4- lb. (or 0.5–2.0 kg) weight gain during first trimester

The recent *Institute of Medicine Report on the 2009 Guidelines for Recommended Weight Gain during Pregnancy* defined recommendations for total weight gain in pregnant women according to the different classes of pre-gravid BMI, as shown in Table 4. While the first trimester is usually characterized by only a slight total weight gain of approximately 1–4 lbs. (or 0.5–2.0 kg), the second and third trimesters feature the predominance of the weight gain during gestation. Figure 1 shows early and late GWG contributions to maternal and fetal units. Gestational weight gain is inversely related to pre-gravid BMI. For example, women with normal to underweight pre-gravid BMI are recommended to gain weight at a rate of approximately 1 lb. (~0.4–0.5 kg) per week during the second and third trimesters, with overweight women recommended to gain 0.6 lbs. (~0.3 kg) per week, and obese women 0.5 lbs. (~0.2 kg) per week [40]. The current guidelines state that women with GWG that exceeds these recommended ranges are more likely to retain weight postpartum and are at increased risk for subsequent obesity. Indeed, abnormal or excessive GWG is a strong predictor of pregnancy outcomes for both women and infants. For example, the odds of developing abnormal glucose tolerance in the third trimester of pregnancy are greater with higher rates of GWG [41]. Maternal obesity and weight retention postpartum are also associated with excessive GWG [42]. In addition to these maternal outcomes, excessive GWG is associated with infants born large for gestational age, and excessive neonatal and infant weight [43–45].

What Causes GWG?

GWG can be brought about by a variety of factors. The physiological alterations discussed later in this chapter are some of the contributing factors, but others include age, race, and pre-gravid BMI. Increased maternal age has been found to be associated with an increased risk for low birth weight and small-for-gestational-age children [46, 47]. Furthermore, Gross and colleagues found that obese women ≥35 years

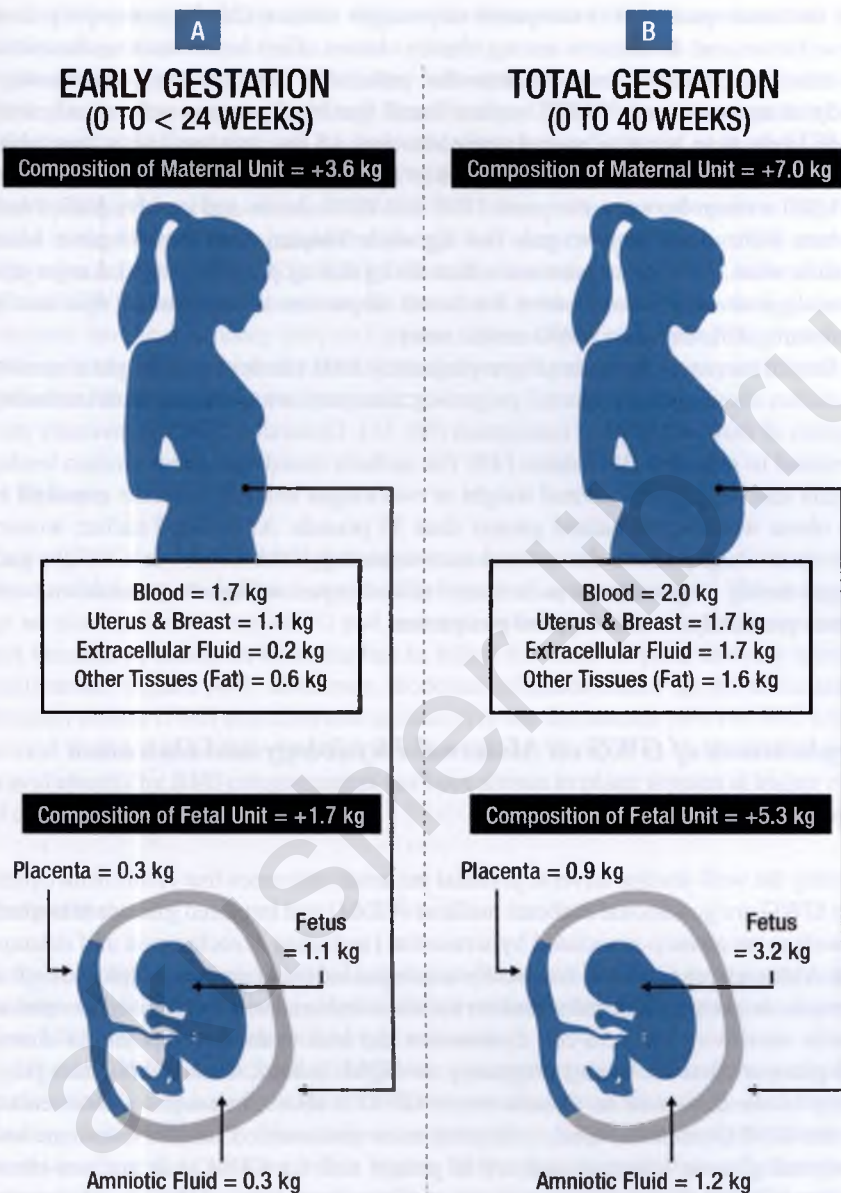


Fig. 1 Components of gestational weight gain (GWG) since last menstrual period. Maternal and fetal components of GWG are noted. Panel (a) represents Early GWG (0–<24 weeks) and Panel (b) represents the Total GWG (0–40 weeks). Late GWG contributions are simply the difference between Total and Early GWG. The stated contributions to GWG are from those of a healthy BMI woman who gains within the recommended IOM weight gain guidelines throughout pregnancy. Women who gain above the recommended guidelines are expected to contribute larger GWG in both the maternal and fetal units. (Percentages adapted from Pitkin RM. Nutritional support in obstetrics and gynecology. Clin Obstet Gynecol. 1976 Sep;19(3):489–513)

old had inadequate GWG compared to younger women (25–29 years) [48]. How these factors and differences among obesity classes affect birth outcomes has yet to be elucidated. Race is another factor that influences GWG; a large epidemiology study of approximately 53,000 women found that black women were significantly more likely than white women to gain less than 15 lbs., but less likely than white women to gain greater than 34 pounds [49]. Further, the IOM noted a study of 913,320 women between the years 1995 and 2003. Asian and non-Hispanic black women were more likely to gain 0–9 kg while Hispanic and non-Hispanic white women were more apt to gain more than 20 kg during pregnancy [40]. Larger epidemiological studies that control for health disparities are warranted, specifically comparing differences in GWG across races.

Recent increases in maternal pre-pregnancy BMI has brought to light a number of studies showing that maternal pregnancy outcomes are worsened with increasing degrees of maternal BMI at conception [50, 51]. Generally, GWG is inversely proportional to maternal BMI status [49] The authors found that obese women tended to gain less weight than normal weight or overweight women; however, a quarter of the obese women still gained greater than 35 pounds. As detailed earlier, women who gain weight above the normal recommended IOM Guideline's weight gain ranges during pregnancy are at increased risk of experiencing adverse maternal outcomes prenatally, at delivery, and postpartum.

Implications of GWG on Maternal Physiology and Outcomes

During Pregnancy

Among the well-studied adverse prenatal maternal outcomes that result from excessive GWG are gestational diabetes mellitus (GDM) and impaired glucose tolerance, as well as pregnancy-associated hypertension (including preeclampsia and eclampsia). Although pregnancy is frequently accompanied by a pronounced physiological decrease in peripheral insulin sensitivity, the combination of decreased peripheral insulin sensitivity and beta-cell dysfunction can lead to the development of abnormal glucose tolerance during pregnancy, or GDM. Indeed, women who enter pregnancy as obese, as well as women whose GWG is above the ranges recommended by the IOM Guidelines, tend to develop more pronounced insulin resistance and abnormal glucose tolerance and are at greater risk for GDM than are non-obese women [52–56]. Some studies even report that women whose GWG was below the recommended range had a higher likelihood of GDM [56–58]. However, there have been studies finding no significant association between GWG and glucose tolerance [59–61].

Weight gain above recommended ranges might also increase risk of experiencing pregnancy-associated hypertension. While the association between GWG and hypertensive conditions remains unclear due to limited and inconclusive data [54, 57, 58, 62, 63], some studies (all rated fair or poor in quality) have reported such

an association does exist [58, 63], with others lack consistent control for confounding.

Interestingly, the timing of GWG may influence different physiological and metabolic factors throughout pregnancy. Specifically, GWG above the recommended guidelines in the first trimester has been shown to be predictive of excessive GWG for the entire pregnancy [64]. Women with a normal-weight preconception BMI have a 70% probability of excess total GWG when excess weight gain is experienced in the first trimester, while overweight and obese women have a 90% probability of excess total GWG [65]. While research is limited, excess GWG, independent of total GWG, has been shown to be associated with impaired maternal glucose tolerance later in pregnancy [66] and greater infant adiposity at birth [65], therefore making future adherence to the recommended weight gain guidelines possibly more critical in these early stages of pregnancy.

At Delivery

Excess GWG has also been suggested to increase the risk of complications during labor and delivery, as well as increased likelihood of cesarean section. The evidence for an association between GWG and cesarean delivery is inconsistent, however, in part because of failure in some studies to adjust for route of prior delivery among multiparous women [67]. Moreover, moderate evidence exists on the association between excess GWG and cesarean section over the last decade [63, 68–73], while several recent studies failed to find an association [57, 60, 74]. Additionally, pre-gravid obesity by BMI categorization has been shown to place women at higher risk of cesarean delivery [60, 70–72, 74].

Postpartum

In the postpartum period, potential consequences of excess GWG during pregnancy include weight retention, decreased lactation performance, and postpartum depression, likely as a consequence of weight retention.

Higher GWG is associated with greater postpartum weight retention, yet many studies fail to consistently adjust for dietary intake, physical activity, and breastfeeding behavior [67]. Nonetheless, subsequent postpartum weight retention increases the risk of moving into a higher BMI category regardless of subsequent pregnancies, thereby increasing the risks to the woman and her fetus during subsequent pregnancy, and to the woman's own longer-term health and risk of cardiovascular disease, type 2 diabetes, cancer, and mental health.

While data is inconclusive, unsuccessful lactation, or decreased lactation performance, may also result from excess GWG during pregnancy. One study has examined the relationship between GWG and lactation and did not find any relationship between GWG and either milk quality or quantity [75]. While obese women have been reported to have shorter breastfeeding duration regardless of GWG [76–79],

the evidence for any association between GWG and duration of exclusive or any breastfeeding was rated weak; evidence that low weight gain is associated with decreased initiation of breastfeeding was rated moderate.

Implications of GWG on Infant Physiology and Outcomes

Excess GWG

Historical examinations of weight gain in pregnancy conclude that very little weight gain occurs in the first trimester and weight thereafter increases linearly until delivery [40]. Following the publication of the IOM recommendations for weight gain in pregnancy, the impact of total GWG on maternal and infant outcomes has received increasing attention. Epidemiological studies show that excessive GWG significantly increases the risk for large-for-gestational-age (LGA) infants [80, 81]. A recent study of 650 pregnant women reported that in comparison to adequate GWG throughout pregnancy, excess GWG through 20 weeks, regardless of the change in weight later in pregnancy, significantly increased the risk of LGA infants [82]. Furthermore, a physical activity intervention for healthy management of GWG found that neonates born to women with excessive GWG early in pregnancy not only exhibited greater birth weights, but had significantly more body fat at birth compared to those neonates born to women with adequate GWG or excessive GWG later in pregnancy [83]. A recent study from Overcash et al. [84] suggests that early GWG in obese women of as little as 2 pounds in the first trimester (12–14 weeks) is a strong predictor of exceeding GWG values throughout pregnancy, and that second and third trimesters have the highest relative effect on total GWG. Knabl et al. also reported similar findings in even earlier periods of 8–12 weeks [65]. These studies suggest the timing of GWG may be important for infant outcomes and, in particular, that early gestational weight gain may be more influential for infant outcomes.

Insulin resistance and glucose intolerance during pregnancy can also have effects on GWG. Typically, the risk is higher among mothers who are overweight and obese. Complications can arise for the fetus if the mother has a persistent hyperglycemia because glucose can cross the placenta freely, in turn causing hyperglycemia in the fetus as well. This process is termed “fuel-mediated teratogenesis”; fetal hyperglycemia leads to hyperinsulinemia and can cause an increase in fetal adiposity [85]. Subsequently, this increased fetal adiposity can lead to LGA infants, which could lead to childhood obesity. In a large epidemiological study of more than 27,000 women, abnormal maternal glucose tolerance was associated with higher birth weight and length in the first 3 months of life and more weight gain from months 9–12 [86]. This same group also confirmed this from 6–12 months of life, as well, in mothers with higher fasting glucose levels from weeks 4–12 of gestation [87].

Preterm birth rates (<37 weeks of completed gestation) are also associated with GWG. In an extensive review by Viswanathan et al., there is a U-shaped association between GWG and preterm birth in that women in the lowest and highest ends have

the highest association of giving birth preterm [88]. The recent IOM guidelines state that there is some evidence that the increased risk of preterm birth associated with a higher rate of GWG was greater with increasing BMI [40]. However, most data on this topic are still mixed as to whether preterm births arise from excessive or inadequate GWG.

Excessive GWG can lead to more long-term consequences in the child. Sewell et al. found an association between higher GWG and higher fat mass in newborn infants [89]. Another study from the same group found that in a total of 415 women, GWG directly associates with FM at birth [90]. This was also confirmed in other studies that children born to mothers who enter pregnancy overweight or obese have significantly more adiposity at birth [91, 92]. Furthermore, rapid weight gain during infancy is also related to the development of obesity later in life [93, 94]. Longitudinal studies indicate maternal adiposity has a positive influence on adiposity at 1, 2, 9, and 30 years into life [95–98].

Inadequate GWG

The initial goal of the IOM in 1990 was to assure adequate GWG in order to prevent complications of low fetal growth and negative outcomes associated with small-for-gestational-age (SGA) infants. Since obesity has become more of an epidemic in recent decades, the focus has shifted toward avoiding excessive GWG. Nonetheless, there is evidence showing that inadequate GWG can have negative outcomes on fetal health as well. It is well established that inadequate GWG increases the risk for SGA infants [99, 100].

One of the most severe adverse outcomes in SGA infants is neurodevelopment. A few studies found that SGA children performed worse in school than gestational age-matched controls at 10 years of age and also had a slightly lower mean IQ at 5 years of age [101–103]. Although findings on this topic tend to be inconsistent, the recent IOM guidelines report that SGA is associated with minimal neurologic dysfunction, but no major handicaps (e.g., cerebral palsy).

Body Composition Changes and Impact on Physiology in Pregnancy

Body Composition Changes

Body composition changes throughout pregnancy are contributed to by not only the physiology and metabolism of the mother, but also the growth of the developing fetus. The relationship between maternal changes and fetal development could possibly interact with each other and cause changes in homeostasis accordingly. This section will further outline described changes in maternal body composition and

physiology during pregnancy. In addition, it will outline changes contributed by the fetus including the products of conception (placenta, fetus, and amniotic fluid), which are thought to contribute up to a third of gestational weight gain [39].

Maternal Fat and Fat-Free Mass

A landmark study in 1991 by Hytten and Chamberlin found that almost half of FFM accumulated in pregnancy is due to the development of the fetus, with the remaining contribution being attributed to the uterus, maternal blood, placenta, and the breasts [104]. Assessments of the amounts of total body protein accrued were derived from measurements of total body potassium. Various studies have investigated protein accrual during pregnancy and found the amounts to be somewhat negligible at less than 1 kg [29, 105, 106]. Depending on the model of body composition being considered, total body water can also fall into the category of FFM. Hytten and Chamberlin in the same report found that on average 7–8 L of water is accumulated during pregnancy [104]. The water accumulation breakdown is described as: 32% fetus, 20% extracellular fluid, 17% blood, 11% blood-free uterus, 10% amniotic fluid, 7% placenta, and 4% mammary glands. Using BIA, Larciprete et al. reported plasma volume also increases with advancing pregnancy and found that TBW correlated with birth weight [107].

The recent IOM guidelines for GWG have established that much of the variance in total GWG can be accounted for by variable increases in FM. Fat mass accumulation throughout pregnancy is shown to have an inverse relationship with pre-gravid BMI [12]. This study also showed that fat mass parallels, and is positively associated with, gestational weight gain, although it is inversely associated with pre-gravid weight. Studies using MRI of body composition show that the majority of fat accumulation (upwards of 76%) arrives in subcutaneous compartments, with almost half of that being in the lower trunk, a third in the upper trunk, and the rest spread throughout the limbs [108]. There is a major gap in our understanding of the partitioning of fat in pregnancy in the abdominal cavity to visceral compartments and also the accumulation of lipid in other non-adipose tissues such as the skeletal muscle and liver. Hopefully, with the expanded use of MRI in pregnancy research, the deposition of lipids in adipose and non-adipose tissues will soon be understood.

Products of Conception

Placenta

According to the IOM report, placental weight for singleton births can range from 143 g at week 20 up to 478 g by week 37 [40]. Bleker and Hoogland analyzed placental volume using ultrasound and found a linear increase in placental volume up to 24 weeks, plateauing at around the third trimester [109]. Placental growth is believed to occur in two phases [40]. The first phase, lasting up until 36 weeks, is noted by increases in both the parenchymal and non-parenchymal tissue. The

parenchymal tissue consists of intravillous space, the trophoblast tissue, and fetal capillaries of peripheral and stem villi. The non-parenchymal tissue consists of the decidual and chorionic plates, intercotyledonary septa, fetal vessels, connective tissue, and fibrin deposits. The second phase occurs when the placenta is maturing, and lasts from the end of phase 1 up until term, and growth during this phase is primarily characterized by an increase in the size of the fetus. The placenta is comprised of approximately 88% water, 11% protein, and 1% fat [40].

Fetus

The human fetus weighs approximately 1 kg by 28 weeks and then, over the next 12 weeks, gains approximately 2.5 kg [40]. Halfway through the second trimester, fetal fat tissue begins to accumulate, and therefore FFM as a percentage of total body weight is reduced. Fetal growth curves relating to viable fetuses rely on clinical data from the halfway point of the second trimester (~30–32 weeks of gestation). As summarized in the IOM report, the growth rate of the fetus is relatively identical up until this time point, after which deviations may occur, leading to different sizes of fetus at birth [40]. According to work by Catalano et al., fetal body fat comprises approximately 10% of weight at birth [110]. Acknowledging that fat mass at birth is likely impacted by the size of the infant, Koo et al., using DXA, found that neonates whose birth weight was <2500 g were composed of 6–14% body fat, whereas neonates weighing >2500 g at birth had 8–20% body fat and infants large for gestational age (3500 g), had 16% body fat [111]. Studies using air displacement plethysmography echo these later observations and further describe a linear relationship between infant adiposity and GWG [112].

Amniotic Fluid

Fluid flows in (fetal urine and lung-liquid) and out (fetal swallowing and intramembranous absorption) of the amniotic sac during the later stages of gestation [113]. There is a wide variation in the amount of amniotic fluid present throughout normal pregnancies. On average at week 8 of gestation, amniotic fluid increases at a rate of approximately 10 mL per week, at week 13 this increases up to 25 mL per week, and by week 21, 60 mL per week before finally maximizing volume at around 33 weeks of gestation [114].

Maternal Metabolism

Carbohydrate and lipid metabolism change during pregnancy to help nurture the developing fetus [115]. Studies on substrate utilization during the early period of gestation are lacking; however, in general, studies suggest that the change in substrate oxidation throughout pregnancy is not altered by maternal obesity.

Plasma-free fatty acids have been shown to be elevated in the later stages of pregnancy [116, 117]. This is also the case in overweight and obese pregnant women during the second and third trimesters, which has implications for an increase in lipolysis due to higher insulin resistance during these periods, particularly during the third trimester, where fat oxidation is the highest [118]. In a larger cohort of 60 obese women, Sivan et al. also confirmed that carbohydrate oxidation decreased approximately 80% from the second to third trimester of pregnancy, suggesting that free fatty acid levels should be higher than usual during this period [119]. This was later confirmed in another study with obese women with significant increases in fat oxidation of 50–80% during late pregnancy from basal levels with a more remarkable change, however, coming from early to late pregnancy [120]. Freinkel coined the term “accelerated starvation” as a possible explanation of these physiological changes [121]. These studies confirm this concept in that during late pregnancy, there is a switch from carbohydrate oxidation to increased fat oxidation in order to provide energy from carbohydrates to the growing fetus. Whether or not changes in substrate use in early pregnancy can influence the size of the baby at birth has yet to be elucidated and is an important consideration for future research. Protein and nitrogen metabolism are altered early on in pregnancy. There is a notable decline in serum total α -amino nitrogen, as well as the rate of urea synthesis and the rate of transamination of branched-chain amino acids [122]. However, protein turnover by weight does not change [122]. Although there is a gradual decline in serum total protein and albumin such that by term, they are 30-fold lower than non-pregnant values [104].

Early on, glucose tolerance is normal or improved slightly, and peripheral sensitivity to insulin and hepatic basal glucose production are normal or can increase up to 15-fold [123–125]. Throughout pregnancy, nutrient-stimulated insulin responses increase gradually [126]. Later on, insulin action is 50- to 60-fold lower than in non-pregnant women [123–125, 127, 128]. By the third trimester, basal and 24-h mean insulin concentrations can increase twofold [129]. These changes bring about a lowering in the ability of insulin to blunt lipolysis [130]. Insulin sensitivity may increase or decrease during early pregnancy based on pre-gravid insulin sensitivity status of the woman. For women who are highly insulin-sensitive, insulin sensitivity tends to decrease, and is subsequently followed by a rise in basal metabolic rate. On the other hand, for insulin-resistant women, especially those who have obesity or gestational diabetes, insulin sensitivity increases and basal metabolic rate subsequently falls [120]. These differences may help explain why obese women gain less weight during the early stages of pregnancy compared to lean, insulin-sensitive women.

New Directions in Body Composition Assessment

Currently, there is a lack of information on the short- and long-term outcomes of body composition changes during pregnancy on maternal and offspring outcomes, and also whether these associations vary by pre-gravid BMI and body composition

changes during pregnancy as they relate to changes in FM and FFM. Limited information is largely the result of the challenges related to the methodological issues and challenges of measuring body composition during pregnancy. Indeed, the influence of earlier compared to later gestational weight gain and body composition changes is an important avenue to explore. Clearly, exploring the changes in visceral fat accumulation across pregnancy and the relationship to future risk for maternal metabolic disease or infant outcomes at birth and early in life are also of great interest. MRI protocols need to be developed and shared to allow for data to be more easily combined across studies, and for abdominal fat distribution, the anatomical landmark used to quantify subcutaneous and visceral fat is important given changes in maternal posture and organs throughout gestation [28].

Given the importance of not only GWG but also the likely distribution of GWG, particularly the expansion of adipose tissue stores, an opportunity exists to merge data from the previously reported, carefully controlled studies of body composition to develop models of body composition changes in pregnancy. To our knowledge, Thomas and colleagues contributed the only published work detailing a dynamic mathematical model for pregnancy that derives predictions of the changes in dietary energy intake necessary to support GWG on the basis of pre-gravid weight, height, and age [131]. Future models might explore the impact of energy intake by trimester on GWG as it pertains to the absolute and/or rate of visceral and subcutaneous fat deposition during gestation, and further implicate these to maternal and infant outcomes. Indeed, the availability of more complex imaging technology such as MRI will be required to undertake this work. Even more simply, similar to the guidelines for GWG, more complex models of body composition might provide clinicians with improved tools to understand the potential risk of early weight gain to future metabolic consequences for the mother and her child.

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Iron Requirements and Adverse Pregnancy Outcomes

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Keywords Pregnancy · Anemia · Hemodilution · Iron deficiency · Ferritin · Neonate Heme · Placenta

Key Points

- Optimal Fe status across gestation is needed to support the increased maternal Fe demands of pregnancy and to fully endow the developing fetus with sufficient iron.
- There may be key windows of gestation at which time insufficient iron supply to the fetus may have persistent adverse consequences on fetal brain development.
- The placenta mediates iron transport to the fetus in response to both maternal and fetal iron regulatory signals.
- Maternal Fe is obtained from dietary heme and non-heme iron sources. At this time little attention has been given to the different mechanisms of absorption and utilization of heme versus non-heme iron across pregnancy.
- Normative data on Fe status biomarkers across gestation and their relationship to maternal and neonatal outcomes are limited. These data are needed to improve the assessment and interpretation of maternal Fe status and to provide normative data that can be used to evaluate iron biomarkers, iron regulatory hormones, and risk of anemia in the neonate at birth.
- Nutrient–nutrient interactions are increasingly recognized to influence maternal iron status and the risk of anemia. These interactions and their impact on iron requirements, utilization and risk of anemia across gestation require further attention.
- Currently there are no national longitudinal data evaluating the impact of Fe supplementation in pregnant North American women. Research addressing this gap is needed to fully evaluate the possible benefits and adverse consequences of maternal Fe supplementation.

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Introduction

Anemia remains a significant public health problem in both developed and developing countries. The prevalence of anemia during pregnancy is highly variable ranging from 17–31% in Europe and North America to 53–61% in Africa [1]. In the United States, National Health and Nutrition Examination Survey (NHANES) data found that 18% of pregnant women were Fe deficient (ID) while 5.4% were anemic [2]. Rates of ID in some populations increase nearly fourfold as gestation progresses from 6.9% in the first trimester to ~28% by the third trimester [2], consistent with the marked increases in fetal Fe demands that occur during late gestation. Because the majority of maternal anemia is attributed to Fe insufficiency, attention has been placed on ensuring that dietary Fe intake across gestation is sufficient. Maternal Fe requirements should also be sufficient to ensure that sufficient Fe is available during key periods of fetal growth and to endow the neonate with Fe stores that are sufficient to support early infant development and the rapid growth that occurs over early infancy and the first year of life.

Several reviews have evaluated the efficacy of multiple-micronutrient supplements and daily or intermittent oral Fe supplementation on maternal birth outcomes and Fe status [3–5]. Results on daily or intermittent Fe supplementation regimens have highlighted the positive impact of Fe supplementation on reduced risk of maternal anemia and low Fe stores, but effects on maternal birth outcomes (preterm birth and low birth weight) vary between studies. The US Preventive Services Task Force recently released an updated systematic review on Fe supplementation and screening practices for ID across pregnancy [6]. This report concluded that the existing body of evidence is inconclusive with respect to the ability of prenatal Fe supplementation to improve maternal or infant clinical health outcomes, and highlighted the need for further data to target existing gaps in the current literature [7].

Iron Balance in Pregnancy

Iron Demands of the Mother and Fetus

Across the 266 days of a human gestation, the fetus must accumulate roughly 300 mg of Fe [8]. This net transfer of Fe to the fetus is substantial when compared to the 1–2 mg of absorbed Fe per day that is typically sufficient to maintain a positive Fe balance prior to pregnancy [9]. Fetal utilization of Fe across pregnancy is not linear; the majority of fetal Fe accretion occurs during the last 90 days of pregnancy [10]. At this time the fetus accrues approximately 5–8 mg of Fe per day [8]. This requirement is four times higher than the amount of Fe typically absorbed per day in non-pregnant women, and represents nearly 50% of the 20 mg of Fe that is released daily from the catabolism of senescent red blood cells [9]. Substantial alternations in maternal Fe absorption, tissue Fe utilization, and Fe partitioning are

needed in order to meet the Fe demands of pregnancy. Recent studies have provided new information on how pregnant women modify non-heme and heme Fe absorption and mobilization of maternal Fe reserves to accommodate Fe requirements across gestation.

In early gestation, pregnant women experience a net Fe gain due to the cessation of menses. These savings that may occur during the early stages of gestation are highly variable, given that daily menstrual losses of Fe can range from 0.65–4.88 mg/d [11, 12]. By the second trimester of pregnancy, Fe requirements increase substantially to support the ~50% increase in plasma volume and the concurrent ~35% increase in red blood cell mass [13]. During the third trimester of pregnancy, daily Fe demands peak as the fetus grows significantly in size and accrues the majority of its total body Fe. Iron utilized in support of these increased demands is obtained from maternal body reserves and from increased absorption of dietary and/or supplemental Fe as maternal body Fe stores are depleted. The dynamics of fetal growth, Fe uptake by the fetus, and Fe requirements across gestation are shown in Fig. 1.

Iron Absorption Across Pregnancy

Iron is the only mineral that humans cannot physiologically excrete should excess Fe be accumulated. Because of this unique aspect of Fe physiology, numerous regulatory processes work to tightly control non-heme Fe absorption and release of Fe into the circulation from existing body Fe reserves. These mechanisms are integral to preventing the adverse effects that can be caused by an excess of non-transferrin bound Fe, but these regulatory systems also make it challenging to quickly replete Fe stores when necessary. Three hormones to date have been found to be integral to the maintenance of Fe homeostasis; erythropoietin (regulated in response to hypoxia), erythroferrone (regulated in response to stress erythropoiesis), and hepcidin (regulated by body Fe stores, hypoxia, and inflammation) [14]. Of the three hormones, hepcidin is responsible for regulating Fe export from cellular body stores and from the enterocyte. This negative regulatory hormone is released in greater amounts by the liver in response to increased body Fe stores. Hepcidin binds to the only cellular Fe export protein (ferroportin) and causes this protein to be internalized and degraded, thereby blocking non-heme Fe export into the bloodstream [15].

Using stable Fe isotopes, studies in pregnant women have found that hepcidin explains approximately 30% of the variability in intestinal absorption of non-heme Fe [16]. Similar amounts of variability in Fe absorption are explained by body Fe stores, as monitored by serum ferritin [16]. When Fe stores decrease in pregnant women, Fe absorption increases, but the ability to up-regulate non-heme Fe absorption is limited. During the third trimester of pregnancy Fe absorption has been found to increase on average by 3.6% for every 10 $\mu\text{g/L}$ decrease in serum ferritin concentrations [17].

Nearly all of the focus on Fe absorption across gestation has centered on regulation of non-heme Fe absorption. Using stable Fe isotopes, studies have utilized

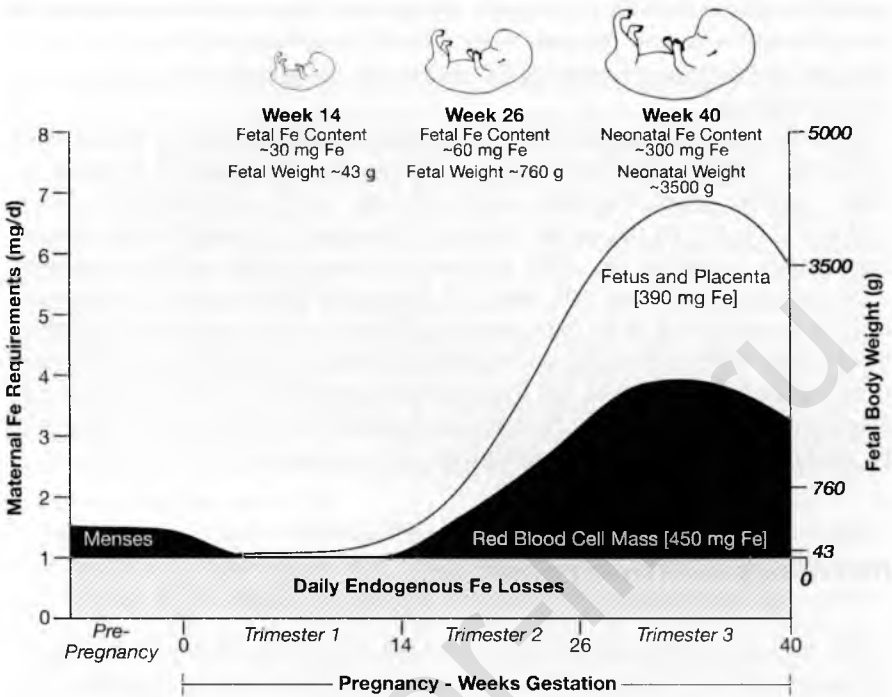


Fig. 1 Maternal and fetal iron requirements across gestation. Maternal and fetal iron demands change markedly across gestation. Early in pregnancy maternal Fe demands decrease due to the cessation of menses and little net Fe is accrued by the first trimester fetus. By the start of the second trimester of pregnancy (week 14 of gestation) increased maternal Fe is needed to support the marked increase in maternal red blood cell mass that occurs as plasma volume is expanded, and to provide the Fe needed to support the rapid fetal growth that occurs between weeks 14 to 26 of gestation. At week 14 of gestation the fetus weighs approximately 43 g and contains roughly 30 mg of Fe [10]. By the start of the third trimester of pregnancy the fetus has doubled its total body Fe content to 60 mg of Fe while increasing its body weight roughly 17-fold [10]. Over the last trimester of pregnancy, 3–8 mg of iron per day is needed to support daily fetal Fe acquisition. [8] An average sized neonate contains approximately 300 mg of iron at birth, the majority of which is found as neonatal hemoglobin. At delivery, additional Fe is lost as the placental and umbilical cord are delivered (~90 mg) and due to maternal blood losses at delivery (~150 mg) [92]. The net iron cost of pregnancy has been estimated to total 580 mg [92]

intrinsically labeled porcine heme Fe to compare absorption of heme Fe to that of ferrous sulfate during the third trimester of pregnancy compared to a control group of non-pregnant women [18]. Using this approach, heme Fe absorption was found to be threefold higher than absorption of non-heme Fe in the non-pregnant women (50.5% versus 15.2% respectively, $p < 0.001$ $n = 11$), but in pregnant women (67% of whom had undetectable hepcidin) the difference observed between heme and non-heme Fe absorption was substantially reduced (47.7% versus 40.4%, $p = 0.04$, $n = 18$). Unlike the significant impact of maternal Fe status on absorption of non-heme Fe, absorption of heme Fe was not associated with Fe status or hepcidin in the

non-pregnant or pregnant women [18]. Relative bioavailability of heme Fe during pregnancy has also been examined in 90 pregnant women who were randomized to receive either ferric fumarate alone (27 mg) or ferric fumarate and heme Fe (24 mg of ferric fumarate and 3 mg heme Fe) from week 20 of pregnancy through 24 weeks' postpartum. Women randomized to the heme-containing supplement exhibited increased Fe stores at the end of pregnancy and greater maternal Fe stores at 24 weeks' postpartum [19].

The mechanisms of enterocyte heme Fe uptake and export remains poorly characterized. Heme has been postulated to enter the enterocyte via a specific cellular protein (heme carrier protein 1 [HCP]/proton coupled folate transporter [PCFT]) or by a less-specific endocytic pathway. Once internalized into the enterocyte, heme may be catabolized into inorganic Fe (using heme oxygenase 1) and exported using ferroportin or if it is not catabolized within the enterocyte, the heme Fe may be exported intact using a heme export protein such as FLVCR1 (feline leukemia virus subgroup C receptor 1) which is known to be expressed in the enterocyte [20]. If heme is exported intact, it may also be preferentially utilized by the fetus. In the isotopic study of heme versus non-heme Fe mentioned above [18], Fe isotopic enrichment of the maternally ingested heme and non-heme Fe were evaluated in neonatal cord blood at birth. Using multiple approaches, in all instances there was a significantly greater neonatal enrichment of dietary Fe of heme origin, even after adjusting for the greater maternal absorption of heme [21]. This study suggests that heme Fe may be exported intact by the enterocyte, and if exported intact as heme Fe, it may be taken up by the myriad of heme trafficking proteins that have recently been found to be highly expressed in the human placenta [22].

Physiological Adaptations in Non-Heme Fe Absorption in Response to Fe Supplementation

Given the known associations between maternal Fe status and non-heme Fe absorption, one would predict that maternal responses to inorganic Fe supplementation would be heavily influenced by baseline Fe status. Most Fe supplementation studies, however, have not attempted to control for pre-pregnancy Fe status or stratify the study population by entry level hematological status. A large Fe supplementation study ($n = 1268$) by Roberfroid et al. supplemented pregnant women with either a daily Fe folate supplement (containing 60 mg of Fe) or a UNIMMAP multiple micronutrient supplement (containing 30 mg of Fe) at entry into the study (week 17.3 ± 7.6 weeks of gestation) [23]. Response to supplementation was uniquely evaluated as a function of entry-level hemoglobin concentrations; women who were anemic at baseline exhibited a significant increase in hemoglobin across gestation while women in the Fe replete population at baseline exhibited a decrease in hemoglobin concentrations across pregnancy (regardless of supplement ingested). Both groups ended the study with comparable hemoglobin concentrations, and 52% of women

remained anemic at late gestation while receiving Fe supplementation [23]. These findings highlight both the physiological decrease in hemoglobin that occurs over the course of gestation and the ability to appropriately regulate absorption of non-heme Fe in relation to gestational Fe demands. Had the study population not been stratified by baseline Fe status, the impact of Fe supplementation from either supplement would likely have been blunted, and the ability to regulate Fe absorption as a function of maternal Fe status may not have been appreciated. This example highlights the responsiveness of the enterocyte to physiological demands and draws attention to the mixed results that may be evident in supplementation studies dependent on the degree of anemia or Fe insufficiency that is evident when supplementation is initiated.

Adverse Effects of Iron Supplementation

In spite of robust regulatory pathways that can control absorption of non-heme Fe, concern exists that routine Fe supplementation of all pregnant women, including those who are asymptomatic and non-anemic, may increase the body Fe burden and possibly cause harm in those who are already Fe replete. Several studies in diverse population groups have found U-shaped associations between maternal hemoglobin and risk of preterm birth and low birth weight [24–26]. It is not clear if those with elevated hemoglobin concentrations have increased Fe stores or if these associations are due in part to a failure to appropriately expand maternal plasma volume across pregnancy.

In the large Fe supplementation study by Roberfroid, risk of hemoconcentration in pregnant women ($Hb > 13$ g/dL) was significantly positively associated with maternal micronutrient intake. Of women in the highest tertile of micronutrient intake, significantly more women become hemoconcentrated between the first and second study measurements (10.0%) compared to 4.8% and 8.6% who became hemoconcentrated in the first and second tertiles of micronutrient intake, respectively [23]. Of note, risk of hemoconcentration was not associated with maternal hemoglobin concentrations at baseline or by the type of Fe supplement ingested (Fe only versus a multiple micronutrient supplement) [23].

The 2015 US Preventive Services Task Force systematic review on Fe supplementation and screening for anemia during pregnancy noted that routine Fe supplementation has been associated with reversible gastrointestinal symptoms such as nausea and constipation [7]. Similarly, the 2001 Institute of Medicine's Dietary Guidelines for Fe also noted that high-dose Fe supplements can cause constipation, nausea, vomiting, and diarrhea [27].

Associations between increased Fe status or dietary heme Fe intake and risk of gestational diabetes mellitus (GDM) have been observed in some studies. In the first study to address this question, a large prospective study of 3158 US pregnant women reported that pregnant women with the highest heme Fe intake in early pregnancy had a 3.31-fold increased risk of developing GDM, and risk of GDM increased with increasing levels of dietary heme Fe intake [28]. A recent meta-analysis of GDM

and Fe intake and/or Fe status found positive associations between increased serum ferritin concentrations and risk of GDM, but no statistically significant associations were found between dietary Fe intake or serum transferrin and risk of GDM [29]. The authors noted that heme Fe intake was associated with increased risk of GDM, but questioned the reliability of these results due to the small number of studies addressing this question [29]. Because ferritin is an acute phase protein, use of this marker alone may reflect increased inflammation and not increased Fe stores. Given the importance of this question and the fact that dietary heme and non-heme intake are modifiable factors, additional attention to the relative impact of dietary Fe intake and Fe status on risk of gestational diabetes is warranted.

Assessment of Iron Status Across Gestation

Anemia during pregnancy is defined when blood hemoglobin or hematocrit concentrations fall below the fifth percentile of trimester-specific normative values [30, 31].

Additional criteria are utilized to adjust these cut-offs for the confounding effects of maternal cigarette smoking, residence at high altitude, and African-American race (Table 1) [32]. The cut-offs used to define anemia are lowest during the second trimester of pregnancy to account for the marked plasma volume expansion that occurs at this time. Hemoglobin concentrations are useful in diagnosing anemia across gestation, but only approximately 50% of anemia during pregnancy is thought to be due to Fe deficiency, as elaborated on below [31]. In order to more fully evaluate causes of anemia, additional data on Fe, vitamin A, folate, vitamin B₁₂ status, inflammatory status, and presence of parasitic diseases and hematological disorders are needed. Hematological data on mean corpuscular volume, mean corpuscular hemoglobin content, erythrocyte count, and reticulocyte count are also useful when identifying types of anemia [30].

Multiple biomarkers are available to help diagnose Fe deficiency anemia during pregnancy. These biomarkers have been reviewed [33], and common biomarkers used to define IDA across gestation are provided in Table 1. Serum ferritin (SF) is frequently utilized as an index of body Fe stores, and ferritin has been identified as the best indicator to assess efficacy in Fe intervention trials [30]. During pregnancy every 1 µg/L unit of SF is thought to represent 10 mg of storage Fe [34]. Iron deficiency during pregnancy can be defined when SF concentrations fall below 12–15 µg/L.[30] Cellular expression of TfR increases in response to a decrease in the labile Fe pool, and a fraction of this receptor is released into the circulation. Tissue Fe insufficiency is typically diagnosed when serum transferrin receptor (sTfR) concentrations rise above 4.4–8.5 mg/L (depending on the assay utilized) [2]. When data on both SF and TfR are available, a ratio between these two indicators can be used to provide additional information based on combined measures of tissue Fe demands and body Fe stores [35]. Validation of this approach against bone marrow aspirate evaluation of body Fe stores has been undertaken in anemic pregnant women, with

Table 1 Cut-off values for anemia and iron status biomarkers in pregnant women^a

	First trimester	Second trimester	Third trimester
Hemoglobin (g/dL)			
Anemia	<11.0	<10.5	<11.0
Reference range ^b	11.6–13.9	9.7–14.8	9.5–15
Hematocrit (%)			
Anemia	<33	<32	<33
Reference range ^b	31.0–41.0	30.0–39.0	28.0–40.0
Transferrin saturation (%)			
Anemia	<16	<16	<16
Reference range ^b	31.0–41.0	30.0–39.0	28.0–40.0
TIBC (µg/dL)			
Anemia	>400	>400	>400
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0
Serum ferritin (µg/L)			
Anemia	<12–15	<12–15	<12–15
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0
Serum sTfR (mg/L)			
Anemia	>4.4 or >8.5	>4.4 or >8.5	>4.4 or >8.5
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0
TBI (mg/kg)			
Anemia	<0	<0	<0
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0
Serum iron (µg/dL)			
Anemia	<40	<40	<40
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0
ZnPP (µmol/mol heme)			
Anemia	>70	>70	>70
Reference range ^b	5.6–7.3	3.4–5.0	0.8–2.0

^aNormative values and ranges are obtained from the literature as summarized by Cao and O'Brien [33]. *TfR* transferrin receptor, *TBI* total body iron, *TIBC* total iron binding capacity, *ZnPP* zinc protoporphyrin

^bReference ranges as reported by the CDC [32].

TfR/SF ratios over 300 being indicative of depleted Fe stores [36]. Combined use of SF and TfR concentrations is also useful in estimation of total body Fe (TBI) based on an equation developed from serial phlebotomy equations in non-pregnant adults [37]. This equation has been utilized in pregnant populations and is similar to the definitions used in non-pregnant populations; TBI values under 0 mg/kg are indicative of body Fe deficiency [2, 38, 39]. Hepcidin concentrations during pregnancy have been evaluated for their association with other Fe status and hematological indicators. Pregnant women with IDA have been found to have low or undetectable concentrations of this hormone, depending on the assay utilized [38, 40]. If the goal is to characterize ID or IDA, it is not clear that hepcidin provides any additional advantage over traditional Fe biomarkers [38]. By evaluating a comprehensive panel of Fe status biomarkers during pregnancy, erythropoietin was recently found to be highly correlated with Hb, SF, TfR, serum Fe, and TBI at both mid-gestation and at delivery [38, 41]. Erythropoietin is not impacted by inflammation and was not found to be significantly associated with any of the inflammation markers measured at mid-gestation or at delivery. [38, 41] In contrast, at delivery hepcidin and ferritin were significantly positively associated with IL-6 and CRP. Therefore, this inflammation-mediated increase in late pregnancy and at delivery may confound the utility of several Fe biomarkers at this time [38, 41]. Approaches to adjust SF concentrations for inflammation are being developed for many population groups [42, 43], but at present there are insufficient data on use of these correction factors during pregnancy. More data are needed to explore other Fe status biomarkers that may be predictive of maternal and neonatal Fe stores, yet are not impacted by the increase in inflammation that is evident in late pregnancy and during labor and delivery.

Anemia and Iron Deficiency Anemia During Pregnancy

While many studies have evaluated Fe status and anemia across gestation, data on the prevalence of Fe deficiency anemia in US pregnant women remain limited. Studies in a predominantly minority pregnant population found that IDA was present in 27.4% of women studied [44], while other studies have found that the prevalence of IDA in Fe-supplemented women ranged from 10–21% [45–47]. Recent studies in pregnant US adolescents ($n = 253$) reported that 25% of adolescents studied were anemic by late gestation, but only 6.1% had IDA [38]. Similarly, in an otherwise healthy population of US women carrying multiples ($n = 83$), ID was evident in 45% of women at delivery (34.8 ± 2.7 weeks of gestation) but only 18% had IDA [41]. National NHANES and CDC data have evaluated risk of ID across gestation in US pregnant women, but data on the prevalence of IDA were not presented [2, 48]. From the limited data published to date, IDA only appears to explain a relatively small percentage of gestational anemia, thus drawing increased attention to the need to evaluate other causes of maternal anemia and nutrient–nutrient interactions that impact hematological status across pregnancy.

Contributions of Other Nutritional Factors to Maternal Anemia during Pregnancy

In addition to the well-known impact of folate and vitamin B₁₂ deficiencies on increased risk of anemia, growing data in pregnant [49] and non-pregnant study populations [50, 51] have linked anemia to deficiencies of vitamin A [50], selenium [51], and vitamin D [49, 52]. There continue to be gaps in knowledge on nutrient–nutrient interactions and risk of anemia. New findings are elucidating mechanistic interactions between Fe and other dietary nutrients that were previously attributed to common dietary deficits. As an example, for many decades rickets and anemia were often noted to co-exist, a finding that was attributed to poor dietary quality among those with rickets [53]. Vitamin D is now known to influence Fe metabolism by modulating hepcidin synthesis and impacting erythropoiesis. Recent observations in those with chronic kidney disease noted that vitamin D supplementation reduced the requirements for erythropoietic-stimulating agents, or improved hemoglobin concentrations [54, 55]. High-dose vitamin D₂ supplementation (100,000 IU) significantly decreased circulating hepcidin concentrations within 24 h post-dosing in healthy adult men ($n = 4$) and women ($n = 3$) [56], and concurrent *in vitro* studies found that treatment of hepatocytes with either 100 nM of 25(OH)D or 5 nM of 1,25(OH)₂D significantly suppressed hepatic transcription of hepcidin [56]. In support of these observations, a large study in healthy adult men and women ($n = 638$) found significantly lower hemoglobin, hematocrit, and serum Fe concentrations in individuals with 25(OH)D concentrations under 20 ng/mL when compared to individuals with 25(OH)D concentrations greater than 20 ng/mL [57]. Mechanistic

studies lend support to these observations, as calcitriol, the active form of vitamin D, increases the sensitivity of hematopoietic cells to erythropoietin [58], and enhances mRNA expression and protein abundance of the erythropoietin receptor in hematopoietic tissues [59]. As more research on nutrient–nutrient interactions are generated, a greater understanding of the relative role of other nutrients in gestational anemia will be appreciated.

Obesity-Associated Inflammation and Maternal Fe Status During Pregnancy

With the increasing prevalence of obesity in the United States, it is now estimated that 3 in 10 women of reproductive age are obese [60], leading to increasing numbers of women entering pregnancy overweight or obese. Because obesity is an inflammatory state, there are concerns that adiposity-induced inflammation may stimulate IL-6 mediated pathways of hepcidin production and adversely impact Fe homeostasis across gestation. Several studies have examined the impact of maternal obesity on Fe status across gestation, with mixed results [61–64]. In some instances the size of the study population was limited and the study was likely underpowered to detect meaningful associations [64]. The largest study to date on this topic was undertaken among a population of 1613 healthy pregnant Chinese women [63], and reported significant positive relationships between maternal pre-pregnancy body mass index (ppBMI) and CRP at mid-gestation. This study, however, did not find any significant associations between maternal ppBMI and SF or TfR at mid-pregnancy in the group as a whole. The authors uniquely analyzed their data to determine if there were thresholds at which maternal ppBMI impacted Fe status indicators at mid-pregnancy. With this approach, relationships between ppBMI and Fe status became evident when maternal ppBMI exceeded 30 kg/m². In this study, maternal ppBMI was not associated with SF, TfR, or TBI in late pregnancy, and data on key determinants of the Fe-inflammation pathway (such as hepcidin and IL-6) were not analyzed [63].

Another study on maternal obesity and Fe status was undertaken among a cohort of 240 pregnant adolescents [61]. In these pregnant adolescents, there was a high prevalence of both maternal anemia in late gestation (28%) [38], and neonatal anemia at birth, based on cord blood hemoglobin concentrations (21%) [65]. In addition, 40% of these adolescents were obese or overweight based on ppBMI. In spite of excess adiposity at entry into prenatal care and excess gestational weight gains in 93% of adolescents studied, maternal ppBMI and GWG were not significantly associated with increased risk of anemia or with any of the Fe status indicators evaluated [61]. In contrast to expectations, a significant positive relationship between maternal ppBMI and cord hemoglobin concentrations was evident in this population [61]. Given the limited and contradictory data to date, additional research is needed to evaluate the relative impact of maternal anemia and inflammation on hepcidin synthesis during gestation. In groups with significant maternal anemia,

the Fe insufficiency signaling pathways may take precedence over inflammation-mediated hepcidin signaling pathways to maintain maternal Fe status at this key life stage.

Maternal Iron Supplementation, Maternal Birth Outcomes, and Iron Status

Several recent reviews have focused on the effects of maternal Fe supplementation on maternal and neonatal outcomes. A recent review of this topic was undertaken by the US Preventive Services Task Force, and findings of the task force have been summarized [7, 66]. The goal of the evaluation was to examine the benefits of routine Fe supplementation of pregnant women on maternal and infant health outcomes while evaluating possible harms that may be evident with these practices. Routine Fe supplementation practices were associated with improved hematologic status and with a tendency to lower the incidence of ID and IDA during pregnancy and at delivery [7]. The evidence in support of a reduction in infant outcomes (low birth-weight and preterm birth) was found to be poor, but supplementation was not found to cause serious harm in relation to infant outcomes. The report concluded that more high-quality data are needed to evaluate the short- and long-term effects of routine Fe supplementation in US pregnant women, including its impact on rates of cesarean delivery, and risk of small-for-gestational-age or low birth weight infants. The report concluded that there were no clear clinical benefits of routine Fe supplementation on maternal or neonatal health, and additional data are needed to address these existing gaps in the literature [7, 66].

Vulnerable Maternal and Neonatal Groups

While data on routine Fe supplementation of all pregnant women have not identified clear clinical benefits, several higher risk maternal and neonatal groups who may benefit from additional Fe supplementation have been identified by others. Common pregnancy-related complications or population groups that may be at increased risk for anemia over the course of pregnancy include women with GDM, women carrying multiples, pregnant adolescents, and women with inflammatory or infectious conditions across pregnancy. Several neonatal and infant groups have been targeted as at increased risk for ID or IDA. The American Academy of Pediatrics (AAP) has highlighted both prematurity and low birth weight as risk factors for ID and IDA at 1 year of age, as birth before 37 weeks of gestation limits the window of opportunity to accrue Fe stores in utero [67]. Other infant groups that were identified as being at increased risk of ID and IDA included infants who are exclusively breastfed beyond 4 months of age who are not supplemented with Fe, infants who are weaned to a whole milk diet low in Fe, and infants with poor

growth, low socioeconomic status, and those with medical concerns that lead to feeding problems [67].

GDM is a common problem of pregnancy and may result in abnormal Fe acquisition by the developing fetus. When net Fe delivered to the developing fetus is limited, Fe may be prioritized to support fetal RBC production over other fetal tissues and Fe storage compartments. Petry et al. have found that the net Fe content of the brain, liver, and heart were 40–90% lower in autopsy studies of infants born to diabetic women when compared to control infants matched for gestational age at birth [68]. This altered Fe distribution has been linked to adverse functional consequences in the neonate and child [69, 70].

Pregnant adolescents and their neonates may also be at increased risk for ID and IDA. Data from the Centers for Disease Control in 2011 concluded that a total of 1100 adolescents give birth each day in the United States; 1 in 10 new mothers is an adolescent, and teen childbearing costs US taxpayers more than \$9 billion per year [71]. A recent evaluation of maternal and neonatal Fe status in a large cohort of pregnant adolescents ($n = 253$) and their newborns ($n = 193$) found risks of ID and IDA that were significantly higher than those reported among adult pregnant women [38, 65]. In late gestation, maternal anemia was evident in 25% of teens studied, and maternal ID was significantly associated with neonatal Fe status at birth [65]. In the otherwise healthy neonates born to these adolescents, 21% were anemic at birth [65]. This is alarming, as US neonates are not routinely screened for Fe status until 12 months of age.

Multiple births comprise approximately 3–4.5% of all births in the United States [72], and this group alone is responsible for 15% of preterm births and contributes 20% of all low birth weight infants born in the United States [73]. Using national data, roughly 65% of women carrying multiples deliver prematurely [74], putting their neonates at increased risk of early anemia. In a large screening study of women carrying multiples and their 197 neonates, maternal ID and IDA were significantly more prevalent than values reported from national NHANES data in pregnant women carrying singletons. In these women, all of whom received the standard of prenatal care, 45% were anemic by term [41]. By tracking hemoglobin concentrations across gestation, women carrying multiples tended to experience an earlier gestational decrease in hemoglobin concentrations compared to normative data from singletons [41]. The United States currently has no specific nutritional recommendations for women carrying multiples, or for their neonates, to ensure Fe stores at birth are adequate. Many gaps in knowledge remain for these obstetric and infant population groups, but there is growing evidence to support screening these higher risk groups during early gestation and at birth to ensure that appropriate follow-up and Fe supplementation is available as needed.

Gaps in Knowledge

Many gaps in knowledge remain concerning the role of Fe across gestation and the optimal amount and type of Fe required to support maternal and fetal outcomes. Because humans have no regulatable route of Fe excretion, Fe balance is controlled at the level of the enterocyte. To date, only a small amount of the variability in Fe absorption can be captured using the available Fe status indicators and regulatory hormones. Using stable isotopes to measure Fe absorption in mother-toddler pairs, only 50% of non-heme Fe absorption could be explained by dietary factors, and Fe status indicators suggesting that inheritance or the shared environment was contributing to variability in absorption [75]. Increased attention to genetic factors that influence maternal nutritional status is warranted for Fe and other key nutrients. For Fe, five genes known to be involved in non-heme Fe absorption and regulation have been found to cause Fe overload disorders in humans. These genes include *HFE*, ferroportin 1 (*FPN1*), transferrin receptor 2 (*TfR2*), hemojuvelin (*HJV*), and hepcidin (*HEPC*) [76]. The role of genetic variability in these proteins on Fe homeostasis during key life stages such as pregnancy has yet to be explored, but has relevance to targeting those at increased risk for gestational anemia so that appropriate interventions or increased anemia surveillance can be implemented.

Placental transport of Fe across pregnancy may be influenced by both maternal and fetal signals. Animal models have shown that the fetus begins to produce hepcidin early in gestation [77]. In humans, recent studies evaluating multiple placental Fe trafficking proteins have found maternal Fe status to exhibit the most significant impact on placental expression of the transferrin receptor, while fetal Fe status was only significantly associated with placental heme trafficking proteins [22]. A greater understanding of the capacity of the human placenta to transfer Fe to the fetus in response to both maternal and fetal signals is needed in order to optimize Fe intake recommendations and sources of dietary Fe that may be preferentially utilized to support Fe demands.

Iron status is known to be essential to optimal fetal brain development, and Fe insufficiency has been linked to a number of detrimental neurocognitive outcomes [78, 79]. Adequate availability of Fe may be particularly important during key gestational windows of fetal brain development. Controlled animal studies have suggested that even non-anemic gestational Fe deficiency can adversely influence neuronal development and subsequent functional outcomes in affected offspring [80]. Gaps in knowledge in this area have been summarized and speak to the need to further characterize functional neurophysiological outcomes in relation to maternal Fe status across pregnancy.

Several challenges in the evaluation of Fe status across gestation have not yet been resolved. Pregnancy is a dynamic state, with marked changes in inflammatory status, plasma volume, and red blood cell mass occurring between conception to term. These factors have a substantial impact on the interpretation of Fe status biomarkers during pregnancy. Studies have utilized various dilution techniques involving infusion of colored dyes, labeled albumin, or hydroxyethyl starch to estimate plasma volume [81–84], but there are currently no easily applied techniques that can evaluate plasma volume expansion over pregnancy, particularly on a population level. This limits interpretation of all Fe status biomarkers, as there is an inherent assumption of similar plasma volume when comparing these values between individuals. Plasma volume is also often estimated based on a per-kilogram basis. At present, when dealing with maternal obesity, there are uncertainties with the degree to which the excess adiposity impacts plasma volume estimates and plasma volume expansion. Similarly, many Fe status biomarkers are impacted by maternal inflammation, and more research is needed on how to adjust or factor this into evaluation of Fe status biomarkers that also function as acute phase proteins.

Many studies have evaluated the impact of maternal Fe status on neonatal Fe status, and findings are often highly variable. Additional variability in the evaluation of neonatal Fe status is introduced due to variability in the clinical cord clamping procedures utilized. Delayed umbilical cord clamping (clamping after the cord has stopped pulsing) can provide an average of 30% more blood volume in the neonate, which has been estimated to reflect up to 60% more red blood cells [85–87]. A Cochrane review of this topic concluded that delayed cord clamping led to both significantly higher Hb concentrations in the neonate at birth and higher ferritin concentrations at 6 months of age, but the need for early phototherapy for jaundice was slightly increased in those with late cord clamping [88]. Clinical cord clamping practices differ widely as a consequence of medical beliefs and birth/delivery circumstances. Increased attention to this variable is necessary when evaluating neonatal Fe stores and the determinants of neonatal Fe status at birth.

Conclusion

Fully two billion women and children worldwide are thought to be Fe deficient [89]. The American Congress of Obstetricians and Gynecologists (ACOG) currently recommends prenatal Fe supplementation and universal anemia screening [90]. Recent systematic review of current Fe supplementation practices noted that while Fe supplementation did have a positive impact on maternal Fe status, there is inconclusive evidence at present to link this practice to improvements in maternal or infant clinical outcomes [66, 91]. Clearly more data are needed to evaluate the relative impact of Fe supplementation practices across gestation and to determine which obstetric and Fe status groups are most likely to benefit from this supplementation. Maternal Fe absorption across gestation is regulated in response to maternal Fe stores and to systemic hepcidin concentrations. There may be threshold effects of Fe

supplementation in that the magnitude of the response to supplementation is likely to be dependent on baseline maternal Fe status. In spite of the availability of multiple Fe status biomarkers, very little variability in Fe absorption can currently be captured using the multiple Fe status biomarkers and the systemic Fe regulatory hormones that have been identified to date. More information is needed to understand the genetic determinants of maternal and neonatal Fe status so that targeted approaches to supplementation can eventually be developed. In addition, basic research is needed to evaluate the impact of maternal Fe supplementation on in utero fetal development to identify if there are key gestational windows at which time Fe availability may be most integral to fetal development and to characterize mechanisms by which Fe status impacts maternal birth outcomes.

Current data on maternal Fe status in relation to birth outcomes may be challenging to summarize, given the variability in the baseline Fe status of the populations studied, the variable timing of the pregnancy measures obtained, and the need to adjust for inflammation if relying on Fe status indicators that also function as acute phase proteins. In addition, optimal requirements necessary to support maternal and fetal health may not correspond to the amount of Fe required to prevent maternal anemia. As the field moves forward, answers to these questions will inform subsequent recommendations designed to promote Fe status and maternal and fetal health during this key life stage.

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Iodine Requirements in Pregnancy

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Keywords Iodine · Pregnancy · Iodine in pregnancy · Iodine in foods
Iodine deficiency in pregnancy · Iodine excess in pregnancy · Iodine supplement

Key Points

- Iodine is an essential micronutrient for thyroid hormone production.
- Pregnant women have increased iodine requirements due to increased maternal thyroid hormone production, increased maternal urinary losses, and fetal thyroid hormone production later in pregnancy.
- Adequate thyroid hormone is critically important for normal fetal development.
- Maternal iodine deficiency can lead to adverse pregnancy and offspring neurodevelopmental outcomes.
- Both iodine deficiency and iodine excess may lead to maternal thyroid dysfunction.
- Use of iodized salt is the mainstay of worldwide efforts to eradicate iodine deficiency, but mild-to-moderate iodine deficiency persists in many countries.
- Although the general population in the USA is considered iodine sufficient, pregnant women are mildly iodine deficient.
- Professional societies recommend that women in many regions should take supplements containing 150 mcg of iodine daily during preconception, pregnancy, and lactation.

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Introduction

Iodine is an essential micronutrient which is required for thyroid hormone production. Thyroid hormone, which depends on iodine for function, in turn, is critically important for regulation of energy expenditure in adults and children and also for growth and development of the fetus. Iodine is found ubiquitously in soil and groundwater, and the ocean is especially rich in iodine that has been leached from soil through glaciation, snow, and rain. Iodine content in soil and water varies geographically, and thus, crops and livestock grown in different areas may have substantially different iodine content [1, 2]. Once consumed through food or supplements, iodine is readily absorbed through the stomach and duodenum. Iodine, in the form of iodide, is then either transported to the thyroid gland in varying amounts (10–80%) depending on an individual's iodine nutritional status or is excreted through the kidney. When taken up by the thyroid gland, iodide is used to make thyroid hormones. Renal clearance accounts for more than 90% of iodine excretion, making urinary iodine concentration (UIC) a good marker for recent iodine intake [2–4].

The public health ramifications of chronic iodine deficiency (ID) have long been recognized [5]. Cretinism, found only in the most iodine deficient regions, is characterized by mental deficiency, goiter (thyroid gland enlargement), and abnormalities in motor and neurodevelopment. In the twentieth century, the efficacy of iodine supplementation in preventing cretinism was shown in several landmark trials in Papua New Guinea, Zaire, and China [6]. In the early twentieth century, the high (26–70%) prevalence of goiter due to chronic ID in children from the Great Lakes, Appalachia, and Northwestern regions of the USA led to this region of the USA being referred to as the “goiter belt.” [7] In the 1980s, the term “iodine deficiency disorders” (IDD) was introduced, with worldwide recognition of the broad effects of ID such as decreased intelligence quotient (IQ) and adverse obstetric outcomes, in addition to goiter. By the early 1990s, it was estimated that more than 1.5 billion people worldwide were living in iodine-deficient areas, and the World Summit for Children at the United Nations established the global elimination of IDD as a goal [8]. A subsequent worldwide campaign for universal salt iodization (USI) has achieved a significant decrease in the prevalence of IDD. However, a global survey by the Iodine Global Network (IGN), formerly known as the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), in 2013 showed that pregnant women were deemed to be iodine-sufficient in only 8 of the 21 countries studied [1].

This chapter will review measurement of thyroid function, iodine physiology in pregnancy, methods to assess population iodine status in pregnancy, the effects of iodine deficiency in pregnancy, data regarding iodine supplementation in pregnancy, the effects of iodine excess in pregnancy, current recommendations for iodine supplementation in pregnancy, the current iodine nutrition status of pregnant women, and dietary sources of iodine.

Measurement of Thyroid Function

Because iodine is an essential substrate for thyroid hormone production, the effects of ID are thought to be mediated through the effects of inadequate thyroid hormone. Several blood tests are used to measure thyroid function: thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3). TSH, produced by the pituitary gland, stimulates thyroid hormone (T4 and T3) production in the thyroid gland. Thyroglobulin (Tg), a glycoprotein synthesized in the thyroid gland and stored in the thyroid follicle, serves as a source of substrate for thyroid hormones after undergoing iodination. In healthy individuals, small amounts of Tg are secreted into circulation from the thyroid gland along with the thyroid hormones. T4 is a prohormone, which is converted to the active hormone, T3, in peripheral tissues. T3 feeds back to the pituitary gland to inhibit TSH production. Thus, serum TSH levels are elevated in hypothyroidism and suppressed in hyperthyroidism. Both T4 and T3 are bound to thyroxine-binding globulin (TBG) whose level is affected by estrogen and conditions that affect protein levels, such as critical illness, pregnancy, and liver disease. Serum total T4 and T3 levels may not reflect the levels of active thyroid hormone since they are inactive when bound to TBG, and serum free T4 levels (T4 that is not bound to TBG) are generally used to assess peripheral thyroid hormone concentrations.

In overt hypothyroidism, serum TSH level is elevated and free T4 is decreased. In subclinical hypothyroidism, serum TSH level is elevated but free T4 is normal. Similarly, serum TSH levels are suppressed in the face of high free T4 in overt hyperthyroidism, but free T4 levels are normal with suppressed TSH levels in subclinical hyperthyroidism.

Iodine Physiology in Pregnancy

Physiologic changes increase the iodine requirements of pregnant women. Maternal thyroid hormone production increases by approximately 50% in early pregnancy. This is in part due to increased serum TBG, but also due to increased levels of human chorionic gonadotropin (hCG), which has a stimulatory effect on TSH receptors in the thyroid gland [3, 4]. The fetal thyroid gland does not form until 12–13 weeks of gestation and does not produce a significant amount of thyroid hormone until 18–20 weeks of gestation [9, 10]. Consequently, the fetus depends on maternal thyroid hormone crossing the placenta during the critical period of early pregnancy.

Once the fetal thyroid gland starts producing thyroid hormone, sufficient maternal iodine crossing the placenta is essential for adequate fetal thyroid hormone production. Increased renal clearance of iodine in pregnant women due to increased blood volume and glomerular filtration rate, and increased deactivation of thyroid

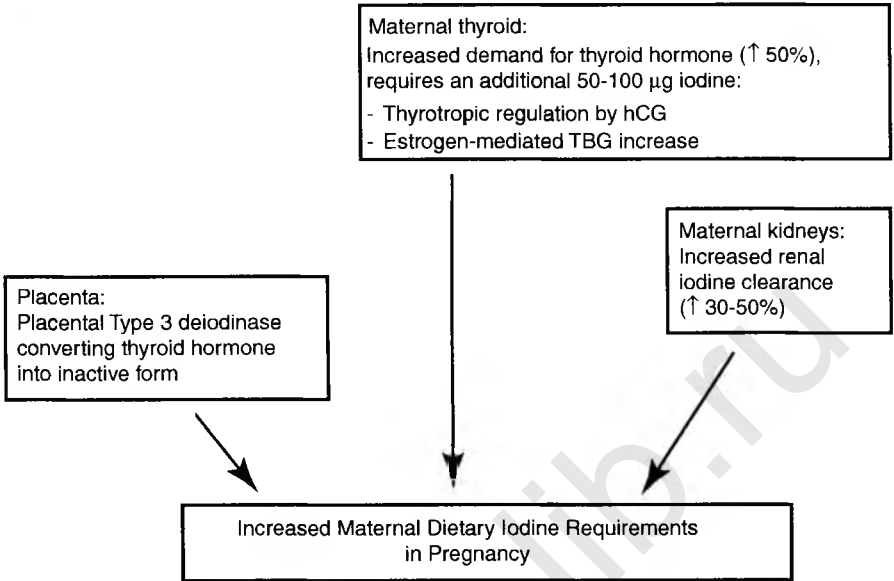


Fig. 1 Physiologic changes in pregnancy leading to increased iodine requirement. *hCG* human chorionic gonadotropin, *TBG* thyroid-binding globulin

Table 1 Recommended daily intake of iodine ($\mu\text{g}/\text{day}$)

Population	US Institute of Medicine [12]	World Health Organization [11]
Pregnant women	220	250
Lactating women	290	250
Women of reproductive age (15–49 years)	150	150
Children <2 years	110–130	90

hormone by the placenta, further increase iodine requirements for pregnant women (Fig. 1) [3, 4]. Given the increased demand for iodine in pregnancy, the World Health Organization (WHO) and U.S. Institute of Medicine (IOM) recommend a higher iodine intake of 220–250 $\mu\text{g}/\text{day}$ in pregnant women compared to that recommended for non-pregnant adults (150 $\mu\text{g}/\text{day}$), as shown in Table 1 [11, 12].

Methods to Assess Iodine Status

The WHO has advocated several methods to assess population-level iodine sufficiency, as presented in Table 2 [11]. Although median UIC can be used to assess population-level iodine sufficiency in pregnant women, spot UIC values cannot be

used as individual biomarkers because UIC reflects recent iodine intake and there is substantial intra-individual variation from day to day, and even within the same day [13, 14]. UIC may also vary over the course of pregnancy [15, 16]. The urinary iodine-to-creatinine ratio and 24-h urine iodine excretion have been suggested as alternative measures for assessing iodine sufficiency in pregnancy [16]. However, the urinary iodine-to-creatinine ratio may underrepresent iodine intake in iodine-deficient areas where thyroidal iodine uptake is increased, and creatinine may be low in protein-deficient populations [11, 17, 18]. For the most reliable assessment, multiple measures of 24-h urine iodine levels are suggested, but this is both cumbersome and expensive. Therefore, median spot UIC is recommended for population-level assessment of iodine sufficiency [19]. There is no reliable and easy measure of individual iodine status at this time [11, 17].

The other measures listed in Table 2 can also be used to assess population-level iodine status. However, measures in school-aged children may underestimate the prevalence of ID in pregnant women [20]. Tg levels have been of special interest in assessing long-term iodine status, as there appears to be a positive correlation between thyroid size (i.e., goiter) and serum Tg levels [21]. However, no clear reference ranges have been established for adults or for pregnancy. Several factors may affect serum Tg levels in adults, such as thyroid nodularity and size, thyroid autoimmunity, the presence of Tg antibodies, serum TSH levels, smoking, and environmental chemical exposures [21, 22].

Table 2 Measures indicating population-level iodine sufficiency [11]

Monitoring indicator	Group for assessment	Levels	Iodine Status
Median UIC	School-age children (SAC) or non-pregnant, non-lactating adults	<20 µg/L	Severely insufficient
–	–	20–49 µg/L	Moderately insufficient
–	–	50–99 µg/L	Mildly insufficient
–	–	100–199 µg/L	Adequate
–	–	200–299 µg/L	More than adequate
–	–	≥300 µg/L	Excessive
Median UIC	Pregnant women	<150 µg/L	Insufficient
–	–	150–249 µg/L	Adequate
–	–	250–499 µg/L	More than adequate
–	–	≥500 µg/L	Excessive
Goiter rate	SAC	<5%	Sufficient
Prevalence of TSH >5 mIU/L	Newborns (by heelstick)	<3%	Sufficient
Tg	SAC	4–40 µg/L	Sufficient

UIC urinary iodine concentration, SAC school-age children, TSH thyroid-stimulating hormone, Tg thyroglobulin

Iodine Deficiency in Pregnancy

Given the increased demand for iodine in pregnancy and fetal dependence on adequate iodine nutrition for normal development, pregnant women and their offspring are especially vulnerable to the effects of ID. In iodine-replete areas, bodies of healthy adults contain 15–20 mg iodine, 70–80% of which is stored in the thyroid gland. With continued sufficient iodine intake, a healthy, iodine-replete pregnant woman is able to meet the increased demands of pregnancy. However, in chronic severe ID, thyroidal iodine stores may be depleted, leading to hypothyroidism, goiter, and adverse effects on pregnancy and offspring [1, 6].

Iodine Deficiency and Thyroid Function in Pregnant Women

Several studies of pregnant women in mildly to moderately iodine-deficient areas have shown 2.5- to 4-fold increases in the prevalence of hypothyroidism (mostly subclinical hypothyroidism) and fourfold increases in the prevalence of hyperthyroidism (mostly subclinical hypothyroidism) [23–26], compared to the reported frequencies in iodine sufficient populations (2–3% for hypothyroidism and 0.1–1% for hyperthyroidism) [27]. In one study, women with an adequate iodine status (UIC 150–249 $\mu\text{g/g Cr}$) had lower median Tg levels, suggesting more optimal iodine status, compared to those with moderate ID (UIC <50 $\mu\text{g/g Cr}$) [23]. However, other studies have reported no significant associations between maternal UIC and thyroid function [28, 29].

Effects of Iodine Deficiency in Pregnancy on Obstetric Outcomes

Severe ID in pregnancy is associated with poor obstetric outcomes, including miscarriage, prematurity, and stillbirth [4, 30]. Studies have also shown that mild ID in pregnancy can adversely affect pregnancy outcomes. Czech women with early miscarriage had lower median UIC values compared to age-matched controls (92 and 117.8 $\mu\text{g/L}$, respectively), even though TSH levels and the prevalence of thyroid peroxidase antibody positivity were similar between the two groups [31]. Mild ID (UIC <150 $\mu\text{g/L}$) has also been associated with preterm birth and low birth weight in offspring [32, 33], lower placental weight [34], and decreased head circumference [33].

Chronic severe ID (iodine intake <50 $\mu\text{g/day}$) can also lead to maternal and fetal goiter as a result of excessive stimulation from high levels of TSH [35]. There is a 10–20% physiologic increase in the thyroid volumes of iodine-sufficient pregnant women due to increased blood flow. Pregnant women residing in iodine-deficient regions have a greater increase (25–30%) in thyroid volumes, likely due to excessive TSH stimulation [36].

Effects of Iodine Deficiency in Pregnancy on Offspring Neurodevelopment

Thyroid hormone affects neuronal migration, neuronal connection, and myelination in the developing brain [37, 38], all of which occur in early gestation [39]. Consequently, adequate maternal thyroid hormone during early pregnancy is essential for proper fetal development. Rat studies have shown that iodine-deficient diets leading to decreased maternal thyroid hormone levels result in delayed hippocampal axonal growth [40] and permanent decreases in brain synaptic function in pups [41]. In maternal ID, mild increases in TSH may drive preferential production of the more active form of thyroid hormone, T₃, which helps to maintain normal thyroid function in the mother. However, T₄ crosses the placenta, whereas T₃ does not, and inadequate availability of T₄ can be detrimental in the fetus [38].

The effects of severe maternal ID on offspring neurocognitive development have been demonstrated by studies of endemic cretinism and its prevention with iodine supplementation [6]. Meta-analyses of maternal iodine status and child cognitive development have shown associations between severe maternal ID in pregnancy and lower IQ in children (7.4 points lower in a meta-analysis of 24 studies by Bougma et al. and 12 points lower in a meta-analysis of 37 studies by Qian et al.) [42, 43].

The effects of mild-to-moderate maternal ID are less clear. However, a growing body of evidence suggests that even mild-to-moderate maternal ID may adversely affect child development. In a UK study, children born to mothers with UIC <150 µg/g Cr in the first trimester were more likely to have lower verbal IQ and reading skills when assessed at age 8 years, compared to children born to mothers with gestational UIC ≥150 µg/g Cr [44]. Similarly, Australian children born to mothers with UIC <150 µg/L had lower language skills assessment scores at age 9 years, compared to those born to mothers with UIC ≥150 µg/L [45]. Children of mothers with UIC in the lowest decile during pregnancy had poorer working memory when assessed at 4 years of age [46], and children of mothers with UIC <50 µg/L during pregnancy had less endurance, attention, and persistence in goal-directed efforts at 12 months of age than children of mothers with UIC ≥50 µg/L [47]. In a small prospective observational study performed in a mildly ID country, children of mothers who did not use iodized salt had lower verbal, performance, and full-scale IQs and a threefold higher prevalence of borderline or reduced cognitive function compared to those of mothers who used iodized salt, despite no significant difference in free T₄ levels. This study also showed a positive association between maternal UIC measured at <12 weeks gestation and child verbal IQ [48]. On the other hand, a Dutch study showed no significant association between maternal UIC <150 µg/g Cr and children's non-verbal IQ assessed at age 6 years [49]. In this study, the number of women with low UIC was small, so that the study may have been underpowered to detect a significant association between maternal UIC and child cognitive function.

Effects of Iodine Supplementation in Pregnancy

In iodine-deficient rats, iodine supplementation in early gestation appears to reverse abnormal cell migration and lead to better behavior performance of offspring, with greater improvement in behavior performance the earlier the intervention [50]. In humans, the most striking study is of the dramatic reduction of cretinism from 4.8% (26/534) to 1.4% (7/498) with treatment of pregnant women with iodized oil in mountainous areas of Papua New Guinea [51]. In the six out of seven cases of persistent cretinism in this study, women were already pregnant when the trial of iodized oil started, suggesting the need for adequate iodine nutrition prior to conception or in early gestation. Other studies in severely iodine-deficient regions have shown improved IQ scores and better psychomotor developmental scores with maternal iodine supplementation [52].

Timing of iodine supplementation is important. Initiation of iodine supplementation in early gestation or prior to conception is likely crucial. A small study in Spain reported that supplementation of pregnant women in a mildly iodine-deficient area with potassium iodide (KI), 200 $\mu\text{g}/\text{day}$, starting at four to 6 weeks' gestation resulted in higher mean child developmental quotient scores compared to scores of children whose mothers started iodine supplementation later in gestation (12–14 weeks' gestation and after delivery) [53]. However, this study was limited by methodological flaws. Another study reported the prevalence of hypothyroxinemia or elevated TSH levels was much lower in pregnant women with a history of long-term iodized salt consumption compared to those who started iodine supplements only after becoming pregnant [54]. Maternal iodine supplementation before the end of the 2nd trimester improved head circumference and psychomotor test scores of children, compared to children receiving iodine at age 2 or children of mothers who received iodine starting in the 3rd trimester [55]. Other studies have also shown that iodine supplementation during the first trimester of pregnancy in areas of mild-to-moderate ID resulted in higher neurocognitive developmental assessments in children at 1–2 years of age [56, 57].

In contrast to the studies described above, some studies have shown adverse effects of maternal iodine supplementation on maternal thyroid function or offspring development. Two studies have shown increased risk for elevated serum TSH values in women starting 150–200 $\mu\text{g}/\text{day}$ iodine supplements during pregnancy in mildly iodine-deficient populations [58, 59]. Two Spanish cohort studies have shown associations between maternal intake of ≥ 150 $\mu\text{g}/\text{day}$ iodine supplements and lower child psychomotor or mental developmental test scores [60, 61]. However, the study of Murcia et al. [60] included pregnant women with thyroid disease and children with other medical conditions and with prematurity. When the association between maternal UIC and child development was assessed, Rebagliato et al. [61] demonstrated a non-significant trend toward higher mental scores in infants of mothers with UIC 150–249 $\mu\text{g}/\text{L}$ compared to those of mothers with UIC < 100 $\mu\text{g}/\text{day}$. A small study of 59 mother–child pairs in Australia did not show any effect of supplementation with 150 μg iodine/day before 20 weeks' gestation on child cognitive, language, and motor skills assessed at age 18 months (median UIC of mothers at

enrollment was 87 $\mu\text{g/L}$). However, the study was halted early and thus was substantially underpowered [62].

Observational studies have reported conflicting findings, as described above. There is a lack of robust randomized controlled trials (RCTs) assessing the effects of maternal iodine supplementation on pregnancy outcomes or offspring neurodevelopment in areas of mild-to-moderate ID. The available observational studies are of varying quality and frequently utilized small sample sizes. A systematic review of 27 observational studies and two meta-analyses showed that maternal iodine supplementation in severely iodine-deficient areas increased birth weight and infant head circumference and decreased infant death [63]. A more recent systematic review of eight RCTs showed that iodine supplementation during pregnancy in severely iodine-deficient areas reduced the risk of cretinism and improved some motor functions, but did not unequivocally demonstrate improvement in child intelligence, gross development, growth, or pregnancy outcomes [64]. In this review, a subgroup analysis of small trials of iodine supplementation in areas of mild-to-moderate ID did not show beneficial effects on childhood development, growth, or pregnancy outcomes [64]. Another meta-analysis of nine RCTs and eight observational studies reported a lack of RCTs examining the effects of maternal iodine supplementation on infant neurodevelopment [65]. In that analysis, maternal iodine supplementation decreased maternal thyroid volume and serum Tg levels, but had variable effects on maternal thyroid function. Finally, a pooled analysis of two RCTs showed that maternal iodine supplementation resulted in higher perceptual reasoning and global cognitive function in school-age children, but there was significant heterogeneity of the studies [65].

Iodine Excess in Pregnancy

In addition to ID, iodine excess in pregnancy can also have adverse thyroidal effects. When there is excess iodine available, the thyroid responds by transiently decreasing thyroid hormone production to prevent hyperthyroidism; this is known as the acute Wolff-Chaikoff effect [66]. When there is continued exposure to excess iodine, the healthy thyroid gland escapes from the acute Wolff-Chaikoff effect within 24–48 h by decreasing iodine uptake into the thyroid [67, 68]. However, individuals with underlying thyroid dysfunction, such as a previous history of autoimmune thyroid disease, may be unable to appropriately escape from the acute Wolff-Chaikoff effect, leading to hypothyroidism [69]. The fetus is at especially high risk of developing hypothyroidism with excess iodine exposure in utero, as the fetal thyroid gland is not able to fully escape from the acute Wolff-Chaikoff effect until approximately 36 weeks' gestation [70, 71].

Studies have investigated maternal thyroid function in areas of iodine excess, mostly in East Asia where typical diets contain high amounts of iodine-containing foods such as seafood and, especially, seaweed. A study in Japanese pregnant

women showed no significant association between serum-free T4 levels and UIC levels, including among those women with UIC >500 $\mu\text{g/L}$ [72]. On the other hand, studies of Chinese pregnant women showed an increased prevalence of subclinical hypothyroidism in regions with high drinking water iodine content, compared to those with optimal iodine intakes (19.7% vs 6.8% in one study, and 20% vs 2.3% in another) [73, 74].

Several case reports describe neonatal hypothyroidism and goiter as a result of maternal excess iodine ingestion or exposure from diets excessive in iodine or from iodine-containing medications [75–77]. Among Japanese pregnant women with high iodine intakes, no adverse effects of elevated maternal UIC levels were documented for scores of fetal maturation or child development at 12 months of age [78]. However, in that study, women with high UIC in the first trimester had been advised to decrease their iodine intake, potentially normalizing their UIC levels later in pregnancy [78]. In contrast, higher TSH levels were found in the cord blood of neonates born to Chinese mothers in a region of excessive iodine intake compared to those in the regions of adequate iodine intake [79]. A Dutch study reported increased risk of thyroid dysfunction in newborns of mothers with UIC >500 $\mu\text{g/L}$ [80].

A recent cross-sectional study of 7200 Chinese pregnant women in early gestation (4–8 weeks) in an iodine-sufficient region reported a U-shaped association between maternal UIC levels and the prevalence of thyroid dysfunction: the lowest serum Tg concentrations were seen in mothers with UIC 150–249 $\mu\text{g/L}$. The prevalence of subclinical hypothyroidism and hypothyroxinemia was also lowest in this group, with increased risk of subclinical hypothyroidism in those with UIC <100 $\mu\text{g/L}$ or UIC >250 $\mu\text{g/L}$, and increased risk of maternal hypothyroxinemia in those with UIC >500 $\mu\text{g/L}$. The results of this large study confirm that both iodine deficiency and iodine excess can lead to maternal thyroid dysfunction [81].

Current Iodine Nutrition Status

In 2013, approximately 70% of all households worldwide had access to adequately iodized salt, but 30 countries remained mild to moderately iodine-deficient based on the assessment of UIC in school-age children [82]. According to a recent survey of iodine nutrition in pregnant women in Europe, two-thirds of the 31 countries with nutritional data reported inadequate iodine intakes, and 23 countries had no data available regarding the iodine status of pregnant women [83].

Although the USA is iodine-sufficient overall, recent data suggest that pregnant women in the USA are mildly iodine deficient. According to National Health and Nutrition Examination Survey (NHANES) data, the median UIC for pregnant women in 2005–2010 was 129 $\mu\text{g/L}$, consistent with mild ID (Table 1) [84]. This represents a significant decrease compared to a median UIC of 173 $\mu\text{g/L}$ in NHANES 2001–2002 and 181 $\mu\text{g/L}$ in NHANES 2003–2004 [85]. Although the median UIC for the general US population remains stable and adequate at 164 $\mu\text{g/L}$ [86], the proportion of those with inadequate iodine status among women of reproductive age

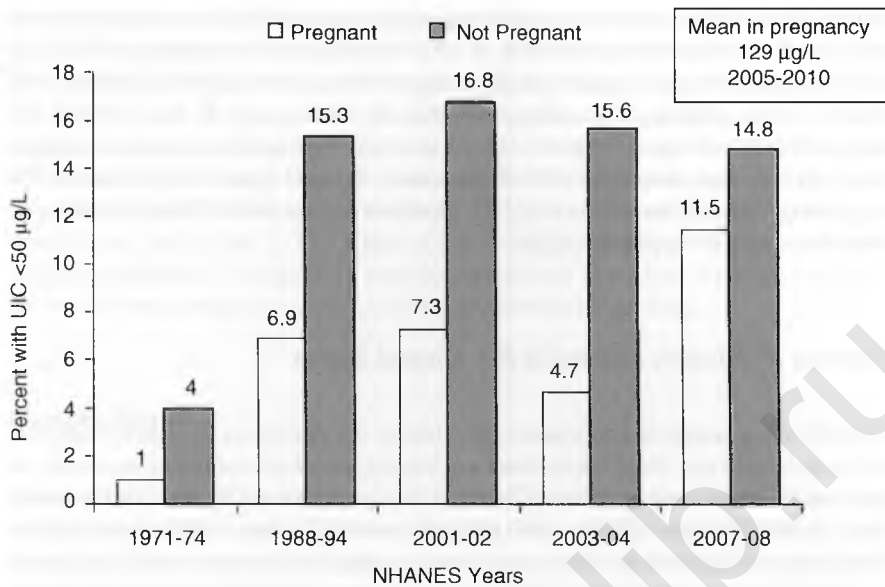


Fig. 2 US Women of childbearing age with low median urinary iodine concentration in National Health and Nutrition Examination Survey (NHANES) [84–86]. *UIC* urinary iodine concentration

and pregnant women has increased almost fourfold in recent years (Fig. 2) [84–86]. A study of 100 pregnant women in the first or second trimester of pregnancy in Boston found the median UIC to be marginal at 149 µg/L [87]. A more recent study of women planning pregnancy in Washington, DC, area showed that the median UIC of 141 women studied was also marginal at 100.5 µg/L [88].

Current Recommendations for Iodine Supplementation During Pregnancy

The WHO recommends increasing iodine intake in the form of a supplement or iodine-fortified foods in countries where less than 90% of households have access to iodized salt [89, 90]. Several professional societies specifically recommend iodine supplementation in pregnancy. The American Thyroid Association (ATA) recommends that women take supplements containing 150 µg of iodine daily during pre-conception, pregnancy, and lactation [91]. This recommendation is also supported by the European Thyroid Association [92], Endocrine Society [93], the American Academy of Pediatrics (AAP) [94], the Neurobehavioral Teratology Society [95], and the IGN [96].

Use of iodine-containing prenatal supplements has not been widespread, at least in the USA. Data from NHANES 1999–2006 revealed that only 22% of pregnant

women reported use of iodine-containing supplements [97]. This may have been from a lack of available supplements. A 2009 study demonstrated that only 114 out of 223 prenatal vitamins commercially available in the USA contained iodine [98]. However, this may have recently changed. In January 2015, the Council for Responsible Nutrition (CRN), the US trade group for supplement manufacturers, issued a recommendation that all multivitamin or mineral supplements intended for pregnant or lactating women in the USA should include at least 150 µg of iodine per daily dose in their supplements [99].

Sources of Dietary Iodine in the United States

It is difficult to ascertain the sources of iodine in the American diet, as iodine content is generally not listed on product packaging, and food iodine content can be quite variable. According to the Total Diet Study conducted by the US Food and Drug Administration (FDA), the average dietary iodine intakes in women 25–30 years of age and 40–45 years of age are estimated to be 14–196 µg/day and 145–197 µg/day, respectively [100]. The main sources of iodine in the typical adult American diet are dairy (~50%) and grain (23%) [100]. Milk contains a large amount of iodine because iodine is added to cattle feed, and iodine-containing solutions are used to clean cow teats and dairy equipment [101]. An analysis of 18 brands of cows' milk in the Boston area showed that all of the samples contained at least 88 mcg of iodine per 250 ml, ranging from 88–160 µg/250 ml [102]. Milk remains an important source of iodine in pregnant women in the USA. US studies have shown a significant association between high milk intake and lower risk of ID or a higher UIC level in pregnant women [103, 104]. Iodate bread conditioners used since the 1940s presumably accounted for a high iodine content in bread, although their use has significantly decreased in recent decades [101]. The iodine content of eggs, meat, and poultry, as well as that of fruits and vegetables is variable depending on the iodine content of animal feed or soil, type of fertilizer used, and irrigation practices [101, 105]. The iodine content of seafood and seaweed is also highly variable [106].

Since its introduction, iodized salt has been an important source of dietary iodine. However, a recent assessment of salt sales in the USA showed that only 53% of table salt sold for household consumption is iodized [107]. Moreover, household table salt only accounts for about 15% of salt consumption in the USA; most salt consumption in USA adults comes from processed or restaurant foods, which typically do not utilize iodized salt [101]. A study of the iodine content of US fast foods revealed minimal iodine in representative foods, except for those containing dairy or fish [108]. Specialty salts, such as sea salt and Kosher salt, are generally not iodized [105].

Individuals who adhere to restricted diets may be at an increased risk for ID. A study of meals from three US commercial weight-loss programs showed that daily

iodine contents of these meals were low, with mean iodine content ranging from 12.2 to 70.1 $\mu\text{g}/\text{day}$ [109]. Vegans may also be at an increased risk of ID. A study of 141 subjects (78 vegetarians and 62 vegans) in the Boston area reported a median UIC of 78.5 $\mu\text{g}/\text{L}$ in vegans and 147 $\mu\text{g}/\text{L}$ in vegetarians, suggesting mild ID in the vegans. Consumption of cows' milk, soy milk, or bread was associated with higher UIC levels in this study [110]. A study of 70 Danish vegans aged 18–61 years showed the mean iodine intake was only 65 $\mu\text{g}/\text{day}$ compared to 178 $\mu\text{g}/\text{day}$ in omnivorous individuals [111]. These findings suggest that use of iodized salt or iodine supplements in pregnancy may be particularly important for those individuals with dietary restrictions, especially for those who avoid dairy.

Conclusion

Iodine is an essential micronutrient for thyroid hormone production, which is especially important for normal fetal development during pregnancy. Both iodine deficiency and iodine excess in pregnancy may lead to adverse obstetric outcomes and adverse effects on offspring development through their effects on thyroid function. Worldwide, universal salt iodization is the mainstay of iodine deficiency disorder elimination efforts. The main dietary sources of iodine in the USA include iodized salt, cows' milk, and some breads. Although the prevalence of iodine deficiency has decreased in recent decades, pregnant women in many regions remain vulnerable to the effects of iodine deficiency. Because of the lack of an individual biomarker for iodine status and the lack of iodine content labeling on foods, a daily supplement containing 150 μg of potassium iodide is currently recommended for all women preconception and during pregnancy and lactation.

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Vitamin D in Pregnancy and Lactation: A New Paradigm

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Keywords Vitamin D · Cholecalciferol · Pregnancy · Lactation · Health outcomes

Key Points

- The function of vitamin D during pregnancy is diverse, involving genomic alteration that is involved in decreasing birth complications and infant asthma development.
- The vitamin D requirement during pregnancy and lactation has been greatly underestimated.
- Women should take 4000 IU/d vitamin D prior and during pregnancy.
- Lactating mothers should consume 6000 IU/d vitamin D to satisfy her requirement as well as the requirement of her nursing infant.

Introduction

Pregnancy and lactation represent a time of rapid body changes, which include physical proportions, physiology, and responsibility. Arguably, the requirement and metabolism of vitamin D is one of the most important changes during this period, although this would never be surmised from current Institute of Medicine (IOM) recommendations [1]. During these dramatic times of physiologic change, the roles of vitamin D in the pregnant versus lactating woman are quite different. In the pregnant woman, the primary role of vitamin D appears to be immunomodulatory while also retaining its calcium regulating function. During lactation, maternal vitamin D intake serves the primary role of supplying the nursing newborn infant with

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adequate vitamin D for its skeletal integrity function, but may have immunoregulatory functions as well in both mother and her breastfeeding infant.

Brannon and Picciano [2] and Abrams [3] provide a historical perspective of vitamin D recommendations during pregnancy and lactation that covers the past 50 years. In this chapter, we will provide new insights into vitamin D requirements and functions during pregnancy and lactation.

Vitamin D Nomenclature and Metabolism

There are two forms of vitamin D: D₂ and D₃. Vitamin D₂, or ergocalciferol, is made by plants, and vitamin D₃, or cholecalciferol, is made by animals, including humans, and both are often referred to as the “parent compound.” For the remainder of this review, vitamin D will be used as a reference to both compounds unless otherwise noted.

Vitamin D₃ is formed in the skin upon exposure to ultraviolet light exposure [4]; vitamin D₃ is also acquired through dietary supplementation, along with vitamin D₂, with the recommended amount of this supplementation a source of lingering controversy [1, 5–7]. Since we are largely a society that avoids sun exposure, the role of dietary supplementation becomes extremely important. Once in the circulation, vitamin D is converted into 25-hydroxyvitamin D—25(OH)D—the major circulating form of the vitamin. This conversion of vitamin D to 25(OH)D is achieved primarily in the liver, but can also be achieved in a variety of tissues in an autocrine/paracrine fashion [8]. Finally, 25(OH)D is converted into the hormonal form of the vitamin—1,25-dihydroxyvitamin D (1,25(OH)₂D)—in the kidney for endocrine function and other tissues for autocrine/paracrine function [8].

Vitamin D Metabolism During Pregnancy When Compared with the Non-Pregnant State Including Lactation

A striking difference exists in vitamin D metabolism during pregnancy and fetal development compared with non-pregnancy and non-fetal states, a point that has been known for at least the past three decades, but which has received little attention until recently [9–13]. The conversion of vitamin D to 25(OH)D appears unchanged during pregnancy, following first-and-zero-order enzyme kinetics [14]. By contrast, the conversion of 25(OH)D to 1,25(OH)₂D during pregnancy is unique and unparalleled during life. At no other time during life is 25(OH)D so closely linked with 1,25(OH)₂D production. By 12 weeks of gestation, 1,25(OH)₂D serum concentrations are more than twice that of a non-pregnant woman and continue to rise twofold to threefold from the non-pregnant baseline, rising to over 700 pmol/L, attaining levels that would be toxic due to hypercalcemia to the non-pregnant individual, but which are essential during pregnancy [15]. Similarly, in the fetus, cord

blood levels of circulating $1,25(\text{OH})_2\text{D}$ are even more closely tied to fetal levels of $25(\text{OH})\text{D}$ [16, 17]. In neither the pregnant mother nor the fetus does this conversion seem to be controlled by the classic calcium homeostatic mechanisms [15, 18].

The rise in circulating $1,25(\text{OH})_2\text{D}$ concentrations in the mother/fetus is a remarkable observation. Early on, it was thought that this increase was to ensure adequate delivery of calcium to the maternal skeleton preservation and fetal skeletal development. Calcium homeostasis, however, is not linked with this increase in $1,25(\text{OH})_2\text{D}$ because at 12 weeks' gestation there is no increase in calcium demand by either the mother or fetus. In contrast, this increased concentration of $1,25(\text{OH})_2\text{D}$ sustained during pregnancy is not sustained during lactation, when maternal calcium demand is at least as high as during pregnancy [19]. Thus, in the mother and fetus during pregnancy, the rise in $1,25(\text{OH})_2\text{D}$ is dependent on substrate availability—in this case $25(\text{OH})\text{D}$ —and is largely independent of calcium homeostasis [15].

Why is calcium metabolism uncoupled from $1,25(\text{OH})_2\text{D}$ generation during pregnancy and not lactation? One of the leading theories is that $1,25(\text{OH})_2\text{D}$ is an important immune modulator involved in maternal tolerance to the foreign fetus whose DNA is only half that of the mother's. Based on early epidemiological studies involving pregnant women with preeclampsia, a clinical picture of inflammation and vasculitis, vitamin D deficiency has been implicated [20, 21]. Experimental animal models also have strongly suggested vitamin D deficiency as a potential mechanism of placental dysfunction [22, 23].

Obstetrical “Paranoia” with Regard to Vitamin D Administration During Pregnancy

We refer to this type of thinking as “medical lore”; however, in this particular case because it carries forth into current medical care, we view it with serious concern. It happens when medical students are taught something that is based on outdated data that have been carried through to the present. This is absolutely the case with the use of vitamin D during pregnancy. Why is this?

Because of the British experience with idiopathic infantile hypercalcemia attributed to hypervitaminosis D, a terrible inaccurate association occurred that had a profound effect on the potential of vitamin D supplementation, not only during infancy but also during pregnancy. In 1963, Black and Bonham-Carter [24] recognized that elfin facies observed in patients with severe idiopathic infantile hypercalcemia resembled the peculiar facies observed in patients with supravalvular aortic stenosis (SAS) syndrome. Shortly thereafter, Garcia et al. [25] documented the occurrence of idiopathic hypercalcemia in an infant with SAS who also had peripheral pulmonary stenosis, mental retardation, elfin facies, and an elevated blood concentration of vitamin D. This is an interesting observation because in 1964, when the article was published, there were no quantitative means of assessing circulating concentrations of vitamin D. In fact, at that time, it was not even proven that vitamin D was further metabolized within the body. By 1967, vitamin D was viewed

by the medical community as the cause of SAS syndrome [26, 27]. As a result of the theory that maternal vitamin D supplementation during pregnancy caused SAS syndrome [28], animal models were developed to show that toxic excesses of vitamin D during pregnancy would result in SAS [29, 30]. In these earlier cases (22), vitamin D had nothing to do with the etiology of SAS. What was described as vitamin D-induced SAS syndrome is now known as Williams Syndrome [31, 32]. Unfortunately, vitamin D intake during pregnancy is still associated with SAS.

Williams Syndrome is a severe genetic affliction related to elastin gene disruption [31] that is caused by deletion of elastin and contiguous genes on chromosome 7 *g 11.23*. This syndrome is characterized by multiorgan involvement (including SAS), dysmorphic facial features, and a distinctive cognitive profile [32]. Such patients often exhibit abnormal vitamin D metabolism, which makes them susceptible to bouts of idiopathic hypercalcemia [33]. This relationship was suspected as early as 1976 [34]. Subsequently, it was shown that children with Williams Syndrome exhibit an exaggerated response of circulating 25(OH)D to orally administered vitamin D [35]. Thus, the fear of vitamin D-induced SAS is based on studies that are no longer valid yet continue to be cited and feared, and thus impact treatment.

Observational Studies Suggesting the Function of Vitamin D Extended Beyond Calcium Homeostasis During Pregnancy

The role of vitamin D and skeletal function during pregnancy and lactation has been previously discussed [1, 2, 3]. Beyond skeletal functions, what are other functions with respect to vitamin D in pregnancy and lactation? To discover what these might be, we rely on associative or observational studies, and in the past 15 years or so many of these studies have been performed.

Of high interest is the association of dietary vitamin D₃ intakes in pregnant women and preeclampsia. Olsen and Secher [36] point out that in the early 1940s, studies were performed giving pregnant women halibut liver oil, which is rich in vitamin D₃, and decreases in preterm birth and preeclampsia were observed, which was attributed to marine n-3 fatty acids [36]. Through the ensuing decades, it became clear that vitamin D's actions in the human body could exist well beyond skeletal events and, thus, people started looking at the link between vitamin D and other disease states and conditions [20, 21, 37–40, 41–47]. Early observational studies uncovered strong relationships between maternal circulating concentrations of 25(OH)D and preeclampsia [20, 21, 37, 38], altered placental vascular pathology [39], cesarean section [40], glucose tolerance [41], adverse birth outcomes due to race [42], infection rates [43], brain function [44–46], and respiratory function [47].

While public policy cannot be set for supplementation practices based on observational studies, this information is invaluable at pointing research in the direction that could yield public policy changes in vitamin D consumption. These next steps are interventional studies and randomized clinical trials (RCTs). One has to exhibit

caution, however, even with RCTs, as results can be problematic when analyzed on an intent-to-treat basis. There also may be high nonadherence to protocol, thereby diluting the potential good or harm of a given treatment at higher doses. A biomarker of a drug or, in this case, “vitamin” or prohormone is better served. For these reasons, analysis of effect of vitamin D therapies using 25(OH)D concentration is a far better indicator of true “effect.”

Randomized Controlled Trials Investigating Vitamin D Supplementation During Pregnancy

Vitamin D supplementation trials involving pregnant women have been performed since 1980 [48]. Those early studies were small, did not look at meaningful endpoints, and did not supplement with enough vitamin D [48]. As a result, no meaningful information or public policy changes occurred based on these studies. In 2001, our group conceived a large RCT investigating the supplementation of vitamin D to a population of pregnant women. Our study was radical in design in that we proposed supplementing pregnant women who were less than 16 weeks of gestation with up to 4000 IU/d vitamin D₃ until delivery in a double-blind fashion. The goal of the study was to see how much vitamin D was required to raise circulating maternal 25(OH)D concentrations to at least 32 ng/mL by the end of gestation. Using mathematical calculations from previous studies, we calculated how much vitamin D₃ we would need to provide [49, 50]. We selected the 32 ng/mL concentration of circulating 25(OH)D based on the suppression of secondary hyperparathyroidism [51]. We obtained funding from the National Institute of Child Health and Development (NICHD) in 2002; however, because of safety concerns about the use of a 4000 IU/d dose of vitamin D₃ we had to obtain an investigational drug application approval from the Food and Drug Administration (FDA; #66,346). This approval was obtained in 2003 and the study began in early 2004. Along with this NICHD-sponsored study, we also received funding from the Thrasher Fund to perform a parallel study involving vitamin D supplementation of pregnant women in a community-based format. At the initiation of these RCTs, our endpoints were safety of the dosing, attained circulating level of maternal 25(OH)D, growth parameters of the infant, and bone-mineral-density of the mother and infant. As for the other factors mentioned in the previous section on vitamin D relationships based on observational studies, those associations had not been made at study initiation, and as a result we had no idea to even look for them, let alone propose them as endpoints. As such, these endpoints were analyzed as *post hoc* analyses.

The results of these RCTs have been presented and published over the last few years as displayed in Table 1 [15, 52–59]. The main finding of these studies was that a 4000 IU/d dose of vitamin D₃ safely elevates circulating 25(OH)D to a level that, regardless of race, fully normalizes vitamin D metabolism and calcium homeostasis in pregnant women. Further, this dose was safe, with not a single adverse event attributable to vitamin D supplementation (Table 1).

Table 1 Recently completed randomized controlled trials providing vitamin D during pregnancy

Study	Country	Subjects	Trial type	Intervention	Baseline 25(OH)D (ng/mL)	Endpoint 25(OH)D (ng/mL)	Findings	Adverse events
Hollis et al. (2011, 2013) [15, 52]	USA	350	RCT	400, 2000, or 4000 IU/d vitamin D ₃ from 14 weeks' gestation until delivery	400 IU/d: 24.6 2000 IU/d: 23.3 4000 IU/d: 23.2	400 IU/d: 31.6 2000 IU/d: 39.3 4000 IU/d: 44.4	Vitamin D decreased cesarean section and comorbidities of pregnancy	None
Wagner et al. (2013, 2016) [53, 54]	USA	2013: 160 2016: 504	2013: RCT 2016: post-hoc combined RCT	2013: 2000 or 4000 IU/d vitamin D ₃ from 14 weeks gestation 2016: 400, 2000 or 4000 IU/d vitamin D ₃ from 14 weeks' gestation	400 IU/d: 24.6 2000 IU/d: 23.2 4000 IU/d: 22.8	400 IU/d: 30.7 2000 IU/d: 37.1 4000 IU/d: 41.9	Vitamin D decreased preterm births and complications of pregnancy	None
Goldring et al. (2013) [55]	UK	180	RCT	0 or 800 IU/d from ___ weeks onward, or 200,000 IU/bolus given at 27 weeks' gestation	800 IU/d: 10.0 200,000 IU/bolus: 10.0	800 IU/d: 17.0 200,000 IU/bolus: 14.0	Vitamin D tended to decrease infant wheezing but effect was minor	None
Sablak et al. (2015) [56]	India	165	RCT	0 IU vitamin D ₃ ; 60,000 IU/bolus vitamin D ₃ at 20 weeks' gestation; 120,000 IU/bolus vitamin D ₃ at 20 and 24 weeks' gestation or 120,000 IU/bolus vitamin D ₃ at 20, 24, 28 and 32 weeks' gestation	All patients <10.0	0 IU: <10.0 120,000 IU/bolus: 15.2 120,000 IU/4 doses: 26.0	Vitamin D greatly decreased complications of pregnancy	None
Mojibian et al. (2015) [57]	Iran	500	RCT	400 IU/d vitamin D ₃ or 50,000 IU/bolus every 2 weeks vitamin D ₃ starting at 14 weeks' gestation	400 IU/d: 15.3 50,000 IU/bolus every 2 weeks: 14.5	400 IU/d: 27.2 50,000 IU/bolus every 2 weeks: 37.9	Vitamin D significantly decreased incidence of gestational diabetes	None

Chawes et al. (2016) [58]	Denmark	623	RCT	800 or 2800 IU/d vitamin D ₃ from 24 weeks' gestation	800 IU/d: 13.0 2800 IU/d: 31.0	800 IU/d: 29.0 2800 IU/d: 43.0	Vitamin D tended to decrease infant wheezing but was not statistically significant	None
Litonjua et al. (2016) [59]	USA	881	RCT	400 or 4400 IU/d vitamin D3 from 16 weeks' gestation	400 IU/d: 23.0 4400 IU/d: 23.0	400 IU/d: 27.0 4400 IU/d: 39.0	Vitamin D significantly ($p < 0.051$) decreased asthma and wheezing in infants up to 3 years follow-up	None

When our studies were completed in 2009, we were aware of the observational data suggesting favorable effects of vitamin D on pregnancy outcomes beyond calcium homeostasis. When analyzed on an intent-to-treat basis, the data clearly demonstrated increased vitamin D supplementation, decreased complications of pregnancy, and C-section births [15, 52]. Further, RCT data and analysis by our group and others have clearly demonstrated that higher doses of vitamin D during pregnancy improve birth outcomes [52, 54]. RCT studies beyond our own have recently demonstrated vitamin D to greatly decrease complications of birth and gestational diabetes [56, 57].

Supplementing Vitamin D during Pregnancy to Prevent Childhood Asthma

In 2006, Dr. Hollis was contacted by Scott Weiss, MD of the Harvard Medical School with an idea to conduct a RCT using vitamin D supplementation during pregnancy to prevent the development of childhood asthma. Dr. Weiss was aware of our ongoing RCT and had excellent observational data suggesting vitamin D supplementation during pregnancy could reduce childhood asthma rates [60, 61]. Subsequently, we obtained funding for this project from the National Institute of Heart, Lung and Blood (NHLBI) and the Vitamin D Antenatal Asthma Reduction Trial (VDAART) was born. It was a collaboration between Boston University, Brigham and Women's Hospital, Harvard Medical School, Kaiser Permanente South California Region, Medical University of South Carolina, and Washington University in St. Louis, and NHLBI. This was a double-blind RCT performed at three clinical centers: Boston, St. Louis, and San Diego, and involved giving supplemental vitamin D₃ (400 or 4400 IU/d) to pregnant women across the three major racial/ethnic groups in the USA from 16 weeks of gestation until delivery. The primary endpoint was prevention of asthma/wheeze in the infant/child at 1, 2, and 3 years post-birth. Nearly 900 high-risk subjects were enrolled and completed the study, which was recently published [59]. The results of this study are quite clear: vitamin D supplementation during pregnancy will decrease asthma or recurrent wheezing rates in children (Fig. 1).

A nearly identical RCT study performed in Denmark has also been published [58]. The journal in which these articles appeared, *JAMA*, has attempted to minimize the results and impact of these studies with an editorial [62]. In response to this negativity, the authors of these two RCTs performed a meta-analysis [63]. Keep in mind that a meta-analysis of RCTs is the highest form of validation for Therapy/Prevention/Etiology/Harm as defined by The Centre for Evidence-Based Medicine

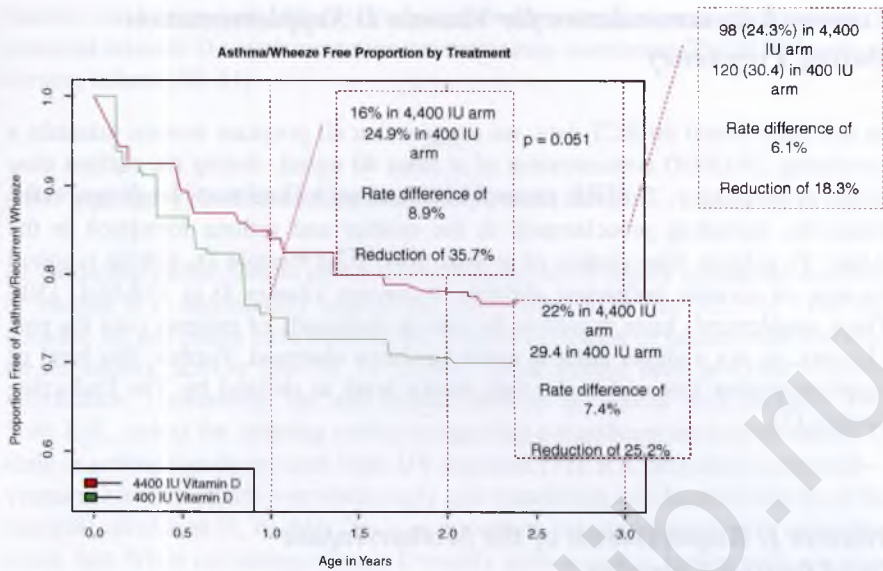


Fig. 1 Kaplan-Meier survival estimates. Error bars indicated 95% CI estimates at intervals of 1, 2, and 3 years. The hazard ratio for the time to first event of asthma or recurrent wheeze was 0.8 (95% CI, 0.6–1.0; $p = 0.051$). Adapted from Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. [59]

at Oxford University [64]. The results from these RCTs and meta-analysis studies are quite clear: vitamin D₃ given to a pregnant woman will prevent asthma/wheeze in her child [58, 59, 63]. The mechanisms by which this occurs remain unknown, but it is proposed that epigenetic *in utero* changes triggered by the vitamin D administered to the pregnant women impart functional change in the fetus.

What is clear from these recent RCTs is that a 4000 IU/d vitamin D₃ supplement is beneficial to both mother and child, and these benefits are not via the classic role of vitamin D in calcium homeostasis. What is not resolved is the dose and time of administration to achieve optimum results. We propose that a target concentration of 40 ng/mL circulating 25(OH)D be achieved in pregnancy as early as possible. Because of biochemical heterogeneity in attaining a given concentration of 25(OH)D, we further propose that all women should consume at least 4000 IU/d vitamin D₃ prior to conception [50]. Also in question is whether vitamin D administration during pregnancy can impact autoimmune disease and neuropsychological development. More rigorous vitamin D trials are needed to answer this question, but observational and RCT data suggest it to be promising [44–46].

Current Recommendation for Vitamin D Supplementation During Pregnancy

At this time, based on RCT data, we suggest that all pregnant women maintain a circulating 25(OH)D concentration of at least 40 ng/mL during the earliest time points of pregnancy. This will ensure maximum protection from pregnancy complications, including preeclampsia in the mother and asthma formation in the infant. To achieve this, intakes of at least 4000 IU/d vitamin D₃ will be required because of variable individual abilities to convert vitamin D to 25(OH)D [50]. These supplements have proven to be safe in thousands of patients over the past 15 years, as not a single adverse event has been observed. Further, this level of supplementation lies within the safe intake level as defined by The Endocrine Society [7].

Vitamin D Requirements of the Mother/Infant Dyad During Lactation

Breast milk has long been held as the “perfect” food for the human neonate with one caveat: it contains insufficient vitamin D for nursing neonates to maintain minimal circulating levels of 25(OH)D, and thus skeletal integrity. When compared with formula-fed infants, solely breastfed infants are at increased risk of developing rickets [65, 66]. This is especially true in African American breastfed infants [67]. Vitamin D activity in “normal” lactating women’s milk is known to be in the range of 5–80 IU/L, depending on the method of assay [68–70]; however, the vitamin D content of human milk can be greatly increased by maternal oral vitamin D supplementation [68, 69] and/or increasing solar exposure of the mother [71]. Infants solely breastfed by women with vitamin D intakes of 400 IU/d typically attain a circulating 25(OH)D concentration in the marginally sufficient-to-severely deficient (<5.0 ng/ml) range [72]. Therefore, to address this risk of deficiency, vitamin D supplementation of all breastfeeding infants beginning within a few days of birth has been recommended by both the American Academy of Pediatrics (AAP) [73] and the Institute of Medicine (IOM) [74]. Although this has been the recommendation for decades, it is rarely followed for various reasons, with low compliance ranging from 2% to 19% [75–77], leaving the nursing infant at significant risk for vitamin D deficiency.

The amount of vitamin D required by a lactating woman to normalize her own vitamin D status and ensure adequate vitamin D concentrations in her milk for her breastfeeding infant is predicted by known pharmacokinetics about vitamin D

transfer into human milk [78, 79]. Early studies demonstrated some effectiveness of maternal vitamin D supplementation on increasing circulating 25(OH)D levels in nursing infants [80, 81].

Altering the Vitamin D Content of Human Milk

As mentioned earlier, human milk has long been known to supply inadequate amounts of vitamin D to nutritionally support the solely breastfed infant [65, 66]. Over the decades, we and others have reported the vitamin D content of human milk and thus its anti-rachitic activity [68–70, 79, 82–84]. These studies have provided valuable information. Universally, the anti-rachitic activity of human milk is quite low, 5–80 IU/L, unless the lactating mother is ingesting a significant amount of vitamin D daily or getting significant total-body UV exposure [71]. It is the parent compound—vitamin D itself—which overwhelmingly gets transferred into human milk from the maternal circulation [8, 70, 84]. This is an important, yet almost universally misunderstood, fact. While circulating vitamin D readily gains access to human milk, circulating 25(OH)D does not. The transfer relationship of vitamin D occurs over a massive range of vitamin D intakes and/or circulating concentrations [78, 79]. Thus, one cannot assume that because a lactating mother's circulating 25(OH)D concentration is adequate, her milk vitamin D activity will be. This is because circulating vitamin D in the mothers is almost always low, and, in many cases, undetectable (<2.0 ng/mL), making mother's milk a poor source of vitamin D activity. This occurs because the circulating half-life of 25(OH)D is three to 4 weeks, and that of vitamin D is ~12–24 h, reflecting their binding affinity to vitamin D binding protein [8]. This reduced affinity of vitamin D allows the unbound vitamin D to diffuse across cell membranes from blood into the milk. This concept is discussed in depth elsewhere [8]. Thus, a daily dose of vitamin D is required to sustain both circulating and milk concentrations of vitamin D in the lactating woman.

From the standpoint of nature, low vitamin D content in breast milk is an odd circumstance. Would nature allow so little vitamin D in breast milk that the nursing infant would develop rickets from ingesting it [65, 66]? We did not think so. We hypothesized that breast milk was deficient in vitamin D due solely to lack of solar exposure and dietary recommendations for vitamin D put forth in recent decades [1]. The current IOM recommendation for vitamin D intake during lactation is 400–600 IU/d, yet historical data suggest that this level of maternal supplementation does nothing to increase the vitamin D content of a woman's milk [70] and/or support adequate nutritional vitamin D status in her nursing infant [72]. This is precisely why the AAP recommends every nursing infant receive a daily supplement of 400 IU vitamin D [73].

This last recommendation, however, treats only the infant and does not address the core problem of why breast milk has such a low concentration of vitamin D.

Interventional and RCTs to Determine If Maternal Vitamin D Supplementation Can Supply Adequate Vitamin D to the Nursing Infant

Many studies have been performed to define the vitamin D content of human milk and ways to alter it [68, 69, 82, 83]. However, one of the most important questions is, how much vitamin D does a lactating woman need to ingest so she passes enough vitamin D to the nursing infant to maintain a circulating 25(OH)D that matches a 400 IU/d of direct supplementation to the infant as recommended by the AAP [73]? From the past investigation we know that the circulating concentration in the infant taking 400 IU/d is approximately 40 ng/mL [70, 85, 86]. Thus, when designing clinical trials investigating this topic, the critical endpoint should be the maintenance of infant circulating 25(OH)D in the range of 40 ng/mL.

The first trials to assess whether maternal vitamin D supplementation could be effective at raising the nursing infant's circulating 25(OH)D concentrations were performed by investigators in Finland in the mid-1980s [80, 81]. While these studies clearly demonstrated that this strategy could work, the amount they administered to mothers, 1000–2000 IU/d vitamin D₃, was simply not enough to elicit enough change. Ironically, in their 1986 paper, the authors became concerned that dosing these mothers with 2000 IU/d could prove harmful to them, based solely on the premise that the recommended daily allowance (RDA) at the time was 400 IU/d [81]. Couple this fear with an Upper Limit (UL) set at 2000 IU/d by the 1997 IOM committee, and all meaningful vitamin D research in this area came to a halt [87].

The skies again opened for vitamin D research in the early 2000s when research demonstrated that vitamin D intakes up to 10,000 IU/d were safe for extended periods of time [50]. This information allowed us to investigate higher vitamin D intakes in pregnancy and lactation after having to obtain an Investigational Drug Approval (IND) from the FDA [15]. Using pharmacokinetic data on the transfer of vitamin D from blood into milk, we determined that an intake of approximately 6000 IU/d would be required to meet the nursing infant's need while putting the lactating mother at no risk [70]. This interventional study was published in 2006 [70], validating our premise, and led to a much larger RCT funded by NIH/NICHD. The efficacy results of this larger trial were recently published, and clearly demonstrated that maternal vitamin D₃ supplementation with 6400 IU/d safely supplies breast milk with adequate vitamin D to satisfy her nursing infant's requirement, and offers an alternate strategy to direct infant supplementation [88]. The results from this study are displayed in Fig. 2. Our trial also demonstrated that a maternal intake of 2400 IU/d was insufficient to maintain adequate circulating levels of 25(OH)D in her nursing infant [88]. This observation has also been reported in other recent publications [89–91].

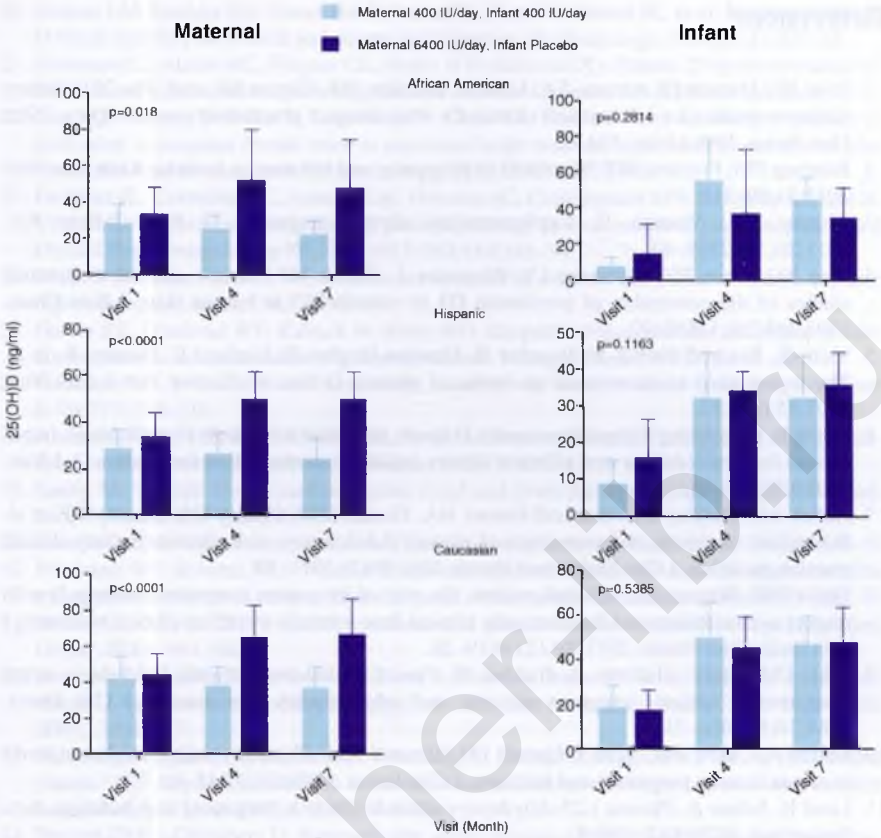


Fig. 2 Total circulating 25(OH)D concentration (nmol/L) by treatment (400 IU vs. 6400 IU groups) of breastfeeding mothers: (a) through Visit 4 (V4); (b) through Visit 7 (V7); and of breastfeeding infants: (c) through V4; (d) through V7

Current Recommendation for Maternal Vitamin D Supplementation During Lactation

At this time, based on RCT data, we suggest that all lactating mothers consume at least 6000 IU/d of vitamin D₃. This daily dose would provide the adequate vitamin D to support circulating 25(OH)D levels in the infant.

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Vegetarian Diets in Pregnancy

Ann Reed Mangels

Keywords Vegetarian · Vegan · Pregnancy · Iron · Cobalamin · Zinc
Omega-3 fatty acids · Calcium · Vitamin D · Iodine

Key Points

- Vegetarian diets, including lacto-ovo vegetarian, lacto vegetarian, and vegan diets, can meet the nutritional needs of pregnant women and may offer health benefits to women and their offspring.
- There is wide variability in food choices of self-described vegetarians so individual assessment of dietary adequacy is recommended.
- Standard recommendations for weight gain and for nutrient needs in pregnancy are used for vegetarian clients. The exception is iron, and possibly zinc; requirements for these nutrients are or may be higher for vegetarians than for non-vegetarians.
- Key nutrients for vegetarian pregnancy include protein, iron, zinc, calcium, vitamin D, vitamin B12, iodine, and omega-3 fatty acids. A vegetarian or vegan diet can meet requirements for all of these nutrients, with fortified foods or supplements being especially useful in meeting recommendations for some nutrients.
- Prenatal supplements identified specifically for vegetarians are available. Individual assessment is needed to determine whether or not a supplement is needed and the amount and type of supplementation.

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Introduction

Definition and Types of Vegetarians

A vegetarian is a person who does not eat meat, fish, seafood, poultry, or products containing these foods [1]. Within the broad category, there are numerous subcategories. The most common are lacto-ovo vegetarians, lacto vegetarians, and vegans. Lacto-ovo vegetarians are vegetarians who eat eggs and dairy products. Lacto vegetarians use dairy products but not eggs, and vegans (pronounced VEE-guns) avoid all animal products including dairy products, eggs, honey, and gelatin.

Other types of vegetarian (or near vegetarian) diets include macrobiotic, raw foods, and fruitarian diets [2]. Macrobiotic diets consist mainly of grains, vegetables, especially sea vegetables, beans, fruits, nuts, soy products, and possibly fish. As the name suggests, those choosing a raw foods diet mainly or exclusively consume uncooked and unprocessed foods. Foods used include fruits, vegetables, nuts, seeds, and sprouted grains and beans; unpasteurized dairy products and even raw meat and fish may be used [3]. Fruitarian diets are based on fruits, nuts, and seeds and often include vegetables that are botanically fruits like avocado and tomatoes; other vegetables, grains, beans, and animal products are excluded [2].

Many people, who do not strictly avoid meat, fish, or poultry, describe themselves as vegetarian [4–6]. This can have a significant impact on food choices and nutrient intake so individual assessment of the diets of self-identified vegetarian clients is essential.

Reasons for Vegetarianism

Reasons for vegetarianism are highly individual and include health considerations, environmental concerns, and animal welfare issues [7]. Other factors include religion, economics, ethical issues, and a desire to reduce world hunger [5].

How Many Vegetarians Are There?

No information is available on the number of pregnant vegetarians in the United States. We do know, based on a poll conducted in 2015, that 3.4% of the adult population consistently follows a vegetarian diet and that about 15% of vegetarians follow a vegan diet [8]. In most countries, as in the United States, only a small percentage of the population is vegetarian. In India, about 30% of the population follows a vegetarian diet [9].

Adequacy of Vegetarian Diets in Pregnancy

The Academy of Nutrition and Dietetics (formerly known as the American Dietetic Association) has reviewed current information on vegetarian diets and concluded that, “Well-planned vegetarian diets are appropriate for individuals during all stages of the lifecycle including pregnancy, lactation . . .” [1] Similarly, *Dietary Guidelines for Americans, 2015–2020* identifies a vegetarian diet as suitable for pregnancy [10]. Although few research studies have been conducted on vegetarian pregnancy, available information suggests that vegetarian women who have adequate amounts and sources of food will have pregnancy results that are similar to those of non-vegetarian women [11–14].

Health Advantages of Vegetarian Diets

Numerous health advantages are associated with use of a vegetarian diet. These include: [1]

- A lower body mass index (BMI)
- Reduced rates of cardiovascular disease and of risk of death from ischemic heart disease
- Lower blood pressure and markedly lower rates of hypertension
- Reduced risk of type 2 diabetes
- Lower risk of colorectal cancer

Dietary Guidelines for Americans, 2015–2020 identifies a “Healthy Vegetarian Eating Pattern” as a recommended way to eat that can help reduce the risk of chronic disease [10]. Another benefit of vegetarian diets is that vegetarians typically have higher intake of plant foods. Those eating vegetarian or near-vegetarian diets eat more legumes, nuts, grains, and fruits and vegetables than do non-vegetarians [15]. One study reports that vegans ate fewer sweets and snack foods than either non-vegetarians or lacto-ovo vegetarians [15].

Women and their offspring can benefit from the use of a vegetarian diet, both in the long-term and during pregnancy. One study found that vegetarian women had a lower risk of excessive gestational weight gain [16]. The higher fiber content [17, 18] of many vegetarian diets can help to alleviate the constipation that commonly occurs in pregnancy. Another positive aspect of vegetarian diets is that pregnant vegetarians tend to have higher intakes of both folate and magnesium than do non-vegetarians [19, 20]. A marked reduction in risk of preeclampsia in vegans compared to the general population was reported in one small study; [21] however, another study did not find this reduced risk [22]. Diets high in plant foods have been associated with a lower risk of preeclampsia [23, 24]. Although limited information

is available about the impact of maternal vegetarianism on children's health, one study found that offspring of women whose diets during pregnancy were low in animal protein had a lower risk of obesity in young adulthood [25].

Weight Gain and Birth Weight in Vegetarian Pregnancy

Vegetarians as a group tend to be leaner than do non-vegetarians, with vegans tending to have a lower BMI than other vegetarians [26, 27]. This suggests that vegetarian women tend to begin pregnancy with a lower BMI than do non-vegetarians. Ideally, all women, including vegetarians, should have BMIs within the normal range prior to conception [28]. Standard weight gain recommendations [29] should be used for vegetarians. Weight gain of pregnant lacto-ovo vegetarians and vegans is generally adequate [21, 30, 31]. Birth weights of infants of vegetarian women have been frequently shown to be similar to those of infants born to non-vegetarian women and to birth weight norms [30–33]. Low birth weights have been reported in some macrobiotic populations [34, 35]. These low birth weights appear to be due to low maternal weight gain secondary to inadequate energy intake [34, 35].

Suggestions for vegetarian women who have difficulty gaining weight in pregnancy include:

- Use small, frequent meals and snacks
- Emphasize concentrated sources of energy and nutrients such as nuts and nut butters, full-fat soy products, dried fruits, and bean spreads
- Use some refined foods (i.e., enriched grains, fruit juices) if dietary fiber intake is high
- Increase use of unsaturated oils in cooking
- Make beverages count—instead of drinking tea, coffee, seltzer, or diet drinks, try smoothies (made with fruit, juice, and milk) or milkshakes

Nutritional Considerations

Recommendations for most nutrients do not differ based on vegetarian status, although the main sources for some nutrients may vary. These include protein, vitamin B₁₂ and omega-3 fatty acids, and calcium and vitamin D (for vegans). Iron and possibly zinc requirements are higher for vegetarians than for non-vegetarians [36]. Other nutrients, including vitamin C and vitamin A (as beta-carotene) are generally adequate in the diets of vegetarians eating a wide variety of foods.

Table 1 Protein content of foods commonly eaten by vegetarians

Food, serving size	Protein (g)
Soybeans, 1 cup	31
Tofu, firm, 1 cup	23
Lentils, cooked, 1 cup	18
Tempeh, 1/2 cup	17
Seitan (wheat gluten), 3 oz.	15–24
Dried beans, cooked, 1 cup	13–20
Milk, 8 oz.	8
Peanut butter, 2 T	7
Veggie dog, 1	7–16
Yogurt, 8 oz.	7–24
Soymilk, 8 oz.	7
Cheese, 1 oz.	7
Veggie burger, 1	6–20
Egg, 1 large	6
Soy yogurt, 6 oz.	6
Grains, cooked, 1 cup	4–8
Nuts, 2 T	2–4

Adapted from USDA Nutrient Database for Standard Reference, Release 28, 2015; and manufacturers' information

Protein

Protein is rarely below recommendations in the diets of vegetarian women [2, 17, 18]. If, as women increase their energy intake in pregnancy, their protein intake also increases, then they will achieve the higher protein intake recommended for pregnancy. One study found a mean protein intake by pregnant lacto-ovo vegetarians of 78 g/day [5], which is close to the current RDA of 71 g/day in the second and third trimesters [37]. Choosing foods that are good sources of protein (Table 1) along with adequate energy can ensure that protein needs during pregnancy are met. The Institute of Medicine has concluded that the protein requirement for vegetarians consuming a variety of plant proteins is not different from that of non-vegetarians [37]. Conscious combining of proteins within a meal is not necessary when a variety of plant foods is eaten over the day [1].

Iron

Iron in vegetarian diets is in the form of non-heme iron. Non-heme iron is much more sensitive than heme iron is to factors affecting absorption. Absorption of non-heme iron is increased markedly in iron-deficient individuals [38]. Non-heme iron

absorption is also affected by factors in foods. Phytate, a phosphorus-containing compound found in whole grains, legumes, nuts, and vegetables, inhibits non-heme iron absorption, as do coffee, calcium, and tannic acids in tea and some spices [2]. Vitamin C and other organic acids enhance non-heme iron absorption, and can partially counteract the inhibitory effects of phytate. Because bioavailability of iron from plant-based diets is lower than that from animal-based diets, the Institute of Medicine states that the requirement for iron is 1.8 times higher for vegetarians [36]. For pregnant vegetarians, this would result in a recommended dietary allowance (RDA) for iron of 48.6 mg/day, a level that is difficult to achieve without the use of iron supplements. (See Chapter 2: Iron Requirements and Adverse Pregnancy Outcomes by Kimberly O. O'Brien and Carrie E. Thomas for further discussion on meeting iron needs.)

Pregnant vegetarians are more likely to use iron supplements than are non-vegetarians, and may have higher iron intakes [39]. Possibly because of their awareness of the importance of iron, vegetarian women in Western countries are no more likely to have iron deficiency anemia than non-vegetarian women [40]. Vegetarians, however, are more likely to have lower iron stores, as indicated by serum ferritin [40]. Dietary iron intakes of vegetarian women of childbearing age vary, with mean iron intakes of 11–15 mg/day reported for lacto-ovo vegetarians and 14–23 mg/day for vegans [2]. Mean dietary iron intakes of 13.8 mg/day and 17 mg/day have been reported in pregnant lacto-ovo vegetarians; supplemental iron increased total mean iron intake to 57 mg/day and 37 mg/day, respectively [5, 32].

Iron sources for vegetarians include dried beans, whole and enriched grains, soy foods, enriched meat analogs, pumpkin and squash seeds, dried fruits, and baked potatoes.

Iron supplementation, if indicated based on iron status, should be started early in pregnancy so that maternal iron status is adequate throughout both pregnancy and the postpartum period [41, 42]. The Centers for Disease Control and Prevention (CDC) recommends a low-dose (30 mg) iron supplement beginning early in pregnancy [43].

Zinc

Both vegetarian and non-vegetarian pregnant women are likely to have zinc intakes that are lower than the recommended amounts [44]. Vegetarian women's intakes are commonly lower than those of non-vegetarians, but serum/plasma zinc concentrations are similar [44]. Factors in vegetarian diets, including phytate and calcium, can interfere with zinc absorption [45]. The Institute of Medicine has not specified a zinc RDA for vegetarians, but suggests that the dietary requirement for zinc may be as much as 50% higher, especially for those relying mainly on high-phytate grains and legumes [36]. Thus, zinc recommendations for adult pregnant vegetarians may be as high as 16.5 mg/day. Zinc sources include dried beans, wheat germ, fortified cereals, and nuts and seeds. Food preparation techniques such as leavening bread and soaking and sprouting beans can increase zinc bioavailability [46]. A zinc

supplement or a prenatal supplement containing zinc may be necessary, especially if a woman's diet is high in phytate [47].

Iodine

Vegetarians who do not use iodized salt may be at increased risk of developing iodine deficiency because, in general, plant-based diets are relatively low in iodine [48]. This is of special concern in pregnancy because of the effects of iodine deficiency on the developing brain [49].

The American Thyroid Association recommends that pregnant and breastfeeding women take a prenatal supplement that contains at least 150 micrograms of iodine daily [50]. Some, but not all, prenatal supplements contain iodine [51]. Use of iodized salt in cooking and at the table will help to meet the iodine RDA for pregnancy of 220 mcg/day. Sea vegetables like nori and hiziki can provide iodine, but their iodine content is quite variable [52]. Excessive maternal iodine (2300–3200 mcg/day) from sea vegetables has been linked to hypothyroidism in newborn infants in Japan [53] and to postpartum thyroiditis in China [54].

Calcium and Vitamin D

Although calcium absorption increases in pregnancy [55], low calcium intakes can be problematic. Pregnant women with a habitually low calcium intake (<500 mg/day) experience calcium losses from bone that may adversely affect maternal bone status [56]. Effects of low maternal calcium intakes on bone health of offspring are inconsistent [55]. Many lacto-ovo vegetarian women have intakes of calcium that meet current recommendations [17, 18]. Vegan women tend to have lower calcium intakes [18, 57] and may benefit from information about non-dairy calcium sources.

Non-dairy sources of calcium include low-oxalate green vegetables (bok choy, collards, Chinese cabbage, kale, broccoli, turnip greens, and okra), almonds, figs, soybeans, calcium-set tofu, and fortified foods (plant milks, fruit juice, and breakfast cereals) [1, 58].

Table 2 categorizes vegetarian calcium sources by their calcium content to assist in menu planning. For example, a pregnant vegan might choose 16 oz. of calcium-fortified soymilk, 1 cup of collards, and 1 cup of black beans to meet the RDA of 1000 mg/day of calcium.

Sources of vitamin D for vegetarians include fortified foods (milk, soy and other plant milks, breakfast cereals, margarine), egg yolks, and vitamin D supplements [1]. In addition, vitamin D requirements can be met by sun exposure. Factors such as season, skin pigmentation, location, and sunscreen use can affect cutaneous vitamin D synthesis, so dietary and supplemental vitamin D are often used to meet needs.

Table 2 Calcium sources for vegetarians

Foods, serving size	Approximate calcium content (mg)
Collards, cooked, 1 cup	300
Milk, 8 oz.	
Orange juice, fortified, 8 oz.	
Soy milk, fortified, 8 oz.	
Yogurt, 8 oz.	
Blackstrap molasses, 1 T	200
Energy bar, calcium-fortified, 1 bar	
Kale, cooked, 1 cup	
Soybeans, cooked, 1 cup	
Soy yogurt, calcium-fortified, 6 oz.	
Tofu, calcium-set, 1/4 cup	
Turnip greens, cooked, 1 cup	
Bok choy, cooked, 1 cup	150
Cheese, 3/4 oz.	
Mustard greens, cooked, 1 cup	
Okra, cooked, 1 cup	
Almonds, 1/4 cup	100
Almond butter, 2 T	
Broccoli, cooked, 1 large stalk	
Dried beans, cooked, 1 cup	
Figs, dried, 7	
Tahini, 2 T	
Tempeh, 1/2 cup	

Adapted from USDA Nutrient Database for Standard Reference, Release 28, 2015; and manufacturers' information

Vitamin B₁₂

A regular source of vitamin B₁₂ is essential in pregnancy since maternal dietary intake of vitamin B₁₂ has a stronger influence on infant status than maternal stores [59, 60]. Low maternal vitamin B₁₂ concentrations in pregnancy have been associated with an increased risk of intrauterine growth restriction (IUGR), impaired infant neurodevelopment, and obesity and insulin resistance later in life [61–63]. Infants may be born with low vitamin B₁₂ stores if maternal status during pregnancy is marginal [64]. Dairy products, fortified foods, and supplements containing vitamin B₁₂ are reliable sources of vitamin B₁₂ for vegetarians.

Fortified foods include some brands of plant milks, breakfast cereals, nutritional yeast, energy bars, tofu, and meat analogs (Table 3). The low amounts of vitamin B₁₂ added to fortified foods helps with absorption; 60% of low dose (less than 5 mcg) of vitamin B₁₂ is absorbed [65]. Foods such as sea vegetables, tempeh, and miso cannot be counted on as reliable sources of vitamin B₁₂ [1]. About 5% of the

Table 3 Vitamin B₁₂ content in vegetarian foods

Food, serving size	Vitamin B ₁₂ (mcg)
Cereals, fortified, 1 oz.	0.6–6
Cow's milk, 8 oz.	1.1
Egg, large, 1	0.4
Meat analogs, fortified, 1 oz.	0.5–1.2
Soymilk, fortified, 8 oz.	0.8–3.2
Almond milk, fortified, 8 oz.	3.0
Energy bar, fortified, 1 bar	0.6–2.0
Tofu, fortified, 3 oz.	1.2
Vegetarian support formula nutritional yeast, 1 T	4.0

Adapted from USDA Nutrient Database for Standard Reference, Release 28, 2015; and manufacturers' information

vitamin B₁₂ in a supplement containing 25 mcg of vitamin B₁₂ is absorbed [66–68]. A lesser amount, 1% or less, of the vitamin B₁₂ in a supplement containing more than 100 mcg of vitamin B₁₂ is absorbed [65, 67].

Omega-3 Fatty Acids

Unsupplemented vegetarian diets contain little, and vegan diets contain virtually no, docosahexaenoic acid (DHA) or its direct precursor, eicosapentaenoic acid (EPA); these omega-3 fatty acids are mainly found in oily fish. Humans can synthesize DHA from the essential fatty acid alpha-linolenic acid (ALA) but the rate of conversion is low [69]. Additionally, high intakes of ALA may inhibit conversion of ALA to DHA [70]. ALA supplements in pregnancy did not improve either maternal or infant DHA concentrations [71]. Although further study has been recommended, it is likely that ALA cannot substitute for DHA [72]. Some evidence suggests that infants of vegetarian women have lower cord DHA concentrations than infants of non-vegetarian women [73].

DHA-rich microalgae provides a direct, non-animal-derived source of DHA [74, 75]. Microalgae-derived DHA, when used by pregnant women, has effectively increased maternal and cord DHA concentrations [76]. Some commercial supplements contain microalgae-derived DHA either in liquid or vegan gelatin capsules. Eggs from hens fed DHA-rich microalgae are another potential source of DHA and have been effectively used to increase the DHA intake of pregnant women [77, 78]. Other foods that have been fortified with microalgae-derived DHA include milk, soymilk, energy bars, yogurt, and veggie burgers. Both microalgae-derived supplements and fortified foods appear effective in enhancing DHA status [79]. Due to the beneficial effects of DHA in pregnancy, intakes of 200 mg per day are recommended [80].

Practical Considerations

Family Concerns

Pregnant vegetarians may face pressure from non-vegetarian family members who are concerned about the adequacy of the vegetarian diet during pregnancy. Dietetics professionals can provide support for the vegetarian client by providing accurate current information about vegetarian nutrition [1]. An unbiased evaluation of the pregnant woman's diet and nutritional status, with recommendations for dietary modifications if necessary, may reassure family members, support the client's dietary choices, and improve nutritional status.

Becoming Vegetarian During Pregnancy

Some women may decide to adopt a vegetarian diet during pregnancy. Dietetics professionals can assist the new vegetarian by assessing nutritional status, providing specific guidelines for planning meals during pregnancy, and providing information about meeting needs for key nutrients.

Foods that Are Frequently Included in Vegetarian Diets

Vegetarians typically eat a variety of fruits, vegetables, breads, cereals, beans, and possibly dairy products and eggs. A number of products, while not unique to vegetarians, may be less familiar to practitioners. The list below provides information about some foods that are commonly used by vegetarians:

Deli slices: Meat analogs made to resemble meats commonly used in sandwiches, such as bologna, salami, and ham.

Egg replacer: A commercial powder containing potato starch and tapioca flour used to replace eggs in baked products.

Hummus: A dip or sandwich spread made from pureed chickpeas, tahini, and spices.

Meat analogs: A general term for imitation meats, usually made from soy but sometimes made from wheat gluten, grains, beans, and/or nuts.

Nori: A sea vegetable available in flat sheets and often used in making sushi.

Nutritional yeast: A yeast that is grown on a nutrient-rich medium; good source of vitamins and minerals (specific nutrients and amounts vary by brand).

Rice milk: A rice-based beverage that can be used in place of cow's milk or soy milk, but is lower in protein. Often available in fortified form.

Seitan: A meat substitute made from wheat gluten.

Soy milk: A beverage made from soybeans that can be used in place of cow's milk. Often available in fortified form and a variety of flavors.

Tahini: A spread, similar in consistency to peanut butter, made from ground sesame seeds.

Tempeh: A product made from fermented soybeans and sometimes grains, pressed into a solid cake.

Textured soy protein (TSP) or textured vegetable protein (TVP): A product made from soy flour, available in granules or chunks, and used in place of ground beef or other meat in dishes such as chili, stews, soups, etc.

Tofu: A mild-tasting product made from coagulated soy milk. Tofu prepared using calcium sulfate as a coagulating agent is higher in calcium than tofu coagulated with nigari (magnesium chloride). Tofu can be purchased in a variety of textures (soft, silken, firm, extra firm).

Tofu hot dogs: Meat analogs that resemble hot dogs and are made of soy.

Veggie burgers: Vegetarian burgers made from a variety of products including tofu, TSP, soybeans, other beans, grains, wheat gluten, and nuts. Commercially available frozen, refrigerated, and as a powdered mix.

Use of Soy Products in Pregnancy

Soy products, including soymilk, tofu, textured vegetable protein, and meat analogs, are often used by vegetarians to replace animal products, for convenience, and to add dietary variety. Isoflavones, phytoestrogens found in soy, appear to be transferred to the fetus [81]. Fetal exposure to isoflavones does not appear to cause adverse developmental or reproductive effects [82, 83].

Nausea

Vegetarian women, like non-vegetarian women, may experience nausea and food aversions, especially in early pregnancy. Suggestions for coping with nausea and food aversions can be modified to meet the needs of vegetarians. Bland, starchy foods like rice, pasta, cereal, potatoes, and crackers are frequently better tolerated than sweet or fatty foods. For many women, the salads and raw vegetables that are dietary mainstays may not be appealing in early pregnancy. Vegetables incorporated in soups or mixed with mashed potatoes or rice may be better tolerated. Vegetable juice is another option.

Meal Plans

A number of food guides have been developed for pregnant vegetarians [2, 84, 85]. These can serve as a general guide, but will need modification depending on individual energy needs, preexisting conditions, and food preferences. Figure 1 shows a sample menu for pregnancy that features three meals and three snacks, a pattern that can be useful for women who prefer frequent small meals.

BREAKFAST

2 slices whole-wheat toast
 1 cup fortified soymilk
 1 cup oatmeal
 ½ cup blueberries

LUNCH

Black bean and sweet potato burrito:
 Wholewheat tortilla with ¾ cup black
 beans, ½ cup steamed, cubed sweet
 potato, 2 T. salsa
 Medium apple
 1 cup steamed collards

DINNER

¾ cup firm tofu stir-fried with ½ cup
 broccoli, ½ cup carrots, and soy sauce
 1 cup brown rice
 Medium orange

SNACK

½ whole-wheat bagel with 1 T. almond
 butter

SNACK

½ cup granola
 1 cup fortified soymilk
 Medium banana

SNACK

2 cups popcorn
 ½ cup grapes

Nutritional analysis of sample menu

2,385 calories
 90 g protein (15% of calories)
 72 g fat (27% of calories)
 367 g carbohydrate (62% of calories)
 1,576 mg calcium
 22 mg iron
 15 mg zinc
 2.4 mg thiamin
 2.4 mg riboflavin
 21 mg niacin
 4 mcg vitamin B12
 5 mcg vitamin D
 648 mcg folate

RDA

71 g
 1,000 mg
 49 mg (supplemental iron may be needed to
 meet the iron RDA for vegetarians)
 11 mg
 1.4 mg
 1.4 mg
 18 mg
 2.6 mcg
 15 mcg (supplement/sun exposure indicated)
 600 mcg

Fig. 1 Sample menu plan for pregnant vegans

Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) provides vouchers for food to low-income pregnant, postpartum, and breast-feeding women and their infants and children up to age 5 years. The WIC program provides vouchers for foods acceptable to vegetarians including milk, breakfast cereals, fruits and vegetables, whole-wheat bread, juice, cheese, dried beans, and peanut butter. Substitution of soy-based beverages, tofu, and yogurt for dairy milk

is allowed. In 2015, all states and the majority of territories allowed a soy-based beverage as a substitute for milk, while 61% of states allowed tofu to be substituted for milk [86]. About half of the states allowed shelf-stable varieties of soy-based beverages; 84% allowed refrigerated varieties [86]. Most states require the purchase of specific brands of soy-based beverages as a cost-containment measure. Other plant-based milks are not authorized.

States can allow brown rice, bulgur, barley, oatmeal, whole-wheat pasta, or corn or whole-wheat tortillas to replace whole-wheat bread, allowing more culturally diverse foods. Brown rice and tortillas are allowed by most states. Oatmeal, bulgur, whole-wheat pasta, and barley are less commonly authorized [86].

Supplements

Pregnant vegetarians who consume an adequate diet do not routinely require a daily multivitamin-mineral supplement, although supplements of individual nutrients such as iron or vitamin B₁₂ may be indicated. The Institute of Medicine recommends that all women capable of becoming pregnant consume 400 mcg of folate daily from supplements, fortified food, or a combination of fortified food and supplements. Multivitamin-mineral supplements specifically identified as “vegetarian” or “suitable for vegetarians” are available for women whose diets may not be adequate or who have increased needs.

Vegetarian Multivitamin-Mineral Supplements

Multivitamin-mineral supplements marketed to vegetarians differ widely in nutrient content. Some contain herbs, amino acids, bioflavonoids, fiber, DHA, and other substances. Some provide large amounts of vitamins, especially thiamin, riboflavin, niacin, vitamin B₆, and vitamin B₁₂ that are much higher than Dietary Reference Intakes.

Other prenatal supplements contain no iodine or are low in calcium, two nutrients that may be low in diets of some vegetarians. If dietary calcium is low and a woman’s prenatal supplement is also low in calcium, then a calcium supplement is indicated. Calcium supplements can interfere with iron and zinc absorption, so are best used between meals.

Table 4 compares several brands of vegetarian prenatal supplements. Individual assessment is needed when determining whether or not a supplement is needed and the amount and type of supplementation. Since supplement content and availability may vary, clients should be encouraged to bring in their supplement label and practitioners should be aware of commonly used products.

Table 4 Levels of selected nutrients in several brands of vegetarian prenatal supplements

Supplement ^a	Serving size	Vitamin D (mcg)	Folate (mcg)	Vitamin B ₆ (mg)	Vitamin B ₁₂ (mcg)	Calcium (mg)	Iron (mg)	Iodine (mcg)	Zinc (mg)	Other nutrients at levels >100% of pregnancy DRI	Comments
Country Life Baby Care PreNatal (a) ^b	6 caps	5	1000	100	40	800	18	225	15	C, E, Thia, Ribo Nia	Also contains 13 mg DHA, ginger, bioflavonoids, and other substances
Deva Vegan Prenatal (b) ^c	1 tab	10	550	12.5	100	100	21	150	15	C, E, Thia, Ribo, Nia, Se, Cu	Also contains choline, bioflavonoids, lutein, and other substances
Emerald Laboratories Prenatal (c) ^b	4 caps	37.5	800	50	200	200	25	75	15	C, E, Thia, Ribo, Se	Also contains raw whole food blend, lutein, ginger, and other substances
Freedra One Daily Prenatal (d) ^b	1 tab	20 (D ₂)	800	3	10	200	27	-	15	C, Thia, Ribo, Nia, Cu	Also contains choline and other substances
FreedraKPN Prenatal with Extra Calcium (d) ^b	3 tabs	10 (D ₂)	800	3	6	1000	27	-	22.5	C, E, Thia, Ribo, Nia,	Also contains bioflavonoids and other substances
MegaFood Baby & Me Daily- Foods (e) ^b	4tabs	15	800	4	20	75	18	150	15	E, Thia, Ribo, Nia,	Also contains bioflavonoids, ginger, anthocyanins, and other substances
My Kind Organics Prenatal (f) ^c	3 tabs	25 (vegan D ₃)	800	10	30	5	18	150	5	E, Thia, Ribo, Nia, Se	Also contains organic food blend, ginger, and other substances
Perfect Prenatal (g) ^b	3 tabs	25	600	5	30	75	18	90	7.5	E, Thia, Ribo, Nia	Also contains herbal extracts, sprouted seeds, and other substances

Rainbow Light Prenatal One (h) ^f	1 tab	10 (D ₂)	800	15	25	200	30	150	15	C, E, Thia, Ribo, Nia, Se, Cu	Also contains bioflavonoids, inositol, digestive support formula, and other substances
Realfood Organics Prenatal (a) ^b	3 tabs	11	800	2.5	8	27	18	150	-	E, Thia, Ribo, Nia	Also contains organic food blend and other substances
Solaray Prenatal ^b	1 cap	25	800	5	16	10	30	150	15	A, C, E, Thia, Ribo Nia, Se, Cu	Also contains 2.5 mg DHA, choline, ginger, and other substances
Solgar Prenatal Nutrients (i) ^b	4 tabs	10	800	2.5	8	1300	27	150	15	C, Thia, Ribo, Nia, Mg, Cu	Also contains choline, soy protein, and other substances
SuperNutrition PreNatal Triple Powder (j) ^b	1 tab	75	1000	35	150	200	30	150	32	C, E, Thia, Ribo, Nia, Se, Cu, Mo	Also contains papaya and green food blend and other substances
VitaTrue Prenatal Multivitamin (k) ^c	1 tab	15 (D ₂)	1400	25	12	150	30	150	15	E, Thia, Ribo Nia, Cu	Also contains 300 mg DHA from algal oil
RDA, pregnancy, 19–50 years		15	600	1.9	2.6	1000	27	220	11		

Thia thiamin, *Ribo* riboflavin, *Nia* niacin, *Mg* magnesium, *Se* selenium, *Cu* copper

Product formulations frequently change so it is important to update the information in this table regularly

^aSources of product information: (a) www.country-lifevitamins.com; (b) www.devanutrition.com; (c) www.ultralaboratories.com; (d) www.freeedavitamins.com; (e) www.megafood.com; (f) gardenoflife.com; (g) www.newchapter.com; (h) www.rainbowlight.com; (i) www.solgar.com; (j) www.supernutritionusa.com (k) www.vitaminedmrx.com

^bSupplements were identified on the product label or website as being vegetarian

^cSupplements were identified on the product label or website as being vegan

Conclusion

Appropriately planned vegetarians diets can be healthful and nutritionally adequate, and are appropriate for use in pregnancy. Key nutrients for pregnant vegetarians include protein, iron, zinc, vitamin B₁₂, omega-3 fatty acids, and calcium and vitamin D (for vegans). Practitioners should be aware of good sources of these nutrients and be able to assess the need for supplements. Practitioners should also be able to provide current, accurate information about vegetarian nutrition and foods (see Tables 1, 2, and 3).

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Sleep, Pregnancy, and Nutrition

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Keywords Sleep and nutrition · Sleep and pregnancy
Obstructive sleep apnea and pregnancy · Restless legs syndrome and pregnancy
Willis-Ekbom disease and pregnancy

Key Points

- Sleep both influences and is influenced by nutritional choices.
- Short sleep duration and poor sleep quality during pregnancy have been shown to negatively impact birthweights, neonatal Apgar scores, and cesarean section rates.
- Rates of obstructive sleep apnea (OSA) are higher during pregnancy and may be related to reductions in pharyngeal dimensions and nasal patency associated with pregnancy.
- OSA during pregnancy is associated with increased rates of fetoplacental hypoxia, preeclampsia, preterm birth, cesarean delivery, and neonatal intensive care unit admissions.
- Restless legs syndrome (RLS) is the most common sleep-related movement disorder associated with pregnancy and has been found to be associated with adverse pregnancy outcomes such as lower birth weights, preterm birth, pregnancy-induced hypertension, and preeclampsia.

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Introduction

The quality of sleep and the presence of sleep disorders vary greatly throughout the lifetime of women. Never is that variation greater than during pregnancy, when physiologic and hormonal changes occur in a relatively short timeframe. The role of sleep, the emergence of sleep disorders, and the potential impact of these factors on pregnancy outcomes have been widely studied over the past decade. However, research on the nutritional influences on sleep has been less studied, and there is a paucity of research that involves all three areas (sleep, pregnancy, and nutrition). It remains an area that is ripe for new investigative studies. This chapter will discuss what is known about the interaction between sleep and nutrition. Additionally, it will provide an overview of two of the most common sleep disorders that occur during pregnancy (i.e., obstructive sleep apnea and restless legs syndrome) and the role that nutritional intake may directly and indirectly play in their occurrence.

Nutrition and Sleep

Insufficient sleep, also known as sleep restriction, is a common occurrence [1] and is known to negatively impact hormonal and metabolic function [2, 3]. A systematic review of the literature on sleep restriction and weight [4] suggests that short sleep duration is an independent risk factor for weight gain and obesity. One mechanistic explanation is that weight gain may be due to greater daily caloric intake by those individuals who have insufficient sleep [5]. Sleep restriction appears to be associated with an imbalance of both leptin and ghrelin, the hormones that influence appetite regulation [6, 7]. Individuals who are sleep deprived tend to have higher daily total energy intake and higher total fat intake than their well-slept counterparts [8]. Short sleep duration and poor sleep quality during pregnancy have been shown to negatively impact birthweights, neonatal Apgar scores, and cesarean section rates [9, 10].

While the effects of sleep on dietary choices and energy expenditure appear well documented, less is known about how nutritional choices affect sleep. A small randomized crossover study looked at dietary impacts on sleep in both men and women [11]. It showed that ad libitum food intake was associated with a decrease in slow-wave sleep (SWS), which is thought to be deeper, more restorative sleep, and an increase in the time that it takes to fall asleep (also known as the sleep-onset latency (SOL)). Diets that were higher in saturated fat and lower in fiber were associated with lighter, less restorative stages of sleep. Additionally, more arousals during sleep were noted when the diet contained more refined foods, such as simple sugars and non-sugar/low fiber carbohydrates [11]. These increased arousals represent brief brain awakenings that can be fragmenting to sleep.

Obstructive Sleep Apnea and Pregnancy

Obstructive Sleep Apnea (OSA) is a common disorder in which the airway repeatedly closes during sleep. When this occurs, an individual may have pauses in breathing or reduced airflow such that oxygen saturations drop and the brain wakes up repeatedly in order for the individual to start breathing again [12]. While the prevalence of OSA in adults in a large population cohort study was estimated to be 9% in women and 24% in men [13], the prevalence of OSA in pregnancy is not fully known. This may be due, in part, to the fact that typical screening questionnaires for OSA that are used for the general population have been shown to be unreliable in pregnancy [14]. When all sleep-disordered breathing from habitual snoring due to OSA in pregnancy is considered, the reported incidence estimates are 25–41% [15–17]. Reductions in pharyngeal dimensions [18, 19] and nasal patency [20] that occur during pregnancy likely contribute to higher OSA rates. OSA during pregnancy is associated with increased rates of preeclampsia, preterm birth, cesarean delivery, and neonatal intensive care unit admissions [21]. OSA during pregnancy has been associated with fetoplacental hypoxia [22] and may also negatively impact neonatal neurologic status [15]. Continuous positive airway pressure (CPAP) uses pressurized air to stent open the airway and is the gold-standard treatment for moderate to severe OSA. It has been successfully used in the treatment of preeclampsia associated with sleep-disordered breathing such as OSA [23–25].

Restless Legs Syndrome and Pregnancy

Restless legs syndrome (RLS), also known as Willis-Ekbom Disease, is a neurosensory disorder that is characterized by an urge (usually accompanied by an unpleasant sensation) to move the legs that is worse with rest and improved, at least partially, with movement. It has a circadian pattern of occurrence, with symptoms occurring in the evening or night [26]. RLS is the most common sleep-related movement disorder associated with pregnancy [27] and is three times more prevalent in pregnant than non-pregnant women [28]. One in five pregnant women in Western countries will experience RLS [29], and it occurs more commonly in the second and third trimesters, with peak occurrence in the third trimester [27].

The occurrence of RLS during pregnancy has been found to be associated with adverse pregnancy outcomes such as lower birth weights, preterm birth, pregnancy-induced hypertension, and preeclampsia. This may be related to the increased sympathetic tone seen in RLS [30–32]. There is a report that women who had preexisting moderate to severe RLS had higher rates of depression during and after pregnancy [33].

Low serum iron and altered brain iron metabolism have been implicated in the development and exacerbation of RLS [34, 35]. Low iron levels may decrease the

availability of dopamine, as iron is a coenzyme for tyrosine hydroxylase, which is the rate-limiting step in the conversion of levodopa to dopamine [35, 36]. It has been suggested that, in addition to low iron and folate levels, the relatively higher levels of estradiol, progesterone, and prolactin during pregnancy could play a role in the development of RLS [37]. There is also some evidence to suggest that Vitamin D deficiency may increase RLS [38, 39]. Additionally, many antihistamine and dopamine antagonist medications used to treat nausea during pregnancy (e.g., doxylamine, metoclopramide, promethazine, prochlorperazine) can worsen RLS symptoms [40].

Treatment of RLS during pregnancy focuses on non-pharmacologic therapies such as reassurance, leg stretches and massage, adequate sleep, use of compression stockings, moderate exercise, avoidance or reduction of caffeine consumption, and use of sequential pneumatic compression devices [29, 37, 41]. If iron stores are found to be suboptimal, as measured by a ferritin level of <75 mcg/L, oral iron replacement is warranted. Intravenous iron replacement can be used for those women in whom oral iron replacement is not tolerated or is not effective [29, 37]. Pharmacologic therapies are reserved for patients with severe symptoms who have failed treatment with conservative measures and optimization of serum iron stores. The preferred medications for RLS treatment during pregnancy are clonazepam and carbidopa-levodopa, with the goal of using the lowest effective dose for the shortest possible duration. Low-dose oxycodone can be used after the first trimester for the most severe, refractory cases [29].

Most RLS symptoms resolve in the post-partum period [27, 28, 42]. Unfortunately, the recurrence rate in future pregnancies is 30%, and women who experience RLS during pregnancy are more likely to develop primary RLS later in life [28, 43]. For those women who were diagnosed in the second trimester and those women with a higher number of pregnancies, there is an increased likelihood of residual RLS after delivery [27].

Sleep and Pregnancy

According to the 2007 National Sleep Foundation's Sleep in American Poll (which focused on women and sleep), pregnant women are less likely than women in general to get a good night's sleep [44]. Pregnant women also reported more daytime sleepiness and more frequent napping than did women in general [44]. They reported that "having to go to the bathroom" was the most common factor that disturbed sleep [44].

Given the known, increased difficulties with sleep during pregnancy, pregnant women should do the following to improve sleep:

- Prioritize sleep and get 7–9 h per day [45]. If needed, scheduled naps in the early afternoon can be used to increase the total sleep time, as long as they do not interfere with sleep onset at night.

- While staying hydrated during the day, reduce fluid intake in the hours before bedtime to decrease the frequency of urination during the night.
- Maintain a healthy diet that is high in fiber and limits saturated fats and refined foods [11].
- Have an evaluation for OSA if pauses during breathing accompanies snoring during pregnancy.
- Be screened for iron or folate deficiency if RLS develops during pregnancy. Non-pharmacologic RLS treatments (noted previously) may be of benefit.

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Safe Food Handling for Successful Pregnancy Outcomes

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Keywords High risk foods · Listeriosis · Salmonellosis · Safe food handling
Food-borne illness · Food safety during pregnancy

Key Points

- Hormonal changes during pregnancy compromises the immune system of pregnant women making them prone to food-borne illnesses
- Listeriosis and toxoplasmosis are the two major food-borne hazards due to unsafe food handling practices that affect pregnant women
- Cross-contamination during handling of food is found to be one of the major causes of foodborne illness
- Cross-contact needs to be minimized for preventing food safety risk associated with allergens
- The basic principles of safe food handling at the preparation area include “Clean,” “Separate,” “Cook,” and “Chill” that minimize the risk of illness
- Proper care should be given while handling foods at grocery stores to prevent the contact of high risk foods with the fresh produce
- Women are more receptive to food safety education during pregnancy, thus health care professionals need to consider disseminating the knowledge as much as possible for successful pregnancy outcomes

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Introduction

Food-borne illness or food poisoning is a sickness that occurs when harmful microorganisms (bacteria, parasites, viruses) or chemical contaminants from foods or drinking water are ingested [1]. The US Centers for Disease Control and Prevention (CDC) estimates that each year, roughly 1 in 6 Americans (or 48 million people) get sick, 128,000 are hospitalized, and 3000 die of foodborne diseases [2]. Certain groups, such as pregnant women and their fetuses, young children, older adults, people with weakened immune systems, and individuals with certain chronic illnesses, are at higher risk of food-borne illness than others [3, 4]. This group of vulnerable individuals makes up approximately 20% of the American population [4].

Pregnant women are at higher risk of food-borne illness because of hormonal changes that compromise their immune system. During pregnancy, pathogenic microorganisms can cross the placenta, infecting the fetus, whose immune system has not developed enough for self-protection. These infestations can cause miscarriage, premature delivery, hearing loss, intellectual disabilities, blindness, or serious sickness [5, 6]. Thus, safe food handling during pregnancy is critical for the health of the mother-to-be and her baby.

Safe Food Handling

Numerous hormonal changes, including an increased production of progesterone, occur during pregnancy to help prevent the death of the fetus by down-regulating immune function. Even though this change provides an ambient environment for the fetus to grow and develop, it also increases the risk of bacterial infection. Some of the intracellular pathogens that can bring serious diseases to both the mother and/or fetus are *Listeria monocytogenes*, *Toxoplasma gondii*, hepatitis E (HIV) virus, and *Coxiella burnetii*, with the first two accounting for most cases [7, 8]. Thus, to minimize the risk of food-borne disease, it is important for a pregnant woman to follow the common food safety practices: clean, separate, cook, and chill [9]. During pregnancy, foods that are not well processed, such as unpasteurized milk, cheeses, and raw eggs, as well as foods that are potential sources of organochlorides or heavy metals, such as some seafoods (e.g., Albacore tuna) may result in serious health consequences [10].

Principles of Safe Food Handling

Improper handling and preparation of foods in the kitchen is one of the major reasons behind several food-borne illnesses [3]. Lack of knowledge related to safe food handling, and storage practices such as maintaining proper refrigeration temperatures during storage, thawing, and reheating procedures, as well as cleaning and

sanitation practices, are prevalent among consumers [11]. Most of the food safety risks can also be minimized with proper hand washing techniques, usage of thermometers to verify adequate cooking temperatures, preventing cross-contamination from utensils, equipment, and surfaces, and avoiding preparation of certain foods (e.g., sprouts) with a history of high food safety risk [12].

According to the guidelines given by the US Department of Health and Human Services, the following are basic principles of safe food handling for pregnant women [5].

Clean

Maintaining a clean environment in the kitchen including, but not limited to, clean cutting boards, counter tops, and utensils is essential to minimize microbial cross-contamination. After using the bathroom, changing diapers, or handling pets, as well as prior to eating food, hands should be thoroughly washed with soap and warm water. Hands should be lathered with soap at least for 20 s before rinsing with warm water [13]. Warm water is effective in removing grease and grime by increasing the soap's ability to penetrate dirt and oils found on the skin [14]. All utensils used for food preparation such as cutting boards, dishes, knives, and counter tops must be cleaned with hot soapy water [15]. Paper towels are recommended for cleaning kitchen surfaces, but if cloth towels are used, they should be washed thoroughly in hot water. Fruits and vegetables should be washed under running tap water to remove dirt and contaminants. For fresh produce with hard and netted outer surfaces like cantaloupes and melons, scrubbing with a clean produce brush during washing is recommended. The surface of canned goods may also be a source of contamination. Microorganisms on the surface may contaminate the content after opening the can. Cleaning the lid of a canned food prior to opening may help in minimizing the risk of contamination [5].

Separate

Cross-contamination can occur specifically when handling raw meat, poultry, and seafood with other foods. A study carried out by Redmond et al. highlighted the route of microbial cross-contamination in a mock-up domestic kitchen. In their study, 29% of the food preparation sessions resulted in being positive for *Campylobacter* in prepared salads, cleaning materials, and food-contact surfaces [16]. The *Campylobacter* strains isolated from prepared chicken salad were identical to the strains isolated from raw chicken pieces, indicating cross-contamination during food preparation and handling [16]. In a study to rank and identify food-handling and consumption behaviors associated with 13 major food-borne pathogens, cross-contamination during food preparation was the major cause of food-borne illness associated with *Campylobacter jejuni*, *Salmonella* serotypes other than Enteritidis, and *Yersinia enterocolitica* [15]. To prevent cross-contamination, raw meat, seafood, and poultry should be separated from

ready-to-eat foods. The best practice is to keep these foods inside plastic bags during grocery shopping and in sealed containers/sealable plastic bags when storing in the refrigerator at home. The cutting boards and knives that were used for cutting raw meat, poultry, and seafood and those used for fruits and vegetables should be separate. Food preparation counter tops and cutting utensils should be washed properly with hot water and detergent after preparing meat, poultry, and seafood [11]. Cross-contamination can also occur if cooked foods are served on plates that previously held raw meat, poultry, or seafood, potentially leading to food-borne illnesses associated with *Campylobacter jejuni*, *Salmonella* serotypes other than Enteritidis, and *Yersinia enterocolitica* [5, 15].

Women with food allergies must avoid foods that trigger their allergic reactions during pregnancy. Consumer awareness and safe handling practices (minimizing cross-contact) are the two most important strategies to prevent food safety risk associated with allergens [17]. Cooking doesn't guarantee reduction or elimination of allergens from food [18]. Allergens are not easily removed from any utensils, kitchen surfaces, or hand surfaces that were once in contact with allergenic food materials. While cooking several different foods for the family, allergen-free meals should be cooked first. In addition, safe handling practices such as separating allergenic and non-allergenic ingredients and/or products, washing kitchen utensils with soap/detergents, and using clean and closed containers at home help reduce the risk of allergen cross-contamination [17, 18].

Cook

Food must be cooked well enough to kill the potential food-borne pathogens that may be present. The use of a food thermometer is recommended to check if meat, poultry, eggs, or dishes containing eggs, and seafood have been cooked to their safe minimum internal temperatures. Eggs must be cooked until the yolk and white is firm. While cooking in a microwave oven, food should always be covered, stirred during cooking cycles, and should be rotated for even cooking. Sauces, soups, and gravy must be reheated to a boil while hot dogs, luncheon meat, and other deli meats must be reheated until the meat steams or is at 165 °F [5]. Thawing before cooking is important, especially for cooking frozen whole chickens or ground meats, because the interior part of these meats may not reach optimum temperature to kill the associated pathogens [19].

The USDA-FDA recommended safe minimum internal temperatures for meat, poultry, fish, and egg dishes are listed in Table 1 [5].

Table 1 Safe minimum internal temperatures for meat, poultry, fish and egg dishes

Food commodity	Required internal temperature
Beef, pork, veal, lamb, steaks, roasts and chops	145 °F with a 3-min rest time after removal from heat source
Fish	145 °F
Ground beef, pork, veal and lamb	160 °F
Egg dishes	160 °F
Whole, pieces and ground—Turkey, chicken, and duck	165 °F

Chill

Maintaining a constant refrigerator temperature of 40 °F or below will reduce the growth of microorganisms and minimize the risk of foodborne illness. The temperature of the refrigerator and freezer should be checked using an appliance thermometer. Meat, poultry, eggs, seafood, and other perishables must be refrigerated or frozen within 2 h of cooking or purchasing, and the time should be decreased to 1 h if the outside temperature is 90 °F [5]. Perishable foods that are left for more than 2 h at room temperature should be discarded and not consumed [14]. Whenever in doubt, the food should be discarded to avoid potential risk. Large amounts of foods or leftovers must be divided and stored in shallow containers to facilitate rapid cooling. The leftovers must be kept on clean trays and cooled as quickly as possible, should be covered and stored in a refrigerator at 40–45 °F for a maximum of 3 days, or should be frozen if not being consumed soon [20]. Food should not be thawed at room temperature, such as on the counter top, because that practice facilitates the growth of microorganisms. The best practice is to thaw inside a refrigerator, or in cold water, or in a microwave oven. The latter two processes of thawing requires immediate cooking [5]. In a consumer focus group study, Jevsnik et al. observed a lack of consumer knowledge about the existence of insulated cooling bags that could be used for transporting frozen or refrigerated foods. Half of the focus group reported defrosting meat on working surfaces; only one-third washed knives and cutting boards with hot water and detergent for reuse, and 44% didn't know the correct temperature for storing perishable foods [11].

Safe Food Handling at Grocery Store/During Transportation

Safe food-handling practices during shopping will reduce the risk of food-borne illness. Food labels provide important information; shoppers should carefully read the labels to make sure products are not past their “sell by” date. Cross-contamination from the high-risk foods such as raw packaged meat, poultry, or seafood can be minimized by double bagging raw ingredients inside a plastic bag before putting them in the shopping cart. Keep fresh fruits and vegetables separate from raw meat, poultry, fish, and seafood. Unpasteurized products such as juices, milk, cheese, and dairy products may contain harmful microorganisms and should not be consumed during pregnancy. Unshelled eggs must be bought from the refrigerated section of the store. When shopping for fresh produce, items that are bruised, damaged, moldy, or that show signs of insect damage, should be avoided. Canned goods should be free from any dents, cracks, or bulging lids, and the lid must be cleaned before opening. Perishable foods exposed to warm temperatures may provide a favorable environment for the growth of microorganisms. Pre-cut fruits and vegetables should be selected from the refrigerated section. High-risk and perishable foods should be added to the shopping cart just before the checkout, and must be refrigerated within 2 h of purchase. Using ice coolers to hold perishable foods during summer months maintains the quality and safety of the foods during transportation [5].

Importance of Personal Hygiene and Sanitation

Many food-borne illnesses are a result of unsanitary and unhygienic practices during food preparation and handling at home. Consumer food safety education provides awareness of mal-practices and increases understanding of food safety risk at the consumer level [21].

Personal hygiene translates to cleanliness of external body parts (skin, hands, hair, eyes, mouth, nose, nasopharynx, and excretory organs), which can be responsible for the contamination of food. These body parts act as direct or indirect carriers of harmful microorganisms. Hand hygiene is a must in the prevention of colds, flu viruses, and diarrhea, but despite widespread knowledge of the importance of handwashing, this practice remains a major challenge in controlling infection [22].

The microbial flora of hand surfaces may be transient or resident bacteria [23]. The transient microbes such as *Listeria monocytogenes*, *E. coli* O157:H7, *Salmonella*, etc. are often picked up by hand during direct contact with infected persons or from contaminated environmental surfaces, and colonize the superficial layers of the skin. Resident bacteria (e.g., *Staphylococcus epidermidis*), which are the normal microflora of skin surfaces, get on hands by touching the external parts of the body [23]. Food handlers should follow clean and hygienic handwashing practices such as washing hands with warm water and soap or detergent and a scrubbing or rubbing action for at least 20 s. Approximately 38% of food contamination results from inadequate washing of hands. Washing hands with warm water and soap or detergent kills most of the harmful microorganisms [13]. Alcohol-based hand sanitizers cannot substitute for hand washing, but may provide an additional 10- to 100-fold of microbial reduction if applied after hand washing [23].

Kitchen aids and shopping containers can harbor pathogens and contaminate food. Simple cleaning and washing may not be adequate to minimize the food-safety risk from food contact surfaces. Recent studies revealed the capability of microorganisms to colonize on processing areas like granite, marble, stainless steel, and stilt stones to form a biofilm, which may be highly resistant to regularly used cleaning reagents [24]. Thus, personal hygiene, proper cleaning, and sanitation are important to minimize the food safety risk at the consumer level.

Food Selection

In addition to the following basic safe food-handling principles, vulnerable groups like pregnant women should be careful while selecting foods and avoid high-risk foods. High-risk foods are foods that have the potential for contamination and support growth of *L. monocytogenes* or other harmful pathogens, ready-to-eat foods, unpasteurized foods, food that requires refrigeration, or foods that have an extended shelf life [25]. The food items that fall into the category of high-risk food, associated food-safety risks, and practices to minimize the risk are highlighted in Table 2.

Table 2 Common high-risk foods, their associated food safety risk, and best practices to minimize the risk

High-risk foods	Concerned food safety risk	Food safety practices	References
Raw sprouts	<i>E. coli</i> O157:H7 <i>Salmonella</i>	Thoroughly cooking	[26]
Unpasteurized juice	<i>E. coli</i> O157:H7 <i>Salmonella</i>	Make sure juice has been pasteurized or treated enough to kill harmful bacteria; if unpasteurized then bring it to boil for a minute before consumption	[5, 19]
Unpasteurized milk	<i>Listeria monocytogenes</i> , <i>Salmonella</i> , <i>E. coli</i> O157:H7, <i>Campylobacter</i>	Consume pasteurized milk	[5]
Dairy products from unpasteurized milk (like soft cheeses, yoghurt, pudding, ice cream or frozen yoghurt)	<i>Listeria monocytogenes</i> , <i>E. coli</i> O157:H7, <i>Salmonella</i>	Use pasteurized milk	[5]
Raw or undercooked 'runny' eggs	<i>Salmonella</i> , <i>Cryptosporidium</i>	Fully cooked eggs with firm yolk and white; avoid raw/undercooked eggs and products from them like homemade mayonnaise and salad dressings, custards, ice cream, raw cookie dough and egg batter	[5, 27]
Raw/undercooked meat/poultry	<i>Clostridium perfringens</i> , <i>Campylobacter</i> , <i>E. coli</i> O157:H7	Cook to a safe minimum internal temperature	[5]
Raw/undercooked fish/shellfish/sushi	<i>Campylobacter</i> , <i>Vibrio vulnificus</i> , Norovirus, <i>Salmonella</i>	Use/consume fully cooked fish (cook till 145 °F) or sea food; limit consumption of high mercury shellfish and fish (including tuna, yellowtail). Low mercury alternatives like salmon, crab, and shrimp can be consumed more regularly	[5, 27]

Food-Borne Hazards

Major food-borne hazards relevant during pregnancy are:

1. Listeriosis
2. Toxoplasmosis
3. Methylmercury

Apart from these, Salmonellosis, Campylobacteriosis, and contamination with *Cryptosporidium*, *Clostridium perfringens*, *Escherichia coli* O157:H7, *Norovirus*, and *Vibrio vulnificus* can also occur in pregnant women and cause food-borne illness [5]. Since listeriosis and toxoplasmosis are most likely to affect pregnant women due to unsafe food-handling practices, we will discuss these two in detail.

Listeriosis

Listeriosis is a type of food-borne hazard that occurs because of ingestion of food contaminated with *Listeria monocytogenes*. Approximately 1600 illness and 260 deaths due to listeriosis occur annually in the United States [28]. Listeriosis has been a major issue as a food-borne illness although it is uncommon but potentially fatal [29]. Its severity can lead to meningitis, septicemia, and abortion; additionally, it has an almost 20–30% fatality rate, has a long incubation period, and affects predominantly immune-suppressed people [25]. *L. monocytogenes* also is known as a hardy organism, which can survive in the most unfavorable conditions like refrigeration temperatures, food preservatives (i.e., high salt concentration), wide pH range, and conditions with little or no oxygen [6, 25]. According to CDC, pregnant women are ten times more likely to be infected by listeriosis than people in general, whereas others report that they are 20 times more likely to contract the illness [7, 30], and about one in seven, i.e. 14%, of the cases of *Listeria* infection happens during pregnancy [28].

A pregnant woman will experience mild flu-like symptoms, fever, chills, headache, backache, occasionally upset stomach, abdominal pain, and diarrhea. Listeriosis can lead to gastrointestinal problems, with symptoms appearing within a few hours to 2–3 days, and disease appearing 2–6 weeks after digestion. The illness can grow even more severe and can lead to death [5]. It may even lead to miscarriage, stillbirth, premature delivery, or serious infection of newborn, neonatal sepsis, chorioamnionitis, and meningitis [25, 30].

Incidents of Listeriosis were reported when hot dogs, luncheon meats, cold cuts, fermented or dry sausage, and other deli-style meat and poultry products were improperly reheated and consumed. Food prepared in retail environments like cut melon and hummus were also known to be responsible for the illness. Unpasteurized (raw) milk and soft cheeses made with unpasteurized (raw) milk, smoked seafood, salads made in stores like ham salad, chicken salad, or seafood salads, and raw vegetables are other risk-associated foods. Mexican-style soft cheese, *queso fresco*, made from unpasteurized milk, pasteurized milk products, hot dogs, and deli meats have all been associated with listeriosis outbreaks in the United States; likewise, there were outbreak cases associated with raw-milk soft cheese (Brie), pork tongue, and rillettes (pork paté) in France and Denmark [31]. The Food Safety Inspection Service (FSIS) recommends people at risk of listeriosis to reheat hot dogs and deli meats until steaming before consumption to kill any *Listeria monocytogenes* that

can be present. A recent survey with pregnant women indicated that surveyors reheat those foods to preserve quality and not because of food safety concerns [29].

Toxoplasmosis

Toxoplasmosis is an infection caused by the parasite *Toxoplasma gondii*, which can infect cats if they eat raw meat or rodents, and it remains in the cat's feces for 2 weeks. The general mode of infection in humans is by consuming undercooked, infected meat, or by handling soil or cat feces containing the parasite [32, 33].

Toxoplasma gondii infects many people at some point of their lives, but causes little or no harm, and creates immunity against it for the future. However, almost 85% of pregnant women in the United States are susceptible to toxoplasmosis infection because of their weakened immune system, leading to the fetus acquiring the infection too, which can cause spontaneous abortion or severe problems such as microcephaly, hydrocephalus, seizures, mental retardation, and chorioretinitis [32].

General symptoms of this infection are flu-like, which usually appear 10–13 days after eating, and can last months [5]. Infection can be avoided if meat is cooked until the pink color vanishes and juice runs clear, by wearing gloves while gardening, washing hands carefully after handling raw meat, fruits, vegetables, and soil, washing all fruits and vegetables before consumption, and not coming in contact with cat feces or raw-meat cat food [32, 33].

Other Pathogens

For other pathogens that are responsible for food-borne illnesses, the symptoms and foods associated with the pathogen are as follows [5].

Salmonellosis caused by *Salmonella typhi* is itself not a major risk to pregnant women, but it may pass to the fetus, resulting in abortion, stillbirth, or premature labor. It is estimated that around 1.2 million cases of Salmonellosis occur each year in the United States [6], resulting in approximately 15,000 hospitalizations and 400 deaths [34]. Symptoms of Salmonellosis are stomach pain, diarrhea (can be bloody), nausea, chills, fever, and/or headache, and usually appear 6–72 h after eating, potentially lasting up to 4–7 days. Salmonellosis especially affects immunosuppressed people like pregnant women, and can lead to serious complications that can result in death. Foods associated with this illness are: raw or undercooked eggs, poultry and meat, unpasteurized (raw) milk or juice, cheese, seafood, and fresh fruits/vegetables.

Campylobacteriosis is caused by *Campylobacter jejuni* and is responsible for 2.4 million human infections annually, killing approximately 100 people yearly, with the majority of the affected group being infants, elderly, or immunosuppressed individuals [34]. The major sources for this infection are the consumption of untreated or contaminated water, unpasteurized “raw” milk, and raw or undercooked meat,

poultry, or shellfish. General symptoms that can be seen when encountered with this illness are fever, headache, and muscle pain, followed by diarrhea (sometimes bloody), abdominal pain, and nausea. Symptoms generally appear 2–5 days after eating and may last up to 10 days. It can also spread to the bloodstream, potentially causing a life-threatening infection.

Clostridium perfringens are bacteria that produce toxins harmful to humans, and are found everywhere in the environment. Food poisoning from *Clostridium perfringens* is mainly associated with undercooked meats and food left at room temperatures for long periods of time. Food that is categorized as high-risk food will require time-temperature control for prevention of microbial growth and toxin production. Major sources of food that can cause this illness are meats, meat products, poultry, poultry products, and gravy. Consumption of contaminated food will result in the onset of watery diarrhea and abdominal cramps within about 16 h and illness that begins and lasts for 12–24 h. Complications and/or death are rare.

Cryptosporidium is generally found in soil, food, and water, especially that is used for recreational purposes (i.e., swimming pool or lake). Infection occurs when uncooked or contaminated food or water is consumed or a contaminated object is placed in the mouth.

Escherichia coli O157:H7 is one of several strains of *E. coli* that can cause human illness, potentially causing severe diarrhea (often bloody), abdominal cramps, and vomiting, with little or no fever. Symptoms can begin usually 1–9 days after contaminated food is eaten, and may last up to 9 days. Hemolytic-uremic syndrome (HUS) can develop and cause acute kidney failure, leading to permanent kidney damage or even death in the very young. Foods associated with this infection are undercooked beef, especially hamburger, unpasteurized milk and juices, such as “fresh” apple cider, contaminated raw fruits and vegetables, and water. The infection can also be transmitted from person to person.

Norovirus causes nausea, vomiting, and stomach pain, where diarrhea is more common in adults and vomiting more common in children. Foods associated with this infection are shellfish, fecal-contaminated foods or water, and ready-to-eat foods that have been touched by infected food workers (e.g., salads, sandwiches, ice, cookies, and fruits).

Vibrio vulnificus-contaminated food causes diarrhea, stomach pain, and vomiting and can result in blood infection. It may also result in death for people with weak immune systems, such as pregnant women. Foods associated with this infection are undercooked or raw seafood (fish or shellfish).

Importance of Food Safety Education

Food safety education is important for all consumers, but essential for pregnant women [4]. Fortunately, pregnancy is a life-phase when women tend to be more receptive to health-, food safety-, and quality-of-life-related information, and are

often more motivated to change unhealthy habits [3]. However, research has shown that many women are not aware of the potential risks associated with listeriosis and toxoplasmosis exposure to the fetus during pregnancy. Research also points to a lack of education on safe food handling, and safe eating practices from healthcare practitioners [7, 8, 30]. A study conducted in British Columbia showed that about 88% of healthcare providers knew about listeriosis but only 35% counseled women about pregnancy risks [41]. Pregnant women do not consult midwives, registered nurses, registered dietitians, and prenatal educators, who are highly valued as the best sources of food safety information among at-risk patients [30, 35, 41], unless there is a reason to be concerned about food-related illnesses.

Physicians play a very important role in the circle of care [33, 36]. A study from Canada indicated that 92.3% of women met with a physician at least once during their pregnancies [36]. Healthcare professionals should take advantage of the fact that pregnancy can be one of the most important life events for women that prompts them to be nutritionally aware and open to nutrition-related information [37]. Food habits clearly have a major impact on food choices, and this makes it difficult under ordinary circumstances to alter a woman's diet. However, health professionals have an opportunity to play a more influential role in affecting the dietary choices of pregnant women than information from any other sources [38].

Proper nutrition education is vital for successful and positive pregnancy outcomes. Nevertheless, pregnant women rely on midwives as a source of information regarding this subject matter [39], which put midwives in an influential role to deliver food safety education to pregnant women.[40] Other sources of information such as prenatal books, magazines, and web pages may also be a mode to deliver potential food-safety risk information to pregnant women [29].

Conclusion

Pregnant women are at high risk for food-borne illnesses because of hormonal changes that compromise their immune system. Improper handling and consumption of high-risk foods such as unpasteurized milk and dairy products, juices, raw sprouts, raw eggs, and raw meat/poultry/fish/seafood may lead to serious health hazards such as miscarriage, spontaneous abortion, meningitis, premature delivery, and neurological effects. Food-safety risk communication and consumer education to promote safer handling of food would manage the risk of potential food-safety hazards during pregnancy. Studies show that women tend to be motivated to make health-related behavior changes during pregnancy, which may make them receptive candidates for education of food safety. Healthcare professionals should take advantage of client receptivity to health information during prenatal visits to educate them on food-safety considerations in order to optimize the likelihood of a successful pregnancy outcome.

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Part II
Metabolism During Pregnancy

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Improving Pregnancy Outcomes with One-Carbon Metabolic Nutrients

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Keywords Folate · Choline · Vitamin B12 · Vitamin B6 · Pregnancy

Key Points

- The essential nutrients folate, vitamin B12, vitamin B6, and choline participate in one-carbon metabolic reactions, which are required for nucleotide biosynthesis and cellular methylation reactions.
- Although most pregnant women have adequate folate and vitamin B6 status, current intakes of choline and vitamin B12 may be suboptimal.
- Choline and vitamin B12 are predominantly found in animal foods, while folate and vitamin B6 can be obtained from legumes, grains, fruits, and vegetables.
- Common genetic variants in one-carbon metabolic genes can increase risk of nutrient deficiency and adverse pregnancy outcomes.
- Inadequate status of methyl nutrients has been associated with pregnancy complications including neural tube defects, preeclampsia, and spontaneous abortion.
- Preliminary studies suggest higher methyl nutrient intake during pregnancy may have beneficial effects on offspring cognition, stress reactivity, and social behavior.

Introduction to One-Carbon Metabolism

The transfer of one-carbon units for use in cellular reactions comprises an interconnected metabolic network referred to as one-carbon metabolism. This metabolic network is essential for many biochemical processes, including nucleotide synthesis, methylation of DNA and proteins, metabolism of homocysteine, and synthesis of methionine. Folate, choline, vitamin B6, and vitamin B12 play crucial roles in this network, as substrates and cofactors, and are commonly referred to as

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one-carbon or methyl (CH_3) nutrients. An overview of the reactions involved in one-carbon transfers is shown in Fig. 1. Key points, as described below, correspond to numbers in the figure:

1. Folic acid is reduced to dihydrofolate (DHF) and subsequently tetrahydrofolate (THF) by the enzyme dihydrofolate reductase (DHFR).
2. THF can be used for purine synthesis via conversion to 10-formyl-THF using formate as the one-carbon donor. Alternatively, THF can be converted to 5,10-methylene-THF using serine as the one-carbon donor and vitamin B₆ as a cofactor.
3. 5,10-methylene-THF is used for dTMP (thymidylate) synthesis via the enzyme thymidylate synthase (TS) and is also the precursor of 5-methyl-THF, produced by the enzyme MTHFR.

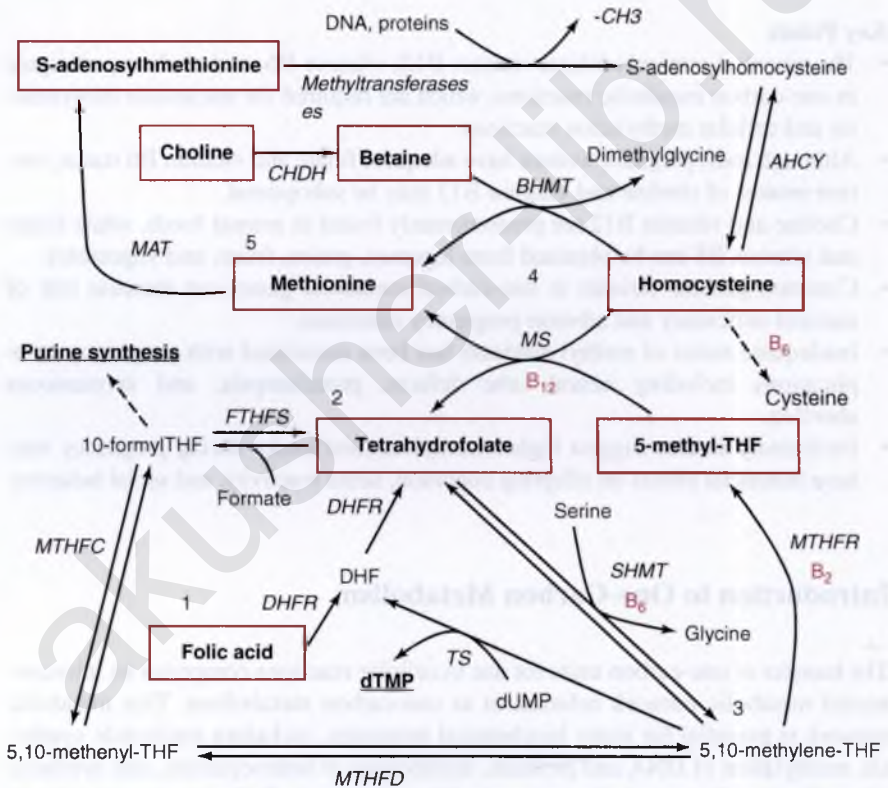


Fig. 1 Pathways of one-carbon metabolism. Key metabolites outlined in red, enzymes listed in italics, and cofactors in red text. *AHCY* adenosylhomocysteinase, *BHMT* betaine homocysteine methyltransferase, *CHDH* choline dehydrogenase, *DHF* dihydrofolate, *DHFR* dihydrofolate reductase, *dTMP* deoxythymidine monophosphate (thymidylate), *dUMP* deoxyuridine monophosphate, *FTHFS* formate–tetrahydrofolate ligase, *MAT* methionine adenosyltransferase, *MS* methionine synthase, *MTHFC* methenyltetrahydrofolate cyclohydrolase, *MTHFD* methylenetetrahydrofolate dehydrogenase, *MTHFR* methylenetetrahydrofolate reductase, *SHMT* serine hydroxymethyltransferase, *TS* thymidylate synthase

- Both 5-methyl-THF and betaine, which is produced from the oxidation of choline by choline dehydrogenase (CHDH), can provide the methyl group for conversion of homocysteine to methionine via the enzymes methionine synthase (MS) or betaine homocysteine methyltransferase (BHMT), respectively. MS requires vitamin B12 as a cofactor, and an inadequate supply of vitamin B12 can lead to a buildup of 5-methyl-THF, trapping folate in this form (the so-called “methyl trap”). This reduces the availability of folate for the synthesis of purines and thymidylate, the rate-limiting factor in DNA synthesis [1].
- Methionine is used both as an amino acid in proteins and for the synthesis of S-adenosylmethionine (SAM) which provides methyl groups for the methylation of DNA, histones, and other proteins and lipids, in reactions carried out by various cellular methyltransferases. In addition to the methylated products, S-adenosylhomocysteine is generated and is subsequently converted to homocysteine.

One-Carbon Nutrients

Folate

Folate, named for its presence in “foliage,” or green leafy vegetables, was first identified in 1931 as a substance in yeast capable of curing macrocytic anemia [2]. Its structure consists of a pteridine ring, p-aminobenzoic acid, and a variable number of glutamate residues [3]. The highly bioavailable synthetic form, folic acid (found in supplements and fortified foods) is fully oxidized and contains a single glutamate residue [3]. Folates found naturally in foods are typically polyglutamated, reduced forms of THF; they require hydrolysis to monoglutamates at the brush border of the small intestine for absorption via a transporter. Conversion to 5-methyl-THF usually occurs in the intestinal cell before export into the portal circulation. 5-methyl-THF is the major circulating form and enters cells by a receptor-mediated process. Cellular retention requires conversion of 5-methyl-THF to THF and then enzymatic polyglutamation of the THF molecule [3]. Folate transporters and receptors are highly expressed in rapidly dividing cells, including erythrocytes, the choroid plexus, kidney, and placenta [4, 5]. As described in the previous text, folate and its derivatives function in the transfer of one-carbon units, thereby facilitating DNA synthesis, DNA methylation, metabolism of homocysteine, and synthesis of methionine.

Vitamin B12

After the characterization in 1855 of pernicious anemia, an auto-immune condition that causes vitamin B12 deficiency, it was determined that raw liver (high in vitamin B12) was an effective treatment [6]. Later, the condition was found to be caused by a lack of the so-called “intrinsic” factor that was required to absorb the “extrinsic

factor.” The intrinsic factor has retained its name; however, the extrinsic factor was isolated and coined vitamin B12 in 1948 [7].

Dietary vitamin B12 is bound by haptocorrin (also known as R binder) in the mouth and stomach, protecting it from gastric acid. After entering the duodenum, vitamin B12 is released from haptocorrin and binds to intrinsic factor (IF). Vitamin B12 is subsequently absorbed in the ileum as an IF-B12 complex; vitamin B12 deficiency develops rapidly in those lacking IF. After absorption by the enterocytes of the ileum, vitamin B12 is largely transported in circulation bound to the carrier protein transcobalamin [8]. Vitamin B12 refers to a number of cobalamins with the same cobalt-containing corrin structure but varying ligands (a methyl, hydroxyl, cyano, or 5'-deoxyadenosyl group). It is a cofactor for only two enzymes: methionine synthase (MS, see Fig. 1), and methylmalonyl-CoA mutase (MCM), which converts methylmalonyl-CoA (a product of fatty acid and branched-chain amino acid metabolism) to succinyl-CoA, an intermediate of the TCA cycle. The active forms of the vitamin are methylcobalamin (used by MS) and 5'-deoxyadenosylcobalamin, used by MCM [9].

Vitamin B6

Vitamin B6 was originally discovered as an essential nutrient in animals; deficiency was associated with skin lesions, convulsions, microcytic anemia, and growth retardation in several species, including rats and dogs [10]. Dietary vitamin B6 is absorbed passively and efficiently in the small intestine with an absorption rate of approximately 75% [11].

Vitamin B6 is found in several forms: pyridoxine, pyridoxal, pyridoxamine, and their 5'-phosphorylated derivatives. Pyridoxal 5'-phosphate (PLP) is an essential cofactor for more than 140 enzymes (approximately 4% of all enzymatic reactions) [12], including serine hydroxymethyltransferase (SHMT), which uses serine as a one-carbon donor to convert THF to 5,10-methylene-THF. This form of folate is used to generate the nucleotide thymidylate. Vitamin B6 is also required for the transsulfuration of homocysteine, an alternative to homocysteine remethylation, whereby homocysteine is metabolized to cysteine (see Fig. 1). The relative balance between transsulfuration and remethylation depends on the supply of SAM; low levels will favor SAM production via homocysteine remethylation, while high levels will favor transsulfuration of homocysteine [13]. Additional enzymes that utilize PLP are involved in the synthesis of heme, production of the neurotransmitters serotonin and dopamine, and metabolism of amino acids and lipids [14].

Choline

Choline, derived from the Greek word “chole,” [15] was first isolated in 1862 by boiling lecithin from pig and ox bile. Nevertheless, its essentiality in human health was not recognized until 1991, when men developed liver dysfunction after consuming a

choline-free diet for 3 weeks [16]. This finding suggested that *de novo* choline synthesis was not sufficient in meeting metabolic needs, and that choline must be obtained through the diet in order to optimize health. In 1998, choline was designated as an essential nutrient, and dietary recommendations were established [17].

As mentioned above and shown in Fig. 1, choline is the precursor of betaine, which donates one of its three methyl groups to generate methionine and, subsequently, SAM [4]. The remaining two methyl groups associated with dimethylglycine (DMG) can subsequently be used as one-carbon units in folate-mediated one-carbon metabolism. Betaine also functions as an organic osmolyte to regulate cell volume and protect cells from osmotic stress [9, 10]. Through the cytidine diphosphate (CDP)-choline pathway, choline is used to generate phosphatidylcholine (PC), a major component of cell membranes and very-low-density lipoproteins [4]. PC and its metabolites (e.g., diacylglycerol) also modulate cell signaling pathways crucial to normal placental and fetal development [18]. PC can also be synthesized endogenously through the phosphatidylethanolamine *N*-methyltransferase (PEMT) pathway using SAM as the methyl donor. This pathway is upregulated during pregnancy [19, 20] to generate a PC molecule enriched in docosahexaenoic acid (DHA) [21], which is crucial to fetal brain development. Choline is also used to synthesize the neurotransmitter acetylcholine, which is involved in attention and memory formation [19], and signaling pathways in non-neuronal tissues [22]. In particular, the human placenta contains a large amount of acetylcholine, where it regulates amino acid transport, hormone release, placental vascularization, and parturition [23, 24].

Recommended Dietary Intake Levels of One-Carbon Nutrients During Pregnancy

Recommended daily allowances (RDAs) are based on the nutrient level that is adequate for 97.5% of healthy individuals, and are calculated by adding two standard deviations to the estimated average requirement (EAR), which meets the needs of 50% of individuals. If data are insufficient to establish an EAR, an adequate intake (AI) is given. The tolerable upper intake level (UL) represents the maximum amount that can be consumed per day with no increased risk of adverse effects [17]. The recommended intake levels and upper limits for folate, vitamin B6, vitamin B12, and choline during pregnancy are shown in Table 1.

Table 1 Dietary requirement of one-carbon nutrients

Dietary requirements during pregnancy								
Age	Folate ($\mu\text{g}/\text{day}$)		Vitamin B6 (mg/day)		Vitamin B12 ($\mu\text{g}/\text{day}$)		Choline (mg/day)	
	RDA	UL	RDA	UL	RDA	UL	AI	UL
<19	600	800	1.9	80	2.6	ND	450	3000
>19	600	1000	1.9	100	2.6	ND	450	3500

RDA recommended daily allowance, *UL* upper limit, *ND* no data, *AI* adequate intake

Adapted from Dietary Reference Intakes, Institute of Medicine

Folate

The RDA for folate is expressed as dietary folate equivalents (DFE) and was established using data from human feeding studies in which folate intake was highly controlled [17]. Folate status is typically assessed by measuring serum folate; red blood cell (RBC) folate can provide an indication of long-term status. Deficiency is usually considered to be <3 ng/mL in serum or <140 ng/mL in RBCs [17].

Pregnancy substantially increases the requirement for folate, due to accelerations in cell division and tissue expansion of the placenta and fetus [25]. Studies in pregnant women indicated a need for 200 or more additional DFE per day as compared to the non-pregnant state. Although the protective effects of folic acid on neural tube defects (NTD) are well-established, this was not considered in setting the RDA, because the critical window for neural tube closure occurs before most women recognize they are pregnant [17]. Rather, a separate recommendation intended for women planning to become pregnant suggests an intake of 400 μg per day of synthetic folic acid in addition to folate from the diet, as this intake level of folic acid maximized NTD risk reduction among most women.

The major symptom of folate deficiency is megaloblastic anemia resulting from impaired DNA synthesis in red blood cells [26]. Folate deficiency can arise from dietary inadequacy, vitamin B12 deficiency (due to the trapping of folate as 5-methyl-THF), and gene-nutrient interactions [17, 27]. Additional symptoms of folate deficiency may include fatigue, weight loss, oral sores, heart palpitations, and appetite loss [17]. Folate deficiency is now rare in the United States due to folic acid fortification of the food supply. More than 85% of adults achieve the estimated average requirement [28], and pregnant women consuming supplemental folic acid have circulating serum folate concentrations far exceeding the deficiency cut-off [29]. Nonetheless, among pregnant and non-pregnant women of reproductive age not consuming supplements, the median intake is less than half of the recommended 400 μg of synthetic folic acid per day [30], suggesting that women who are pregnant, or of reproductive age, remain a subgroup of concern. In addition, women carrying multiple fetuses are at greater risk of folate deficiency anemia and may have a higher requirement; 1000 $\mu\text{g}/\text{day}$ has been suggested as a recommended intake [31].

Toxicity from food folate (including fortified foods) has not been reported [17]. However, excessively high doses of folic acid supplements may “mask” a vitamin B12 deficiency; therefore, an upper limit was set at 1000 μg folic acid/day for pregnant women >19 years. More recently, high folic acid consumption was shown to impair MTHFR activity in mice, suggesting there may be clinical implications for individuals consuming high-dose folic acid supplements, particularly among those who are MTHFR deficient [32].

Folate Vs Folic Acid

Although both folates and folic acid can fulfill the dietary requirement, there are several key differences in their absorption [33], which result in a higher bioavailability of folic acid. Because of the difference in bioavailability between folate and folic acid, the unit DFE, or dietary folate equivalent, is used. Since food folate is approximately 60% as bioavailable as folic acid, either 1 μg of naturally occurring food folate or 0.6 μg of folic acid is equivalent to 1 μg DFE [17]. Thus, the amount of DFEs in a meal is equivalent to μg of food folate + (1.7 \times μg of folic acid). To maximize protection from neural tube defects, the National Academy of Medicine, the Centers for Disease Control and Prevention, and the US Public Health Service recommend that pregnant women consume at least 400 μg of their daily intake as synthetic folic acid, either from supplements or fortified foods [34].

Vitamin B12

The EAR for vitamin B12 was established based on data from individuals with pernicious anemia, vegetarians/vegans, and the body's ability to absorb and store vitamin B12. For pregnant women, 0.2 $\mu\text{g}/\text{day}$ was added to account for fetal accumulation of the vitamin [17].

Deficiency can be assessed by one of several biomarkers; a combination of two is more definitive [35]. Plasma or serum vitamin B12 is commonly used but may fail to detect early deficiency, as it remains normal even after tissue levels begin to decline. More specific are methylmalonic acid, which accumulates when methylmalonyl-CoA mutase is unable to function properly without its vitamin B12 cofactor, and holotranscobalamin, which reflects the fraction of vitamin B12 currently bound to transcobalamin. Homocysteine, although not an ideal biomarker since it is affected by the status of several vitamins, may reflect vitamin B12 status, particularly in populations where folate intake levels are high [36].

Like folic acid, long-term vitamin B12 deficiency results in macrocytic anemia, and can lead to potentially permanent neurological symptoms of unknown etiology; therefore, detecting a vitamin B12 deficiency in the early stages is crucial. Excessive intakes of folic acid can "mask" detection of a vitamin B12 deficiency because metabolism of folic acid bypasses the methionine synthase reaction (see Fig. 1) which requires vitamin B12 as a cofactor and is needed to regenerate the forms of folate that function in DNA biosynthesis. In contrast, naturally occurring food folates are typically converted to 5-methyl-THF during absorption and therefore are unable to bypass the methyl-trap phenomenon [9]. Although the average intake of vitamin B12 in pregnant women is well above the EAR [17], a recent controlled feeding study in third-trimester pregnant women that provided $\sim 3\times$ the RDA for

12 weeks (an average of 8.6 μg per day) did not result in elevated serum vitamin B12 levels, but rather maintained them within normal range, with no change from baseline. This finding suggests that intakes higher than the current RDA (2.6 μg per day) may be necessary to maintain vitamin B12 status throughout pregnancy [37].

Because animal products are the only source of vitamin B12, vegetarians and vegans are at greater risk of deficiency and must consume supplements and/or fortified foods [38]. In addition, women chronically exposed to nitrous oxide, which is commonly used in dental procedures, may be at risk of deficiency since methionine synthase can act on nitrous oxide to form a radical which destroys the enzyme and the B12 cofactor [5].

Toxicity has not been shown (likely because absorption is limited to ~ 2 μg at a time) and there is no upper limit [17, 39].

Vitamin B6

Vitamin B6 recommendations for adult men and non-pregnant women were established based on optimal plasma concentrations of PLP (>20 nmol/L). Plasma PLP is the standard marker for vitamin B6 status; it is responsive to intake levels and reflects liver stores [40]. Although PLP levels decline to approximately 10 nmol/L during pregnancy, this is considered a normal physiological occurrence, and the RDA for pregnant women does not attempt to correct this [17]. Rather, 0.5 mg/day was added to the EAR to account for placental and fetal accumulation, based on animal studies, as well as changes in maternal weight and metabolism. Symptoms of deficiency have been reported to include microcytic anemia, depression, seizures, inflammation, and sores of the mouth [41]. Deficiency in vitamin B6 can also lead to hyperhomocysteinemia, due to its role in the transsulfuration pathway. Because vitamin B6 is widely distributed in commonly consumed foods, most Americans are not at risk of deficiency. In addition, symptoms are rarely seen above intakes of 0.5 mg/day [17]. The upper intake level has been set at 100 mg based on possible risk of sensory neuropathy, but risk of toxicity is very low, as this level of intake is rarely seen and can only be achieved through pharmacological doses [17].

Oral contraceptives are associated with decreased levels of PLP, with one study finding that 78% of women currently taking birth control and 40% of past users had PLP levels below 20 nmol/L compared to 20% of women who had never used hormones [42]. However, it is uncertain whether this reflects a true B6 deficiency or simply a redistribution of body stores.

Choline

Very little data were available to the IOM committee for derivatization of an EAR, and thus establishment of an RDA, for choline. As a result, an AI was developed based on the choline intake level needed to maintain normal liver function in men [17]. The

current AI for non-pregnant women is 425 mg choline/day, and was adjusted to 450 mg choline/day for pregnant women [17], based on the observation that pregnant rodents easily become choline deficient due to large amounts of choline being transported to the placenta and the fetus, both of which have poor ability to synthesize choline [43, 44]. Recent data from a 12-week feeding study in third-trimester pregnant women indicate that this recommendation may not be adequate, because pregnant women consuming the AI level have lower plasma concentrations of choline-derived methyl donors and display altered partitioning between the two choline pathways used to synthesize PC and betaine. Notably, both of these can be improved by increasing maternal choline intake [45, 46]. A higher maternal choline intake also decreases the placental transcript level of soluble fms-like tyrosine kinase (sFLT1), which is elevated in women with preeclampsia [47], and corticotropin-releasing hormone, which lowers cortisol concentration in the cord blood [48]. Collectively, these data support a dietary recommendation exceeding the current AI for achieving optimal pregnancy outcome and improving the long-term well-being of the child.

Excessive choline consumption can lead to a fishy body odor, which is caused by increased production and excretion of the choline metabolite, trimethylamine. Furthermore, a high dose of choline can result in hypotension (low blood pressure), increased sweating, vomiting, and salivation secondary to excess production of the neurotransmitter, acetylcholine. To prevent these adverse effects, an upper limit was established at 3500 mg/day for adults [17].

Effects of Genetic Variation on Dietary Recommendations

Folate

Several common genetic variants affect the metabolism of folate and are associated with altered risk of several pregnancy complications. The gene encoding MTHFR (methylenetetrahydrofolate reductase) contains several widely studied single nucleotide polymorphisms (SNPs), including rs1801133 (commonly referred to as 677C→T). This SNP causes an amino acid exchange of valine for alanine in the coding region of the gene, resulting in an enzyme with reduced efficiency (~45% of normal activity) [49]. A second, less severe SNP (1298A→C) leads to ~30% lower activity of MTHFR [49]. Decreased activity of this enzyme leads to an inadequate supply of 5-methyl-THF and often causes hyperhomocysteinemia. Individuals with the 677T allele have a higher requirement for folate; the RDA appears to be adequate for women with the variant allele [50] but not for men [51]. However, a required intake level for pregnant women with the TT genotype has not been established. During pregnancy, this SNP has been associated with a higher risk of miscarriage, placental abruption, and preeclampsia [52, 53]. Consuming a higher amount of folate can partially overcome the deficiencies in MTHFR function, and therefore pregnant women with the TT genotype may benefit from a folate intake above the recommended levels of 600 µg/day to ensure a healthy pregnancy.

The genes for methionine synthase (*MTR*) and methionine synthase reductase (*MTRR*), which regenerates methionine synthase to its active form, are also sites of genetic variation that have been shown to disrupt folate metabolism [27]. Although these SNPs do not lead to elevated homocysteine in all individuals [27], some evidence suggests they may affect risk of pregnancy complications [54, 55]. Because genetic variants interact and one may worsen or mediate the effects of another, it is difficult to definitively determine the effect of any one SNP on an individual's health risks. Studies are now beginning to investigate compound genotypes (individuals heterozygous for multiple SNPs). One study found that SNPs in several folate metabolizing genes, when they occur together, increase risk of preterm birth, despite none of them having a significant predictive effect alone [56].

Vitamins B12 and B6

Limited data are available regarding genetic variants that impact vitamins B12 and B6 and their potential effect on health. Vitamin B12 status has been associated with several polymorphisms in the transcobalamin (*TCN2*) and fucosyltransferase (*FUT2*) genes [54, 57]. *FUT2* is involved in antigen formation; it may influence the risk of vitamin B12 malabsorption [57]. However, it is unknown how these variants may impact B12 requirements of pregnant women.

Vitamin B6 status is affected by SNPs in the alkaline phosphatase gene (*ALPL*). Alkaline phosphatase removes the phosphate group from PLP, forming PL, and a high activity of this enzyme may decrease PLP levels [40]. Notably, serum levels of the enzyme are typically elevated during pregnancy [58], correlating with the reduction seen in PLP. There are several common variants in *ALPL* that are associated with plasma PLP [59]. However, these SNPs do not appear to induce functional changes in vitamin B6 metabolism [40]. Therefore, genetic variants in *ALP* may contribute to variation in individual PLP levels, but may not represent an important risk factor for vitamin B6 deficiency.

Choline

Genetic variants in many choline-metabolizing genes can influence choline metabolism and change the choline requirement for women of childbearing age. One of the most studied SNPs is found in the promoter region of the *PEMT* gene (-744G→C, rs12325817), which is transcriptionally upregulated by estrogen to synthesize choline endogenously. The presence of this SNP makes the gene unresponsive to estrogen and abolishes the estrogen-induced upregulation [60]. As a result, women with this SNP are more susceptible to choline inadequacy and must consume extra choline from their diets to offset the impairments in de novo choline biosynthesis. Women possessing the T allele of the *CHDH* gene (rs12676), the first gene involved

in generating betaine, or the G allele of the *SLC44A1* gene (rs7873937), the gene involved in transporting choline into the placenta [61], may also need to consume extra choline during pregnancy, since they have greater susceptibility to choline deficiency and will develop organ dysfunction when they consume a low-choline diet [60, 62].

Genetic variants in the folate-metabolizing pathway, such as *MTHFR*, *MTHFD1*, and *MTR*, can also increase the requirement for choline among women of reproductive age. Because SAM derived from folate metabolism is needed for the production of PC through the PEMT pathway, these genetic variants dramatically impair the effectiveness of this synthesizing pathway. Consequently, there is enhanced partitioning of choline to the CDP-choline pathway for generating PC. Notably, the metabolic adaptations that occur during pregnancy far outweigh the more modest effects of these SNPs, suggesting that a greater choline intake may be required for all pregnant women, regardless of their genotypes in these loci [63].

Nutrient–Nutrient Interactions

Folate and Vitamin B12

As described above, folate and vitamin B12 are interconnected through the enzyme methionine synthase, and deficiency of either vitamin causes an identical anemia. However, although treatment of vitamin B12 deficiency anemia with extra folic acid may override the methyl trap and cure the anemia, this masks the true deficiency, and can allow further harmful symptoms secondary to ongoing vitamin B12 inadequacy [9].

There are some indications that extremely high folate levels may exacerbate vitamin B12 deficiency, potentially via negative effects of unmetabolized folic acid in plasma [64]. This is a particularly relevant concern in folic acid-fortified populations. Additionally, vitamin B12 deficiency induces a cellular folate deficiency beyond a reduction in THF formation because THF is the form of folate most easily polyglutamated by the cell, allowing it to be retained rather than lost into the bloodstream [9]. Therefore, it is important for clinicians to be mindful of the intake ratio of folic acid: vitamin B12 in their patients, especially in vegetarians and others at risk of low vitamin B12 intake.

Riboflavin

Vitamin B2, or riboflavin, is a precursor of FAD, an essential cofactor for the *MTHFR* enzyme. Because of this, riboflavin intake may affect homocysteine levels; however, this is mostly a concern for individuals with low folate status or the

677C→T TT genotype [65]. Riboflavin is widely distributed in foods, including enriched grain products, vegetables, meat, and dairy; average intake in the US is well above the RDA [17].

Protein Intake and Vitamin B6 Requirements

Several studies have shown a linear relationship between protein and vitamin B6; higher protein intake often results in lower vitamin B6 status markers [66]. However, this association is not consistently seen in all studies; in addition, it may reflect a redistribution of vitamin B6 into tissues rather than a true deficiency [17]. In setting the RDA, the possible effects of varying protein intakes were taken into consideration.

Influence of Folate Metabolism on Choline Requirements

As shown in Fig. 1, choline and folate are metabolically interrelated as they intersect in homocysteine remethylation to form methionine. Because of their interdependence in the methyl cycle, perturbation in folate metabolism due to genetic variations in folate metabolizing genes or an inadequate folate nutriture will result in compensatory changes in choline metabolism and a higher dietary choline requirement, as demonstrated in numerous animal and human studies [67–71].

Common Food Sources for One-Carbon Nutrients

Tables 2, 3, 4, and 5 list common foods that are good sources of folate, vitamin B12, vitamin B6, and choline. Food folate is found in high amounts in green leafy vegetables, citrus fruits, strawberries, legumes, and grains. An additional source of folic acid in the diet is through fortified food products, which include breads, pastas, cereals, and other grain products. Fortification of the US food supply has been mandatory since 1998, for the purpose of preventing neural tube defects during pregnancy. This fortification policy has resulted in a 31% decrease in occurrence of neural tube defects in the US [72].

In contrast, vitamin B12 is found only in animal foods (and some algae and fermented foods), since its synthesis is derived from bacteria [73]. Vegetarian and vegan women at risk of deficiency obtain vitamin B12 through fortified foods (e.g., breakfast cereals, non-dairy milks) or supplements. Approximately 1.5–2 μg of B12 can be absorbed from a single meal [39], consequently, meeting the DRI through diet alone can be accomplished by including a meat or milk product in several meals throughout the day.

Table 2 Dietary sources of folate and folic acid

Good sources of folate and folic acid			
<i>Legumes</i>		<i>Cereal and grains</i>	
1 cup chickpeas	1114 µg DFE ^a	1 cup ready-to-eat breakfast cereals	350–700 µg DFE
1 cup pinto beans	1013 µg DFE	1 cup enriched wheat flour	380 µg DFE
1 cup lentils	920 µg DFE	1 cup cooked enriched spaghetti	167 µg DFE
1 cup lima beans	808 µg DFE	1 cup cooked enriched white rice	150 µg DFE
1 cup navy beans	757 µg DFE	1 medium enriched plain bagel	140 µg DFE
1 cup kidney beans	725 µg DFE	1 cup oats	87 µg DFE
<i>Vegetables</i>		<i>Fruits</i>	
1 cup spinach	260 µg DFE	1 cup orange juice	202 µg DFE
1 cup asparagus	240 µg DFE	½ avocado	82 µg DFE
1 cup artichokes	200 µg DFE	1 cup strawberries	71 µg DFE
1 cup Brussels sprouts	157 µg DFE	1 cup mango	71 µg DFE
1 cup beets	150 µg DFE	1 orange	55 µg DFE
1 cup chopped collards	130 µg DFE	1 cup lemon juice	49 µg DFE
1 cup broccoli	105 µg DFE	1 grapefruit	32 µg DFE

Information on nutrient content was obtained from USDA National Nutrient Database for Standard Reference, Release 27

^aDFE dietary folate equivalent. 1 µg DFE is equivalent to 1 µg of naturally occurring food folate, or 0.6 µg of folic acid in fortified or enriched food products

Table 3 Dietary sources of vitamin B12

Good sources of vitamin B12					
Seafood		Meat products		Milk products	
3 oz. clams	80 µg	3 oz. lamb	3 µg	1 cup Swiss cheese	4.4 µg
3 oz. oyster/mussel	20 µg	3 oz. beef steak	1.6 µg	1 cup shredded mozzarella cheese	2.55 µg
1 filet sockeye salmon	20 µg	3 oz. Turkey breast	1.5 µg	1 cup nonfat milk	1.2 µg
3 oz. crab	8.8 µg	3 oz. pork chop	0.6 µg	1 cup cheddar cheese	1.16 µg
3 oz. canned tuna	2.17 µg	3 oz. chicken breast	0.2 µg	1 6-oz plain yogurt	1 µg

Information on nutrient content was obtained from USDA National Nutrient Database for Standard Reference, Release 27

Good sources of vitamin B6 are widely distributed across the major food groups, including fruits and vegetables, grains, legumes, and meats. However, similar to vitamin B12, vegetarians and vegans may also benefit from fortified foods and supplements, as high rates of deficiency have been found in these groups [74].

Choline is distributed in a wide variety of foods, but animal foods such as eggs, meats, and seafood are the richest sources of choline. Choline is also found in non-animal food products such as legumes and vegetables, which can be alternative choices for vegetarian and vegan women. Most pregnant women have dietary choline intakes below the current recommended level [75–77]. Unlike folic acid, vitamin B12 and vitamin B6, choline is not routinely found in prenatal supplements [78], but it can be found in a variety of forms (e.g., choline salts and

Table 4 Dietary sources of vitamin B6

Good sources of vitamin B6			
<i>Fruits and vegetables</i>		<i>Seafood and meat products</i>	
1 large baked potato	1.1 mg	3 oz. chicken breast	0.9 mg
1 cup cooked Brussels sprouts/spinach/ sweet red peppers/winter squash/sweet corn	0.4 mg	3 oz. cooked Atlantic salmon	0.8 mg
1 small banana	0.4 mg	3 oz. pork chop	0.44 mg
1 cup orange juice	0.2 mg	3 oz. beef steak	0.4 mg
		3 oz. canned tuna	0.4 mg
<i>Cereal and grains</i>		<i>Legumes</i>	
1 cup ready-to-eat breakfast cereals	0.6–2 mg	1 cup lentils/chickpeas	1 mg
1 cup whole-grain wheat flour	0.5 mg	1 cup pinto beans/lima beans	0.9 mg
1 cup cooked brown rice	0.29 mg	1 cup kidney beans/peanuts	0.7 mg
1 cup whole wheat spaghetti	0.11 mg		

Information on nutrient content was obtained from USDA National Nutrient Database for Standard Reference, Release 27

Table 5 Dietary sources of choline

Good sources of choline			
<i>Eggs and meat products</i>		<i>Seafood</i>	
1 large egg	135 mg	3 oz. shrimp	115 mg
3 oz. beef steak	111 mg	3 oz. sockeye salmon	100 mg
3 oz. chicken breast	100 mg	3 oz. scallop	94 mg
1 pork chop	94 mg	3 oz. oyster	86 mg
<i>Legumes</i>		<i>Vegetables</i>	
1 cup baked beans	78 mg	1 cup cauliflower	60 mg
1 cup navy beans	70 mg	1 cup canned green peas/sweet corn	52 mg
1 cup lentils	65 mg	1 large baked potato	45 mg
1 cup lima beans/pinto beans	60 mg	1 medium artichoke	40 mg

Information on nutrient content was obtained from USDA National Nutrient Database for Standard Reference, Release 27

phosphatidylcholine) in commercially available supplements, and should be considered for assisting women in achieving dietary recommendations.

Effects of One-Carbon Metabolic Nutrients on Pregnancy Outcomes

Maternal Outcomes

Anemia

Adequate intake of folate and vitamin B12 are essential for prevention of maternal anemia, which has negative consequences for the fetus, including preterm delivery and low birthweight [79]. However, since folic acid fortification, folate deficiency

anemia rates are especially low [80]. A meta-analysis on folic acid supplementation in pregnancy found a significant effect on megaloblastic anemia, but not on overall unspecified anemia rates [81], likely because iron deficiency is a more common cause of maternal anemia [82]. Similarly, although low vitamin B12 levels have been associated with low hemoglobin [83], vitamin B12 deficiency is not a major cause of maternal anemia [82].

Preeclampsia

Preeclampsia is a disorder of the placenta, resulting from inadequate invasion of trophoblasts into the maternal decidua of the uterus [84]. The cause is unknown; various processes including abnormal regulation of inflammation, angiogenesis, and oxidative stress have been implicated in its etiology [85]. Women with preeclampsia have a higher risk of negative birth outcomes such as preterm delivery and intrauterine growth restriction, as well as long-term health risks including cardiovascular disease and kidney disease [86, 87]. The connection between folate intake and preeclampsia development has been investigated in a large number of studies. While observational data have suggested that low folate levels are associated with later development of preeclampsia [88, 89], and that women who supplement with folic acid experience a protective effect [90, 91], results from a small number of randomized controlled trials (RCTs) have been inconclusive thus far [92]. A large, multicenter RCT (the Folic Acid Clinical Trial or FACT) recently completed in 2016 [93, 94], and is expected to provide important information on this topic. Suggested protective mechanisms of folic acid include decreasing homocysteine, resulting in improved endothelial function; improving genome stability and DNA methylation; and decreasing blood pressure and thrombosis via interactions with nitric oxide and fibrinogen [92].

To date, at least one study has shown an association between vitamin B12 levels and preeclampsia [88], but these findings are uncertain due to lack of a secondary marker of B12 status. A small number of studies have explored using vitamin B6 to prevent preeclampsia; however, thus far there is no evidence of a beneficial effect of supplementation on risk [95].

Although yet to be investigated in a randomized controlled trial, results from human and cell culture studies suggest that choline may reduce risk of preeclampsia through a reduction in sFLT1, which in addition to being a biomarker of risk, is also suggested to be involved in the pathogenesis of preeclampsia [96]. Pregnant women consuming approximately twice the AI for choline (930 mg/day) have significantly lower serum levels of sFLT1, and this finding was replicated in a trophoblast cell culture model [18, 47]. Choline inadequacy in these trophoblasts was also shown to increase levels of inflammatory cytokines, DNA strand breaks, and oxidative damage in placental cells, which have all been implicated in the etiology of preeclampsia [18]. Further, in a murine model, maternal choline supplementation during pregnancy improved placental vascular development in a manner coincident with alterations in the expression of inflammatory cytokines and angiogenic factors [97].

Additional research is needed to clarify the connection between methyl nutrients and preeclampsia. This is complicated by the fact that the crucial window in pre-

eclampsia development may occur before women realize they are pregnant, and therefore clinical trials may start too late to demonstrate a protective effect. Therefore, all women of reproductive age should be encouraged to consume intakes that are aligned with dietary recommendations, regardless of whether they plan to become pregnant.

Spontaneous Abortion (Miscarriage) and Preterm Birth

Loss of a pregnancy or delivery of a severely premature fetus can have serious consequences for maternal and fetal health, respectively. Because of their role in cell division, methyl nutrients support normal growth and development of the fetus. Low folate status has been repeatedly associated with a higher risk of preterm birth [88, 89, 98] and spontaneous abortion [99, 100]. A large cohort study found a substantial reduction in risk of preterm birth (50–70%) in women who supplemented with folic acid during the first trimester [101]. Despite these findings, recent meta-analyses of randomized controlled trials found no preventative effect of folic acid supplementation on miscarriage [102] or preterm birth [81], although many of the included trials were of low quality. There is considerable heterogeneity among studies, resulting from genetic differences between populations, fortification status, prevalence of risk factors, and varying supplementation protocols. Therefore, it is clear that efforts should be made to clarify the factors contributing to differing study results in order to elucidate the effect of folic acid supplementation on these pregnancy outcomes.

Fewer studies have investigated the role of other one-carbon nutrients in spontaneous abortion and preterm birth. Vitamin B6 deficiency was associated with spontaneous abortion in one study, and the effect appeared to act synergistically with folate deficiency [99]. Several studies have found no association between vitamin B12 levels and risk of preterm birth [89, 98]. However, women with the highest serum levels of both folate and vitamin B12 had a higher chance of live birth following assisted reproductive technologies [103]. In addition, women chronically exposed to nitrous oxide, which would impair the activity of vitamin B-12 dependent methionine synthase, had higher rates of spontaneous abortion, suggesting a possible link between vitamin B12 deficiency and miscarriage [104].

Nausea and Vomiting

Pyridoxine has been recognized since 1942 as a treatment for nausea and vomiting of pregnancy [105]. Today it is prescribed both alone and as a combination therapy with doxylamine, which is recommended by the Canadian and American Colleges of Obstetrics and Gynecology as a first-line treatment for nausea and vomiting of pregnancy [106]. Although the mechanism of action is uncertain, PLP appears to be the anti-emetic metabolite [107]. A recent Cochrane review did not find strong

evidence for its effectiveness, although the review was limited by considerable heterogeneity between studies and a small number of RCTs [108]. Nevertheless, it remains an important treatment option, since prescription drugs for pregnant women are limited by safety concerns, and nutritional therapies are a well-accepted and tolerated option.

Offspring Outcomes

Anthropometric Characteristics and Apgar Score

The effect of a higher intake of methyl nutrients during pregnancy on newborn birth outcomes is relatively inconsistent. A recent systematic review [81] indicates that infant birth weight is improved with maternal folic acid supplementation, confirming the finding of an epidemiological study conducted after the implementation of folic acid fortification [109]. Still, there are studies finding no association between maternal folate intake or status and the birth weight of the neonates, or other anthropometric measures such as birth length and head circumference [98, 110]. Some studies fail to find any benefits of improving maternal vitamin B12 status in reducing the risk of being born small-for-gestational-age (SGA) [98], while other studies indicate that maternal vitamin B12 deficiency is a significant risk factor [64, 111, 112]. Interestingly, this risk may be dependent on the maternal folate status such that consuming a diet high in folate may exacerbate the risk of delivering a SGA baby, since an unbalanced folate:vitamin B12 ratio will lead to the methyl trap phenomenon [64]. Although maternal vitamin B6 status has no effect on infant birth weight, birth length, or head circumference [113], one study [114] reports that infants born to mothers deficient in vitamin B6 have lower Apgar scores at 1 min, but this is not supported by a recent Cochrane review [95]. Maternal choline intake at levels exceeding dietary recommendations did not modulate anthropometric measurements or Apgar scores in normal pregnancy [45]. However, a few epidemiological studies have reported associations between cord blood choline levels and birth weight of neonates, suggesting that choline may have a modulatory role in weight gain in some pregnancies [115].

Neural Tube Defects and Other Birth Defects

A beneficial effect of methyl nutrients in reducing the risk of birth defects, most notably neural tube defects (NTDs), is well-established. Approximately 21 days after conception, the neural plate begins to lift upward, comes together, and closes to form the neural tube, which will eventually form into the brain and the spinal cord. When the neural tube fails to close properly at the end of this developmental process on day 28, NTDs, such as spina bifida or anencephaly, ensue. Although the exact mechanisms remain to be uncovered, periconceptional folic acid

supplementation has been shown to dramatically reduce the occurrence and recurrence of NTDs [116]. Deficiency in several folate-metabolizing enzymes due to genetic variations (e.g., *MTHFR* 677TC→ and 1298A→C) also increases the risk of NTDs [116, 117]. Besides folate, maternal vitamin B12 insufficiency and low dietary choline intake during the periconceptional period may also be a risk factor of NTDs [118, 119]. Overall, these data implicate the essential role of these methyl nutrients in the etiology and prevention of NTDs.

Some investigations have been done to evaluate the effect of methyl nutrients on other birth defects, but their results are largely inconclusive. Maternal folic acid supplementation during the periconceptional period is shown to lower the risk of orofacial clefts in some studies but not others [120–122]. The association between the maternal *MTHFR* polymorphisms (677C→T and 1298A→T) and the risk of orofacial clefts is also unclear [123, 124]. For congenital heart defects, a significant risk reduction is observed among infants born to mothers who take folic acid supplements [125]. Animal studies [126] have also demonstrated that fetuses born to choline-deficient dams are more likely to have abnormal cardiac development, but human studies fail to confirm this finding [127]. Information regarding vitamin B12 and vitamin B6 supplementation on birth defects is lacking in the literature. Future studies should clarify the effectiveness of the methyl nutrients in reducing the risk of these malformations.

During meiosis, normal DNA methylation is required to prevent nondisjunction. Given the role of methyl nutrients in DNA methylation, some researchers believe that impairment in their metabolism will increase the risk of genetic disorders such as Down syndrome. Indeed, the presence of genetic variants in the folate metabolic pathway, such as the *MTHFR* 677C→T polymorphism and the methionine synthase reductase 66A→G polymorphism, increases the risk of giving birth to a child with Down syndrome [128], and periconceptional folic acid supplementation is associated with a lower incidence of Down syndrome [116]. Notably, maternal choline supplementation during pregnancy is shown to improve attention, spatial cognition, and emotional regulation in a rodent model of Down syndrome [129, 130]. These data highlight the importance for at-risk individuals to consume adequate amounts of methyl nutrients during the pregnancy.

Autism Spectrum Disorders

Autism spectrum disorders (ASD) is a group of neurodevelopmental disorders characterized by impaired social interaction, disrupted verbal and non-verbal communication, and restricted repetitive behaviors. Its etiology is still poorly understood, but both genetic and environmental factors (i.e., nutrition) are likely involved. Notably, emerging evidence supports the hypothesis that inefficiency in folate metabolism caused by genetic polymorphisms is one possible contributing factor to ASD. A recent meta-analysis shows that individuals with the *MTHFR* 677C→T polymorphism have increased susceptibility of ASD [131], but this risk is reduced

dramatically with maternal periconceptional folic acid supplementation [131–133]. In an autistic mouse model, prenatal choline supplementation was shown to beneficially decrease social behavioral issues [134]. Taken together, these findings reveal that methyl nutrient supplementation is a potentially efficacious and safe prevention strategy for autism.

Beneficial Effects on Offspring Health

Normal offspring development is severely impacted by other adverse pregnancy exposures, and many animal studies indicate that a maternal diet rich in methyl nutrients may be able to mitigate some of the undesirable effects. For example, prenatal alcohol exposure results in lower birth weight, smaller head size, and abnormal reflex responses, all of which can be normalized by maternal folic acid or choline supplementation [135, 136]. In addition, many research studies conducted in rodents have reported that supplementing the maternal diet with methyl nutrients supports normal development of different regions of the nervous system [137–140]. These structural and morphological improvements may contribute to the better cognitive functions observed later in life. In humans, a higher intake of folate during pregnancy and an adequate maternal folate status are associated with better academic performance by the children, as reflected in a higher score on the receptive language test and the reading test [141–143]. In contrast, data on maternal choline or vitamin B12 status are more conflicting. One study [142] reported no relationship between vitamin B12 concentration in the maternal serum and score on a reading or block design test, whereas another study concludes a positive association between a math test score and maternal serum vitamin B12 concentration [144]. Additionally, a higher gestational choline intake was associated with modestly better child visual memory at age 7 years [145], and maternal choline and betaine status, rather than folate or vitamin B12, have been correlated with infant cognitive test scores [146], contradicting several studies which found no effect of supplementing choline or its metabolic derivatives in improving infant cognition [143, 147]. These mixed findings may be attributed to the differences in the study design, including the use of different cognitive tests, the age at which the child is evaluated, and the gestational time point at which maternal nutritional status and intake are assessed.

Defects in the metabolism of methyl nutrients may also be at the heart of fetal programming of adult-onset metabolic diseases. Interestingly, these programming effects appear to be sex-dependent. Male rats born to dams consuming a methyl-deficient diet during pregnancy are more insulin resistant at 6 and 12 months of age, as indicated by a higher HOMA-IR index [148]. Similar observations are reported in an epidemiological study conducted in India, which shows that children of mothers who have a high folate status but are deficient in vitamin B12 have increased adiposity and are at risk of developing type 2 diabetes [149].

This imbalance in folate and vitamin B12 status leading to the methyl trap phenomenon may prevent the regeneration of methionine from homocysteine, and subsequently impair protein synthesis and lean tissue deposition. Animal studies have also shown that maternal choline supplementation decreases prenatal stress-induced anxiety-related behaviors in the female offspring and social behavioral problems in the male offspring [150]. An intervention study [48] found that infants born to mothers consuming twice the current choline AI during the third trimester have lower cortisol concentration in their cord blood, indicating an attenuated hypothalamic-pituitary-adrenal (HPA) axis reactivity, which is associated with a lower susceptibility of developing stress-related metabolic diseases later in life. Other animal studies also suggest that extra choline during prenatal development slows tumor progression in the adult female offspring [151], and normalizes the increased systolic blood pressure and adiposity associated with maternal low-protein exposure [152]. These protective effects likely arise from epigenetic modifications in the placenta and other fetal compartments [48, 153]. In sum, these data illustrate the long-lasting benefits of methyl nutrients on the health of the offspring, and highlight the importance of an adequate dietary intake throughout pregnancy.

Potential Risks of Methyl Nutrient Supplementation

It is possible that some of the long-term health effects in response to maternal methyl nutrient supplementation during pregnancy may exhibit a U-shaped dose-response pattern, such that excessive intake of these nutrients also lead to adverse outcomes. Data from animal research suggests that a maternal diet high in methyl nutrients (folic acid, vitamin B12, and choline) may increase the risk of developing colitis and allergic diseases in the offspring [154, 155]. Further, several animal studies have shown that excessive intake of methyl-nutrients may promote weight gain and other metabolic disturbances by altering pathways involved in energy balance regulation [156]. Although human studies are limited, one study [157] found that high maternal plasma folate and vitamin B12 concentrations in the first trimester of pregnancy, but not folic acid supplementation or maternal genotype at the *MTHFR* 677C→T locus, are positively associated with the risk of developing atopic dermatitis in early childhood. Emerging evidence indicates that the development of the fetal immune system may be regulated through an epigenetic mechanism. Specifically, DNA hypermethylation as a result of the increased availability of the methyl nutrients may inactivate genes that control immune cell growth and function and skew the T cells toward an expression profile in favor of developing allergic diseases [155, 158]. While more research is needed to determine a safe upper limit for methyl nutrient intake during pregnancy, pregnant women should strive to consume recommended intake levels of these nutrients, as they have important roles in improving pregnancy outcomes and fetal development, as discussed throughout this chapter.

Conclusion

Ensuring adequate intake of one-carbon nutrients is essential for a healthy pregnancy. Pregnant women have higher requirements for folate, choline, and vitamins B6 and B12 that may not be easily met through the diet. Clinicians should be aware of the important biological functions of these nutrients and their emerging roles in the prevention and treatment of many adverse pregnancy outcomes. To help clarify the individual relationships between these nutrients and various pregnancy outcomes, gene–nutrient and nutrient–nutrient interactions must be taken into consideration when assessing variable responses to dietary interventions with one-carbon nutrients. Although further studies, notably human clinical trials, are required to confirm beneficial effects for many pregnancy outcomes, it is clear that one-carbon nutrients represent a promising area of research for improvement of both maternal and fetal health.

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Epigenetics and Diet in Pregnancy

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Keywords Pregnancy · Epigenetics · Diet · Famine · Obesity · Diabetes

Key Points

- Epigenetic processes are proposed as a key mechanism by which maternal nutrition influences offspring's life-long health.
- DNA methylation has been most widely studied.
- Maternal under-nutrition, over-nutrition and diabetes have been linked to epigenetic modifications in foetal tissues but more studies are needed to understand the long-term effects on child health.
- Further work is also needed to understand the role of epigenetic transmission of health across generations through the paternal line.

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Introduction

A healthy diet and good nutrition are important during pregnancy and for women who are planning pregnancy. Maternal nutrition impacts fertility, pregnancy outcomes, and foetal development in utero, and has a long-lasting influence on the offspring's health in later life through a phenomenon known as "foetal programming." [1] As described elsewhere in this book increased maternal nutritional demands and energy needs during pregnancy are due to the changes in maternal metabolism and the metabolic demands of the foetus. A healthy diet in pregnancy should thus ensure optimal foetal growth, maternal health, and ability to sustain lactation post-partum. In addition, much evidence from epidemiological studies has highlighted the importance of a healthy diet in pregnancy in the long-term health of the offspring [2–6]. In this chapter, we consider the evidence from studies supporting causal effects of maternal nutrition on offspring outcomes, mediated at least in part through changes in epigenetic processes, including alternations in DNA methylation.

What Is Epigenetics and Why Is it Important?

Epigenetic processes are emerging as key mechanisms through which the influence of developmental exposures is "remembered" with consequences on foetal development that persist into later life. Epigenetic mechanisms have been proposed to underlie the link between maternal nutrition in pregnancy and offspring outcome. Epigenetics are defined as modifications of DNA that occur without changing its sequence, but result in altered gene expression and function with subsequent changes in phenotype. The three main epigenetic mechanisms are DNA methylation, histone modification, and non-coding RNAs (Fig. 1) [7]. Of these, DNA methylation is the most widely studied in pregnancy.

DNA methylation occurs when a methyl (CH_3) group is added to a cytosine (C) nucleotide to form 5-methylcytosine (5mC). This occurs predominantly at cytosines in cytosine-guanine dinucleotide pairs, called CpG sites. Methylation of CpG sites is associated with maintenance of gene silencing. Clusters of CpG sites, known as CpG islands, are often unmethylated (so the DNA can be more easily accessed) and contain a number of known transcription start sites and transcription binding motifs [8]. There is evidence that DNA methylation is a key mechanism that reflects environmental changes. For example, DNA methylation and histone acetylation patterns in monozygotic twins are very similar in early life, but these patterns diverge with age due to differences in diet, physical activity, and/or smoking status [9, 10]. Comparison of the methylation patterns of genomes from blood samples from newborns and elderly individuals also show distinct methylation patterns at each end of the human lifespan, with increased hypomethylation at differentially methylated regions (DMRs) with increasing age [11].

DNA methylation during embryonic development is a complex process [8]. The zygote undergoes global demethylation before implantation, followed by re-methylation after implantation, apart from at CpG islands. Imprinted genes (see below) may be protected from this global demethylation process to distinguish

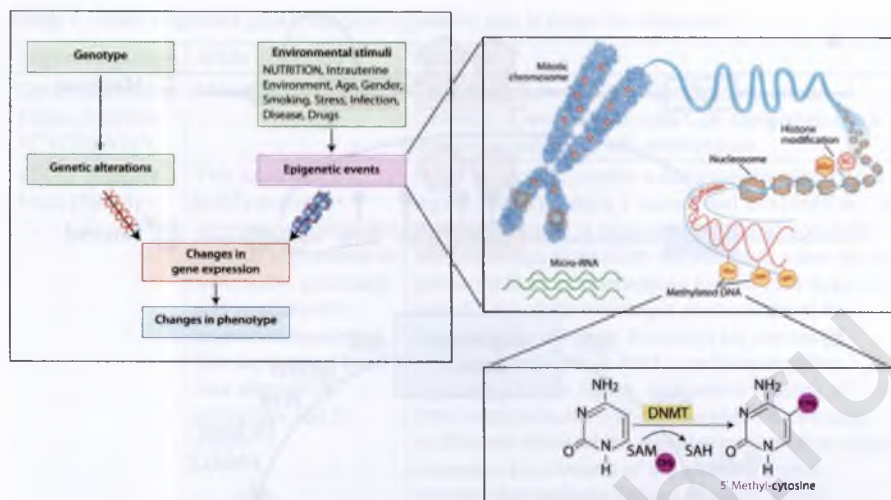


Fig. 1 Mechanisms of epigenetic events. Epigenetic events are thought to be caused by environmental factors, including nutrition. Genetic changes in DNA (genotype) can also cause epigenetic events. Both epigenetic and genetic changes will cause changes in gene expression which will affect the phenotype of the cell. Epigenetic events include DNA methylation, histone modification, and non-coding micro-RNA. DNA methylation occurs when cytosine is methylated in the 5' position to form 5-methyl cytosine. This reaction is catalysed by *DNA methyl transferases* (DNMT) with S-adenosyl-methionine (SAM) acting as a methyl donor. Histones are the four protein-pairs around which DNA is wrapped to form nucleosomes in chromatin. Two of these histone protein-pairs contain tails, which can be methylated or acetylated (as shown), or phosphorylated, ubiquitinated or sumoylated, all of which will affect the ease of access to DNA for gene transcription

between the maternal and paternal alleles. An increasing number of studies have examined whether DNA methylation patterns at birth reflect changes in the intrauterine environment, and have tried to link these to offspring health in later life. One such study of methylation patterns in umbilical cord blood identified several genes where DNA methylation in cord blood correlated with body composition in childhood [12].

Imprinted Genes

Most genes are inherited equally from both the father and mother and both copies are functional (i.e., can be expressed). In contrast, imprinted genes, of which there are ~100 in humans, are those that are expressed only from either the maternal or the paternal allele in a parent-of-origin effect [13]. The non-functional (imprinted) allele is silenced by methylation at imprinting control regions (ICRs) (Fig. 2a). Many imprinted genes are expressed in foetal tissues and the placenta, and are important in development and/or involved in metabolism (Table 1). In the placenta, maternally expressed genes limit foetal growth, whereas paternally expressed genes promote foetal growth. As expression of imprinted genes is sensitive to the intrauterine environment, they can influence placental size and nutrient transport to the foetus, thus regulating foetal growth and development (Fig. 2b) [14].

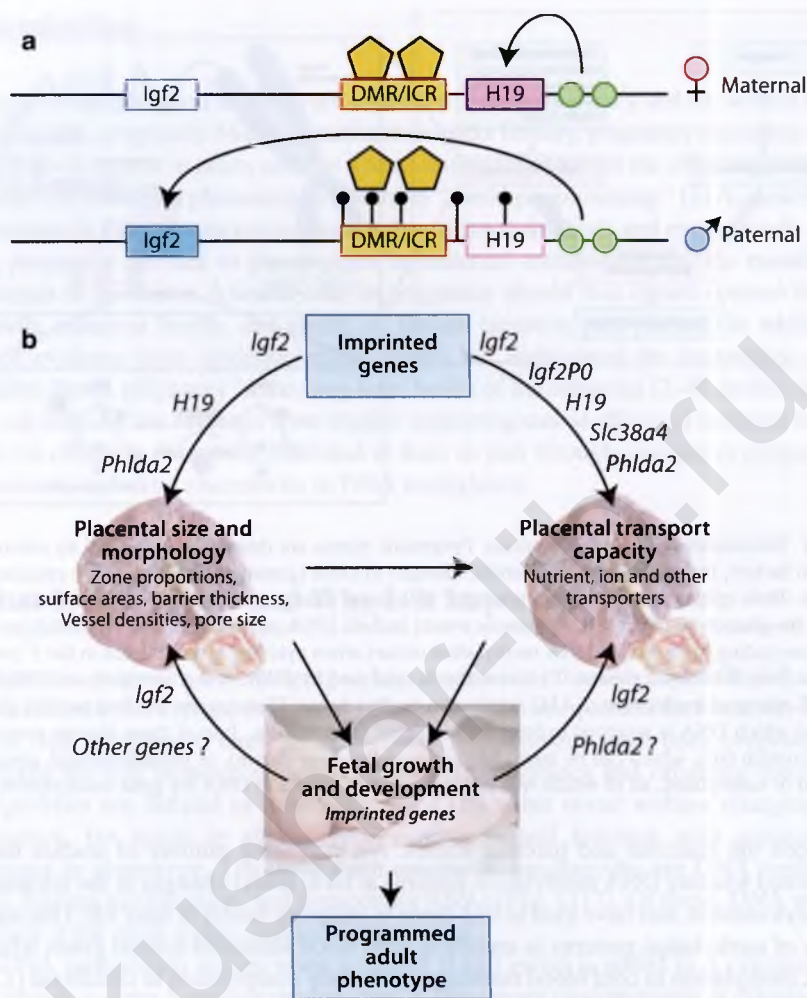


Fig. 2 Mechanisms of imprinted gene control. (a): Diagram of the imprinted genes *H19/IGF2* locus. The maternal (top) and paternal (bottom) alleles are shown. *Maternal allele*: the imprinting control region (ICR), also known as a differentially methylated region (DMR), is unmethylated and protected from being methylated by the binding of an insulator protein (denoted by yellow pentagons). Nearby enhancers (denoted by green circles) allows the maternally expressed *H19* gene to be expressed (filled box), while the paternally expressed *IGF2* gene is not expressed (unfilled box). *Paternal allele*: The paternal allele is methylated at the ICR/DMR so the insulator protein cannot bind and *H19* is not expressed (unfilled box). The enhancers act to enable expression of *IGF2* (filled box). (b): Diagram of the role of a number of imprinted genes in placental function and foetal growth, development and programming, all of which may affect the adult phenotype

Table 1 Some imprinted genes that have a putative role in foetal development

Imprinted gene	Allele expressed	Function ^a
Cyclin-dependent kinase inhibitor 1C (<i>CDKN1C</i>)	Maternal	The encoded protein is a tight-binding, strong inhibitor of several G1 cyclin/Cdk complexes and a negative regulator of cell proliferation
GNAS complex locus (<i>GNAS</i>)	This locus has a highly complex imprinted expression pattern. It gives rise to maternally, paternally, and bi-allelically expressed transcripts that are derived from four alternative promoters and 5' exons	Some transcripts contain a differentially methylated region (DMR) at their 5' exons, and this DMR is commonly found in imprinted genes and correlates with transcript expression. An antisense transcript is produced from an overlapping locus on the opposite strand. One of the transcripts produced from this locus and the antisense transcript are paternally expressed non-coding RNAs, and may regulate imprinting in this region. Alternative splicing of down-stream exons is also observed, which results in different forms of the stimulatory G-protein alpha subunit, a key element of the classical signal transduction pathway linking receptor–ligand interactions with the activation of adenylyl cyclase and a variety of cellular responses
H19 (<i>H19</i>)	Maternal	The product of this gene is a long non-coding RNA which functions as a tumour suppressor
Insulin-like growth factor (<i>IGF2</i>)	Paternal	This gene encodes a member of the insulin family of polypeptide growth factors, which are involved in development and growth. IGF2 is influenced by placental lactogen and plays a role in placental and foetal development
Maternally expressed gene 3 (<i>MEG3</i>)	Maternal	Long non-coding RNA, involved in control of angiogenesis
Mesoderm specific transcript (<i>MEST</i>)	Paternal	This gene encodes a member of the alpha/beta hydrolase superfamily. The loss of imprinting of this gene has been linked to certain types of cancer and may be due to promoter switching. The encoded protein may play a role in development
Neuronatin (<i>NNAT</i>)	Paternal	The protein encoded by this gene is a proteolipid that may be involved in the regulation of ion channels during brain development. The encoded protein may also play a role in forming and maintaining the structure of the nervous system. This gene is found within an intron of another gene, bladder cancer associated protein, but on the opposite strand
Paternally expressed gene 3 (<i>PEG3</i>)	Paternal	Human PEG3 protein belongs to the Kruppel C2H2-type zinc finger protein family. PEG3 may play a role in cell proliferation and p53-mediated apoptosis. PEG3 has also shown tumour suppressor activity and tumorigenesis in glioma and ovarian cells

(continued)

Table 1 (continued)

Imprinted gene	Allele expressed	Function ^a
Paternally expressed gene 10 (<i>PEG10</i>)	Paternal	This gene is expressed in adult and embryonic tissues (most notably in placenta) and reported to have a role in cell proliferation, differentiation, and apoptosis. Knockout mice lacking this gene showed early embryonic lethality with placental defects, indicating the importance of this gene in embryonic development
Pleckstrin homology like domain family A member 2 (<i>PHLDA2</i>)	Maternal	Plays a role in regulating placenta growth
Pleiomorphic adenoma gene-like 1 (<i>PLAGL1</i>)	Paternal	This gene encodes a C2H2 zinc finger protein that functions as a suppressor of cell growth. Overexpression of this gene during foetal development is thought to be the causal factor for transient neonatal diabetes mellitus (TNDM)

^aInformation from Genecards, www.genecards.com

Imprinting has been well characterised in rodents, but not all observations are transferrable to humans, as many genes that are imprinted in mice are not imprinted in humans [15]. Nevertheless, there is evidence that changes in imprinted gene methylation or expression have phenotype effects on the offspring in humans. For example, increased expression of the imprinted gene pleckstrin homology-like domain, family A, member 2 (*PHLDA2*) in umbilical cord was related to reduced birthweight in an Asian Chinese population. In addition, in low birthweight babies, the paternally expressed gene-10 (*PEG10*) was found to be hypermethylated with lower expression than in samples from normal weight babies [16].

Why Might Diet in Pregnancy Influence Epigenetic Processes?

It is conceivable that nutrition in pregnancy influences epigenetic processes, because key micronutrients, which are important for foetal development, are also methyl donors, and thus contribute to the one-carbon (1-C) metabolism pathway (Fig. 3). These include folic acid, vitamins B6 and B12, choline, betaine, methionine, and homocysteine from a variety of dietary sources (Table 2). These nutrients are particularly important in pregnancy, but there is evidence that levels should be maintained throughout life [17].

The Royal College of Obstetricians and Gynaecologists (RCOG) and the Antenatal Care Guideline by the National Institute for Health and Clinical Excellence (NICE) recommend that all women who are planning a pregnancy take 400 µg/day of folic acid [21, 22]. Folic acid supplementation should be continued during the first trimester until approximately 12 weeks gestation in order to reduce the risk of neural tube defects [23]. Higher doses (5 mg) are recommended for high-risk groups, e.g., obese mothers. Folate has effects on neural development during pregnancy through interactions with vitamin B12, methionine, and homocysteine (Fig. 3). Folate is also important for the methylation of DNA and histones in normal developmental path-

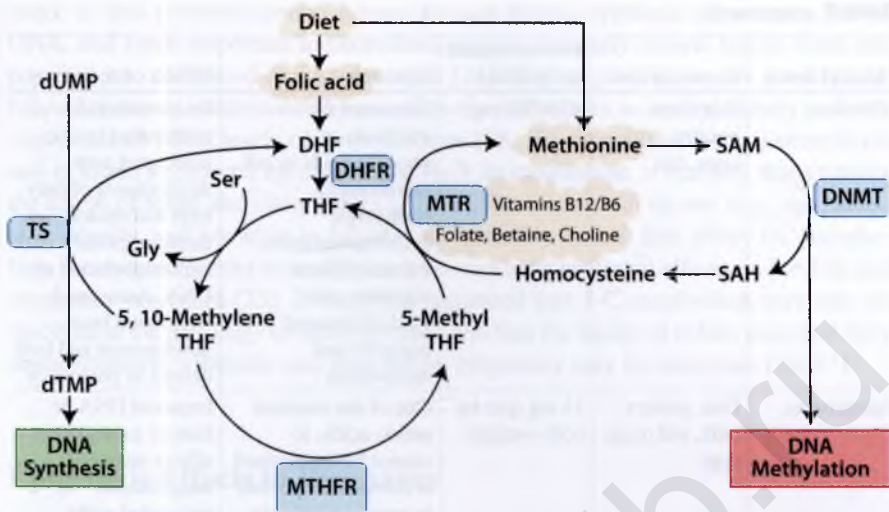


Fig. 3 One-carbon (1-C) metabolism. Folic acid and methionine are both obtained from the diet. Folic acid is inactive, and so is converted to its active forms dihydrofolate (DHF) and tetrahydrofolate (THF) by *dihydrofolate reductase* (DHFR). THF is converted to 5,10-methylene THF with the donation of a methylene group from serine, which is in turn converted to glycine. 5,10-methylene THF is then converted to 5-methyl THF by *methylene tetrahydrofolate reductase* (MTHFR). 5,10-methylene THF interacts with DNA synthesis via *thymidylate synthase* (TS) and is converted back into DHF. Methionine is an essential amino acid that is converted to S-adenosyl methionine (SAM), which in turn donates its methyl groups to DNA as part of the DNA methylation process, catalysed by different *DNA methyl transferases* (DNMT). SAM becomes S-adenosyl homocysteine (SAH) which can act as an inhibitor for DNMTs. SAH is converted to homocysteine, which is a neurotoxin. Homocysteine is converted back to methionine by the donation of methyl groups from 5-methyl THF (shown here) but these can also be given by folate, betaine, choline, and vitamins B6 and B12, catalysed by *methyl THF reductase*. Enzymes are denoted as blue squares; factors obtained from the diet are shown in the pale clouds

Table 2 Methyl donors important in 1-C metabolism and their dietary sources [17–20]

Methyl donor	Source in diet	Recommended daily intake	Function	Effects of deficiency
Folate (vitamin B9)	Green leafy plants; fortified bread and cereals; whole grains, beans, fruit and vegetables	400 µg	Important for biosynthesis of DNA	Anaemia, depression, birth defects in pregnancy; global hypomethylation of DNA
Betaine	Wheat bran wheat germ, spinach, beets; stored in liver and kidney	100–400 mg	Important for energy and lipid metabolism and protein synthesis. Acts as an osmolyte: Regulates cell volume and stabilises proteins	Associations with heart disease and obesity

(continued)

Table 2 (continued)

Methyl donor	Source in diet	Recommended daily intake	Function	Effects of deficiency
Choline	Red meat, poultry, milk, eggs, fish	450–550 mg	Important for synthesis of phospholipids in cell membranes, cholinergic neurotransmission, transmembrane signaling and lipid-cholesterol transport and metabolism	Reduced hepatic methionine levels; associated with development of fatty liver and muscle damage; global hypomethylation of DNA. Associated with foetal brain development and birth defects in pregnancy
Methionine	Fish, poultry, milk, red meat, eggs	15 mg (per kg body weight)	One of the essential amino acids, so cannot be synthesised in humans. Important in protein synthesis; Converted to S-adenosylmethionine (SAM)	Impaired DNA or histone methylation affects neuronal homeostasis; associated with intellectual disability, schizophrenia, autism, depression, and neurodegeneration
S-Adenosyl methionine (SAM)	Synthesised from methionine (not available from the diet)	–	Major methyl donor of the cell; involved in DNA methylation, synthesis of phosphocholine; involved in actions of neurotransmitters, carnitine, creatinine and antioxidants	Impaired DNA or histone methylation affects neuronal homeostasis; associated with intellectual disability, schizophrenia, autism, depression, and neurodegeneration
Homocysteine	Metabolite of methionine	–	Converted by folate, choline and betaine to methionine to reduce toxicity	High concentrations associated with folate and vitamin B12 deficiency
Vitamin B6 (pyridoxine)	Fortified cereals, beans, poultry, fish, and some vegetables and fruits, especially dark leafy greens, papayas, oranges, and cantaloupe	1.3–1.7 mg	Important in converting homocysteine to methionine	Possible association with heart disease due to build-up of homocysteine
Vitamin B12 (Cobalamin)	Fish, poultry, meat, eggs, or dairy; fortified breakfast cereals and enriched soy or rice milk	2.4 µg	Important in converting homocysteine to methionine	Neurological difficulties (e.g., memory loss, hallucinations, tingling in arms and legs)

ways; it also provides methyl groups for use during synthesis of proteins, RNA, DNA, and lipids important in neurodevelopment and early growth before birth and possibly into childhood and adolescence [24]. The micronutrients are interrelated: folate deficiency is attenuated by use of choline or betaine as methyl donors and vice versa, and all affect levels of homocysteine [18, 19]. Homocysteine is a neurotoxin and is usually removed by conversion back to methionine, a reaction that requires the action of folate and vitamin B12 [17, 20]. Environmental factors (e.g., age, nutrition, obesity, and smoking in females and possibly males) that affect 1-C metabolism for about 6 months around conception can have profound effects on fertility and pregnancy outcomes [25]. It has been suggested that 1-C metabolism may also be involved in the aetiology of schizophrenia and that the intake of folate, essential fatty acids, retinoids, vitamins, and iron during pregnancy may be important [26, 27].

Epigenetic Effects in Pregnancy

The Agouti mouse model has been used for epigenetic studies of intrauterine effects that act early in gestation [28]. This model utilises a retrotransposon inserted near the upstream long-terminal repeat (LTR) of the Agouti (A^y) gene that controls coat colour. Hypomethylation of the DMR on the LTR in early development leads to expression of the gene, with a yellow coat and obese phenotype; hypermethylation of the DMR leads to suppression of gene expression, with a dark coat and lean phenotype. This model is ideal to investigate effects of environmental exposures during pregnancy (including diet) on maternal, but not paternal, epigenetic inheritance [29]. A study of genetically identical Agouti mice showed that exposure to the chemical bisphenol-A (BPA, present in many plastics) led to an increase in yellow-coated offspring. When BPA-exposed dams were given dietary supplements of methyl donors (folic acid, vitamin B, choline chloride, and betaine) the effect was reversed and the offspring had dark coats [30], highlighting the link between maternal diet and epigenetic processes.

Subsequent studies using the Agouti mouse model have shown that alcohol exposure during pregnancy also directly affects DNA methylation gene expression and the phenotype of the offspring [31], as well as affecting a number of other neurotoxic mechanisms [32]. Indeed, other toxic exposures to the foetus, including maternal smoking, adversely affect a number of pathways involved in growth and development through epigenetic mechanisms in both the placenta and cord blood. A recent meta-analysis of 13 offspring cohorts (6685 newborns) exposed to maternal smoking during pregnancy and their controls showed that a large number of CpG sites ($n = 6073$) were significantly differentially methylated (false discovery rate [FDR] at 5 %) and 568 of these CpG sites survived Bonferroni correction. Differential methylation of some of these CpG sites ($n = 4473$) was maintained in older children ($n = 3187$) in separate cohorts. Differentially methylated CpG sites occurred on numerous loci and affected many different pathways. These data show that, in addition to the direct effects of cigarette smoke-derived toxins, smoking during pregnancy has epigenetic effects, which may help to explain the many detrimental effects on the offspring [33].

Micronutrients and Epigenetic Effects

A number of studies have demonstrated links between maternal micronutrients in the diet and offspring DNA methylation. Methylation at the *H19/IGF2* locus in cord blood of offspring is linked to maternal folic acid intake before and/or during pregnancy. There was no difference in methylation of *IGF2*, but hypomethylation of *H19* occurred with increasing folic acid intake [34]. Maternal intake of vitamin B2 (riboflavin) was positively correlated with methylation levels of *PLAGL1*, which in turn correlated with offspring weight and BMI at 1 year of age [35]. Another study found an association between vitamin B6 (pyridoxal phosphate) and methylation levels of *MEG3*; vitamin B6 levels were associated with offspring weight gain between birth and 3 years of age, but only in males [36]. A more recent and larger epigenome-wide study also showed differential methylation of a number of genes, most of which were hypomethylated with increasing folic acid intake. The pathways that were affected were not specific to 1-C metabolism, nor were they imprinted, but they were pathways related to birth defects, neurological function, and embryogenesis [37].

Under-nutrition in Pregnancy

The Dutch Hunger Winter Family Study highlights the impact of under-nutrition in pregnancy on offspring outcomes [38], with recent evidence consistent with underlying epigenetic mechanisms. During World War II, between November 1944 and March 1945, the Netherlands experienced a period of famine due to a reduction in rations (bread and potatoes). In November 1944, people were living on less than 1000 kcal/day; by April 1945 intake was as low as ~500 kcal/day. Food supplies were restored in May 1945 after liberation. Early studies showed that birthweight, crown-to-heel length, and head circumference were all lower in offspring exposed to famine in late gestation compared with those exposed in early gestation [39]. In follow-up studies, there was an increased risk of obesity at aged 19 years in individuals exposed in early, but not late gestation [40], suggesting a critical window of exposure to nutrient deficiencies in pregnancy. Under-nutrition in the first or second trimesters of gestation was also associated with impaired glucose tolerance and insulin resistance at 58 years of age [41], increased prevalence of coronary heart disease and diabetes [42], and in women, increased total cholesterol levels [43]. Exposure to famine around conception or early in pregnancy may have also influenced mental health in the offspring: exposure to famine in the first trimester of gestation was associated with poorer employment outcomes, possibly due to lower cognitive ability and increased hospitalisation [44], as well as addiction to drugs or alcohol, but only in males [45].

Recent studies have suggested that epigenetic mechanisms may underpin these effects. Peri-conceptual exposure to famine was associated with decreased DNA

methylation of five CpG sites within the imprinted *IGF2* gene in blood samples collected from individuals ~60 years after famine exposure [46]. These findings are consistent with early-life epigenetic changes persisting throughout life. Examining epigenome-wide methylation patterns, six DMRs were associated with prenatal famine exposure. These occurred at genetic regulatory regions and mapped to genes involved in early development and growth, as well as those affecting metabolic functions [47]. Further DNA methylation analysis of individuals exposed during specific 10-week periods of gestation showed that differential methylation of four CpG sites were associated with exposure to famine during the first 10 weeks of gestation. These CpG sites were located on or near genes involved with cell growth and differentiation, nutrient supply, and cholesterol metabolism. Although the absolute methylation differences were small, the subsequent effect on outcomes is of moderate but clinically relevant effect [48]. However, the Dutch famine represents an example of extreme under-nutrition in pregnancy, and so the relevance of these observations to more normal variations in maternal diet is not known.

Over-nutrition in Pregnancy

Obesity is a recognised global problem with a significantly adverse impact on health. Recent data from the World Health Organization (WHO) has shown that in 2014, around 39 % of adults over 18 years old were overweight [49]. The Global Burden of Disease Study 2013 [50] showed that the prevalence of overweight women increased from 29.8 % in 1980 to 38.0 % in 2013. Numerous studies have shown that maternal obesity is associated with increased risk of complications during pregnancy [3, 51, 52]. In addition, maternal obesity has been associated with longer-term adverse outcomes in the offspring, including cardiovascular disease and premature mortality [53, 54], mental health problems [55], and increased susceptibility to allergies and atopic disease [56]. Insights from experimental studies support causal effects of maternal obesity on offspring outcomes, mediated at least in part through changes in epigenetic processes, including alternations in DNA methylation [57].

An increasing body of evidence links maternal obesity with DNA methylation changes in placenta, umbilical cord, or cord blood, and in several studies these methylation changes have been correlated with offspring outcomes in later life. Using a candidate gene approach, changes in DNA methylation in key genes involved in metabolism have been observed in association with maternal obesity and/or gestational diabetes mellitus (GDM), shown in Table 3 [58–63].

One group studied DNA methylation and gene expression in the blood of offspring of obese women before and after they had undergone bariatric surgery. Mothers who had undergone surgery were older but had significantly improved nutritional and anthropometric measurements, as did their offspring. Differential DNA methylation and gene expression was observed between offspring whose

Table 3 Candidate gene studies of methylation in pregnancy

Gene	Function	Tissue and patient group	Epigenetic changes	Reference
Retinoid X receptor alpha (<i>RXRα</i>)	Nuclear receptors mediating the effect of retinoids. Regulate epithelial cell growth and activation of tumour suppressor genes	Cord tissue from healthy neonates	Hypermethylation in cord tissues correlates with childhood adiposity. Higher methylation associated with lower maternal carbohydrate intake during pregnancy	[58]
Leptin (<i>LEP</i>)	The fullness hormone made by adipose tissue. Acts on the arcuate nucleus of the hypothalamus to regulate appetite and energy metabolism	Placenta from women without GDM, PCOS, or familial hypocholesterolaemia	Methylation of leptin gene on foetal side of placenta inversely associated with maternal glucose levels. Methylation of leptin gene on maternal side of the placenta directly associated with maternal glucose levels. Leptin gene methylation correlated with gene expression on both sides of the placenta	[59]
		Placenta and cord blood from mother-child dyads	Lower DNA methylation at specific CpG sites on <i>LEP</i> associated with maternal glycaemia and higher cord-blood Leptin levels	[60]
Adiponectin (<i>ADIPOQ</i>)	Hormone involved in regulating glucose levels and fatty acid breakdown	Placenta from women without GDM, PCOS, or familial hypocholesterolaemia	Lower methylation on foetal side of placenta associated with higher maternal glucose levels. Lower methylation on maternal side of the placenta was associated with higher maternal insulin resistance. No expression of <i>ADIPOQ</i> detected in placenta	[61]

Table 3 (continued)

Gene	Function	Tissue and patient group	Epigenetic changes	Reference
ATP-binding cassette transporter A1 (<i>ABCA1</i>)	Involved in transport of cholesterol from cells to apolipoproteins A-1	Placenta from women without GDM, PCOS, or familial hypocholesterolaemia and offspring cord blood	<i>ABCA1</i> DNA methylation on maternal side of placenta correlated with maternal HDL-cholesterol and glucose levels. <i>ABCA1</i> DNA methylation in cord blood negatively correlated with maternal glucose levels	[62]
Peroxisome-proliferator-activated receptor γ coactivator 1 α (<i>PPARGC1A</i>)	A transcriptional coactivator that regulates genes involved in energy metabolism	Placenta from Chinese women with or without GDM	Maternal glucose levels were correlated with DNA methylation levels of specific CpG sites on <i>PPARGC1A</i> in placenta, but negatively with DNA methylation on <i>PPARGC1A</i> in cord blood	

mothers had surgery and those who had not. These genes were involved in pathways involved in diabetes or autoimmune or vascular diseases [64]. Further analysis of this cohort showed that genes involved in IL-8 signalling were differentially methylated and expressed, which correlated with inflammatory markers [65].

Other groups have used DNA methylation arrays, comparing placenta and/or cord blood from women with GDM or blood from their offspring in childhood. Initial studies found differential DNA methylation on specific genes, but these did not reach genome-wide significance [66–68]. A more recent genome-wide DNA methylation study found significantly differentially methylated sites in placental and cord blood samples from South Asians living in the UK, as these are more susceptible to GDM. KEGG pathway analysis showed enrichment of pathways involved in endocytosis, MAPK signalling, and extracellular triggers to intracellular metabolic processes [69].

A few studies have looked at the effects of over-nutrition on DNA methylation of imprinted genes. One study looked at 14 imprinted genes in cord blood of offspring whose mothers developed GDM and found significant, but small, differential DNA methylation in *MEST*, which was decreased in GDM-exposed offspring [70]. Others found significantly increased DNA methylation at the *GNAS* locus in the cord blood of GDM-exposed offspring, but no differences at DMRs in *IGF2* [71]. DNA methylation of *IGF2* in cord blood was decreased in offspring of obese mothers compared to those of lean mothers. The decreased methylation correlated with increased *IGF2* protein levels in the same cord blood samples, and the elevated *IGF2* levels

were associated with a higher birthweight, suggesting that variations in DNA methylation may affect protein levels of IGF2, which in turn has down-stream consequences [72]. Increased DNA methylation of the *H19* gene in cord blood samples has been associated with obesity at 1 year of age [73].

Paternal Effects and Transgenerational Effects

While the main focus of this chapter is on *maternal* nutrition in pregnancy, there is some evidence that the *paternal* diet may also influence offspring outcomes through epigenetic mechanisms impacting on sperm [74]. Paternal obesity may also affect methylation levels of DMRs of known paternally expressed imprinted genes. DMRs of *IGF2* [75] and *MEST*, *NNAT*, and *PEG3* [76] were hypomethylated in cord blood from the offspring of obese fathers. All changes were small (4–5%), but remained after adjustment for confounding factors, and were present at a level consistent with changes in gene expression or function. Analysis of DNA methylation at imprinted genes in sperm showed that obese men had differential DNA methylation at specific imprinted genes compared with lean men, suggesting that such changes might influence offspring development [77].

There is now evidence that epigenetic processes can act over several generations, particularly through the paternal line. From the Dutch Hunger Winter cohort, the offspring (F2 generation) of women exposed in utero (F1 generation) were found to have a higher ponderal index than offspring of F1-unexposed women [78], suggesting persisting effects of the famine exposure across generations. Some epigenetic traits, possibly those involved in imprinting, may be passed between generations. There are specific time-points in life at which important mechanisms occur that might have more of an effect than others, e.g. the pre-pubertal slow growth period, which is when the sperm development occurs, and hence, may affect the paternal lineage [79]. Nutrition during this slow growth period has been shown to affect the cardiovascular and obesity risks of subsequent grandchildren, as overeating during this time in paternal grandfathers was associated with increased risk of diabetes in their grandchildren [80]. Another study investigated grandparent nutrition and longevity of their grandchildren, and found that the nutrition of paternal grandmothers affected granddaughters, whereas nutrition of paternal grandfathers affected grandsons. For both, better nutrition in the grandparent was associated with poorer survival in the grandchild [81]. Similar results were obtained in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, which looked at food supply during the slow growth period and the mortality of the grandchildren. While there did not seem to be any effect of maternal grandparent food supply during the slow growth period on their grandchildren's mortality, there was a paternal grandparent same-sex effect, with paternal grandfathers affecting their grandsons and the paternal grandmothers affecting their granddaughters. Interestingly, the better the food supply for the paternal grandparents, the higher the mortality for their grandchildren [82]. Thus, changes in nutrition during sperm development as well as conception may have an effect on subsequent generations.

Conclusions

Pregnancy is an optimal time when women focus on their own health and that of their developing child. Moreover, the nutritional status and diet of the mother at conception and during pregnancy can have long-lasting effects on the long-term health of the child. Increasing evidence suggests that both under-nutrition, over-nutrition, or deficiencies in key micronutrients is associated with DNA methylation changes in placenta, umbilical cord, or cord blood, and that these changes are linked to longer term health outcomes in the offspring. Encouraging women to have a healthy diet is therefore of vital importance. Government initiatives such as “Healthy Start” in the UK target women from a low-income background who are unable to access adequate amounts of food [83]. This scheme provides multivitamins to pregnant women during the antenatal period, women with a child under 12 months, and children aged 6 months to 4 years. The Healthy Start women’s multivitamins contain the recommended daily intake of 400 µg of folic acid, 10 µg of vitamin D, and 70 mg of vitamin C. In order to promote healthy eating, Healthy Start vouchers will enable these vulnerable families access to vegetables and fruits, milk, and infant formula. Such initiatives are small but important steps toward improving health of mothers and their offspring.

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<http://2015.studentblogs.med.ed.ac.uk/reproductivesystems5/>.

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Part III
High-Risk Pregnancies

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Management of Obesity in Pregnancy

Hope Barkoukis

Keywords IOM gestational weight gain guidelines · Gestational weight gain · Obesity in pregnancy · Maternal nutrient needs

Key Points

- Maternal obesity, defined by a mother's pre-pregnancy body mass index (BMI) of ≥ 30 kg/m², is a major risk factor for a wide range of maternal and fetal complications;
- The mother's pre-pregnancy BMI is the single greatest predictor of gestational weight gain (GWG) being within the Institute of Medicine's guidelines;
- The 2009 and updated 2015 Institute of Medicine GWG guidelines recommend a range of 5–9 kg for obese mothers;
- Data demonstrate that lifestyle interventions including close monitoring of weight status, use of motivational interviewing, food diaries, and frequent interventions have shown the strongest favorable impact on GWG being within guideline recommendations for obese mothers;
- Obese mothers with GWG most closely aligning with the Institute of Medicine's guidelines have the most successful outcomes with the least amount of complication risk for both mother and fetus.

Introduction

Optimal maternal and child health is foundational, and an important predictor of the future health of our country's citizens. For this reason, *Healthy People 2020* includes major federal government public health initiatives specifically related to improving maternal and infant health [1]. These initiatives include reducing morbidity and

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mortality of pregnant women; decreasing fetal, neonatal, and infant mortality; increasing earlier access to prenatal care; focus on preventative preconception measures; and decreasing the number of elective deliveries that occur prior to 37 weeks and are classified as preterm births [1].

Preconception health of the mother is critical to increasing the chances of a healthy pregnancy with a lowered risk of adverse outcomes. The Centers for Disease Control and Prevention (CDC) has developed a variety of recommendations designed to improve preconception health, and some of these guidelines include dietary supplementation of folic acid (400–800 mg daily) prior to and during the early stages of pregnancy, assessment of iron status to reduce the risk of iron-deficiency anemia, multivitamin-mineral supplementation to improve micronutrient status, and achieving a healthy pre-pregnancy weight [2]. A body mass index (BMI) between 18.5 and 24.9 kg/m² is used by health organizations as an inexpensive and easily determined method of defining a normal, healthy body weight range for adults based on reduced risk of mortality. A BMI of ≤ 18.5 kg/m² is classified as underweight, the overweight range is 25–29.9 kg/m², obese I is 30–34.9 kg/m², obese II is 35–39.9 kg/m², and obese III is ≥ 40 kg/m² [3].

Obesity: A High Risk Obstetric Condition

Globally, the increased prevalence of overweight and obese adults has translated into the reality that currently the most common high-risk obstetric condition facing the clinician is maternal obesity [4]. Maternal obesity is defined by the mother's *pre-pregnancy* BMI of ≥ 30 kg/m². A mother's BMI during pregnancy is not the clinical criteria used for obesity because of the physiologic changes associated with pregnancy, including increases in total body water [5]. In fact, the correlation between pregnancy BMI and body composition of the mother decreases from $r^2 = 0.86$ pre-gravid to $r = 0.54$ by the third trimester [6].

Maternal obesity is a major risk factor for maternal and fetal complications, including mortality, miscarriage, gestational diabetes, cesarean delivery, stillbirth, macrosomia, preeclampsia, and pregnancy-induced hypertension [4]. Macrosomia, defined as term birth weight ≥ 4000 or 4500 g, proportionally increases as maternal BMI increases, and is associated with neonatal hypoglycemia, birth traumas, and severe asphyxia [7]. Infants born to mothers who are obese have increased risks of spontaneous and indicated preterm birth, neonatal death, being large-for-gestational-age, and having later life complications including diabetes mellitus and cardiovascular disease [8]. Using the largest US data set available, from 38 states representing 86% of US live births (3,412,436 births in 2013), it was determined that approximately 25% had pre-pregnancy BMIs classified as overweight and 21% were within obese categories as follows: obese I (12.4%); obese II (5.5%); and obese III (3.5%). Obesity rates were highest among American Indian and Alaskan Native (32.5%) and non-Hispanic black mothers (30.5%) [9].

Obese adolescents experience the same complications as do their adult obese counterparts [10]. It is currently recommended that adolescent pregnancies follow the IOM's pre-pregnancy BMI guidelines for gestational weight gain (GWG), unless the mother is \leq age 16 [11]. Many teen pregnancies are unplanned, so early prenatal care emphasizing the important role of optimal nutrition for the mother and infant is critical.

Maternal Obesity and Metabolic Complications

Mothers who begin their pregnancy obese are more likely to be insulin resistant as compared to normal-weight women, but both groups will experience an approximately 50% decrease in insulin sensitivity during gestation [5]. This occurs secondary to a post receptor defect causing a decreased ability of insulin to mobilize GLUT 4 from the cell interior to the cell surface. Additionally, the role of human placental lactogen (HPL), cytokines, and elevated lipid concentrations have also been identified as important factors correlated with the reductions in insulin sensitivity observed with advancing gestation [5]. The obese mother will therefore be at risk for a constellation of symptoms referred to as the metabolic syndrome of pregnancy. In addition to the reduction in insulin sensitivity, low-grade inflammation and an increased risk for disturbances in macronutrient metabolism are present. The decreased insulin sensitivity relates not only to glucose metabolism, but to lipid metabolism as well [12]. Basal triglycerides, free fatty acids, and cholesterol significantly increase with advancing gestation as insulin is unable to appropriately suppress lipolysis in late gestation. Additionally, using a variety of study models, it is recognized that the presence of obesity and insulin resistance set the stage for the 10–15% increased risk for preeclampsia observed in obese mothers, although the precise mechanisms are not well defined [13]. The decreased insulin sensitivity appears in early gestation and persists to at least three months postpartum [13].

Obesity and Gestational Diabetes

Obese mothers are also at high risk for overt type 2 diabetes during their pregnancy, or gestational diabetes mellitus (GDM). Compared to women with normal BMIs, the odds ratio to develop GDM for overweight, class I, and class III obesity were 1.97, (95% CI: 1.77–2.19), 3.01 (95% CI: 2.34–3.87), and 5.55 (95% CI: 4.27–7.21), respectively [14]. The metabolic defects of decreased insulin sensitivity coupled with inadequate insulin response contribute to this complication. In the USA, approximately 200,000 new cases of GDM are diagnosed each year, representing approximately 14% of all pregnancies [14]. This figure is expected to rise as the International Association of Diabetes and Pregnancy Study Groups consensus panel recently identified new diagnostic criteria for GDM as follows [14]:

- At the first antenatal visit, using either fasting plasma glucose (FPG), HbA1c or a random plasma glucose sample (RPG), the diagnosis is based on FPG between 5.1 and 7.0 mmol/l. A diagnosis of overt diabetes is based on one of these values: FPG ≥ 7.0 mmol/l, HbA1c $\geq 6.5\%$, or RPG ≥ 22.2 mmol/l.
- At 24–28 weeks gestation: A 2-h 75 g oral glucose tolerance test (OGTT) is conducted. GDM is diagnosed with \geq one abnormal value: FPG ≥ 5.1 mmol/l, 1-h value of ≥ 10 mmol/l, or a three-hour value of ≥ 8.5 mmol/l.

Factors Influencing Gestational Weight Gain (GWG)

Numerous factors including ethnicity, age, cultural beliefs, smoking status, socioeconomic status, mother's prepregnancy weight, and physical activity can influence GWG. Prepregnancy BMI, however, is considered the single best predictor of GWG with mean values for underweight and normal weight mothers within recommended IOM guidelines, while more than half of overweight and obese women had GWG higher than these recommendations [15]. After adjustments for prepregnancy weight, African American mothers, as contrasted to Caucasian women, gained an average of three to four times more weight [16].

In a recently published review assessing factors associated with excessive GWG in more than five studies of nulliparous women from different ethnicities, the odds of excessive GWG was 2.5 times more likely in obese compared to normal-weight women and three times more likely in overweight women [17]. That study also showed that socioeconomic status, independent of race and ethnicity, influenced GWG. Women of lower socioeconomic status have an obesity prevalence of 29% as contrasted to 42% of those at less than 130% of the poverty line. Also, having a college degree was protective against excessive GWG for non-Hispanics, but did not make a difference in Hispanic women [17].

The psychosocial factors that influence GWG include a woman's perception of self, her belief in self-empowerment, and her body image [17]. A woman's sense of feeling attractive in mid-pregnancy and fat in late pregnancy was associated with lower total GWG, while perceptions of lower levels of attractiveness in early and mid-pregnancy were related to higher GWG. Additionally, greater perceived disparity between a woman's actual versus ideal body size was associated with greater total GWG.

Many studies have consistently demonstrated that limited or reduced physical activity is associated with excessive GWG, whereas maintaining physical activity during pregnancy, unless medically contraindicated, is associated with lower rates of GWG [17]. The majority of these studies unfortunately did not differentiate among BMI categories. Physical activity when supervised and done in combination with a high-intensity dietary intervention was successful in achieving GWG within IOM guidelines in obese and overweight women [18]. Guidelines for physical activity in pregnant women do exist. The current recommendation from the US Department of Health and Human Services is 150 min of moderate intensity

aerobic activity per week for healthy pregnant women [19]. Moderate physical activity will also assist in the management of constipation often associated with pregnancy [20].

In the plethora of observational studies assessing the role of dietary factors and GWG, several have noted a significant association between total caloric intake, energy density of dietary components, intake of fried foods, and excess GWG. Lower GWG has been associated with higher dietary fiber intake and a plant-based dietary pattern [17]. Generally speaking, the wide array of outcome measures and the broad heterogeneity of intervention types have resulted in a failure to identify a consistent or significant effect of a particular lifestyle intervention on GWG. In a recent meta-analysis of 13 trials, lifestyle interventions that had the strongest favorable impact on GWG in obese and overweight women were those that included close monitoring of weight status, used motivational interviewing, and employed high-intensity dietary interventions that included food diaries to modify individual dietary behavior [21]. Interventions using only generic educational materials or a singular dietary counseling session were only effective in managing GWG in women with normal pre-pregnancy BMI values [22].

Gestational Weight Gain Guidelines

In the 1970s, the American College of Obstetricians and Gynecologists (ACOG) published the first GWG guidelines [23]. Their recommendation was for a total pregnancy weight gain of 10 kg, in contrast to the prevailing customary practice by physicians of recommending 6.8 kg. In 1990, the IOM derived GWG guidelines for obese non-pregnant women, recommending a gain of at least 6.8 kg during pregnancy [24].

From 1990 to 2009, there was a significant increase in the percentage of the population of women of child-bearing ages classified as overweight and obese ($BMI \geq 25.0 \text{ kg/m}^2$), from 37% in 1990 to 59.5% in 2009 [25]. Recommendations for GWG published by the IOM in 2009 were based upon the mother's pre-pregnancy BMI and are shown in Table 1 and at the following link: <http://www.nationalacademies.org/hmd/~media/Files/Report%20Files/2009/Weight-Gain-During-Pregnancy-Reexamining-the-Guidelines/Report%20Brief%20-%20Weight%20Gain%20During%20Pregnancy.pdf>

Table 1 IOM guidelines for gestational weight gain

Pre-pregnancy BMI	Recommended total Gestational weight gain (Lb)
<18.5	28–40
18.5–24.9	25–35
25–29.9	15–25
≥ 30	11–20

The 2009 IOM guidelines reflect a change from a more open-ended weight recommended to a specific range of GWG of 5–9 kg for obese mothers. These 2009 guidelines utilized data on six outcomes as the basis for the maternal weight gain recommendations including small-for-gestational-age percentile (SGA; defined as weight for gestational age below the tenth percentile), large-for-gestational-age percentile (LGA; defined as weight for gestational age above the ninetieth percentile), preterm birth (PTB), cesarean birth, postpartum weight retention (PPWR), and childhood obesity [26].

A strength of the 2009 IOM GWG guidelines was that a multidisciplinary expert committee reviewed all available empirical evidence related to maternal and fetal outcomes to weigh the benefits and risks of high and low GWG by pre-pregnancy BMI. The committee focused on the principle of “doing no harm”; a quantitative risk analysis was conducted, and the resulting guidelines reflected conservative, yet evidence-based guidance [27]. The IOM guidelines were criticized for not delineating more clearly GWG for the various classes of obesity, although the paucity of data in this regard was cited as the reason for this lack of specificity [8]. The guidelines also did not adjust for maternal age or parity, which were recognized as limitations of the report.

Adherence to GWG Guidelines and Outcomes

In a recently published study, nearly 6000 obese women who delivered ≥ 36 weeks were classified based on their adherence to GWG IOM guidelines [26]. Those with GWG above guidelines had increased cesarean sections, gestational hypertension, and macrosomia. GWG less than recommendations were associated with less LGA infants. Minimal weekly GWG, less than the IOM weekly guidelines based on pre-gravid weight, was associated with increased spontaneous preterm birth and more SGA infants. Excessive weekly GWG was associated with increased preterm birth, cesarean section, preeclampsia, neonatal intensive care unit admission, and macrosomia [28].

In a systematic review of 18 studies using five electronic databases from 2009 through July 2014, obese women who gained amounts less than recommended by the IOM had increased odds of preterm birth and SGA, with reduced odds of LGA, macrosomia, cesarean birth, preeclampsia, and gestational hypertension [8]. Aside from an increased risk for SGA and cesarean births in obesity class I, researchers did not observe a graded effect with GWG less than guidelines with any other adverse outcomes with higher obesity classes. Furthermore, when equal weight was mathematically applied to all five outcome variables as originally identified by the IOM, the lowest adverse outcomes were associated with a loss of 7.6 kg or 0.19 kg/week over a 40-week gestational period.

In another recently published study, 10,734 obese women who delivered at 12 different hospitals were categorized according to weight change during pregnancy: weight loss, weight maintained, appropriate GWG using IOM guidelines, or excessive

GWG using IOM guidelines. Maternal and fetal outcomes were then compared to 3112 normal-weight pregnant women. Regression techniques were used to adjust for confounding variables. Across these four weight categories, the average overall change in weight for obese mothers ranged from loss of 7.21 pounds (7.92–6.5) to a gain of 6.1 pounds (5.95–6.25); in the weight maintenance category, an appropriate average weight gain of 15.97 pounds (15.86–16.09 range); and 35.92 pounds, (35.61–36.23) gained in the excessive GWG category. Chronic hypertension and smoking behaviors were noted to be greatest in the weight maintenance and weight-loss categories. Matching the population of obese pregnant women to normal-weight women revealed the following statistically significant associations with pregnancy weight changes and outcomes [29]:

- Obese women who lost weight had a twofold greater risk of low birth weight infants, reflecting a mean decreased infant birth weight of 63 g;
- Adverse outcomes for obese women who did not achieve the IOM GWG guidelines were related to neonate weight, specifically increased risk for low birth weight infants;
- Obese women who gained excessive weight had more than two times the risk of preeclampsia and hypertension, four times the risk for macrosomia, a mean decreased APGAR score at 5 min of 0.09, and an increased infant birth weight of 134 g;
- A trend toward increased odds of preterm birth, without reaching significance;
- The preterm birth rate in all weight change categories did not exceed the national rate of 11.38%.

These authors concluded that their data add to a growing body of information indicating that using weight recommendations *less* than the IOM guidelines for obese women may result in significantly improved maternal and neonatal outcomes [29]. The modest weight loss they observed of 7.21 pounds translates into a total loss of approximately 18–20 pounds when the infant's weight, placenta, and fluid are considered [29]. According to the authors, this ultimately reduced the mother's BMI and had potential to decrease negative long-term health outcomes. They also suggested that repeated fetal ultrasounds could be conducted to monitor fetal growth. In 2013, the American College of Obstetrics and Gynecology made the suggestion that an obese woman who was gaining less than the IOM guidelines for GWG with an appropriately gaining fetus may have an improved benefit as contrasted to following their GWG guidelines [30]. Yet, by 2015 the American College of Obstetricians and Gynecologists (ACOG) provided updated guidelines on the management of obesity in pregnancy and specifically advised that *obese mothers should not gain less than the IOM GWG, even those in the more severe classes of obesity* [31].

When reviewing these recent studies of outcomes from obese women with GWG inconsistent with the IOM 2009 guidelines, specifically *less* GWG than recommended, the important missing narrative is an appreciation for the potential for irreversible effects on these infants who were born SGA. Specifically, SGA is associated with poor school performance, impairments in cognitive and neurodevelopmental performance, or both [32, 33].

There must also be an appreciation for the metabolic implications of these infants' birth body compositions on health in later life. In a recently available secondary analysis of the Maternal Fetal Medicine Networks Study from Catalano's group, 1053 overweight and obese women who either gained greater than the IOM recommendations or 188 women who lost weight or only gained ≤ 5 kg were studied [10]. This study was quite unique in that neonatal morphometry and body composition were identified as primary outcome measures. Trained staff performed the anthropometric measures for neonatal body composition using validated equations as described in their study [10]. In women who gained ≤ 5 kg, infants born had significantly lower birth weights and lengths, with less lean mass, fat mass, percent body fat, and head circumferences as contrasted to women who gained more than 5 kg. Subsequent to all adjustments for the mothers' prepregnancy BMIs, smoking status, parity, glucose tolerance status, gender, and gestational ages at delivery, these differences remained. The odds ratio for SGA remained significantly different at 2.6 (95% CI: 1.4–4.7, $p = 0.003$). Further analysis of obese/overweight study subjects who lost weight during their pregnancy revealed that, in those neonates, there were significant reductions in birth weight, lean body mass, fat mass, percent body fat, head circumference, and proportionally less SGA infants. These results remained significant regardless of the mother's GDM status.

It is clear that the lifelong metabolic consequences of infants born with less lean mass and decreased head circumference are certainly unknown at this time. Will this decreased lean mass impact risk of metabolic dysfunction in later life? At this time, it is impossible to know with certainty, however more studies are needed to understand the full impact on the infant of overweight or obese mothers who gain less than the minimum IOM guidelines or lose weight during pregnancy.

A recent publication from Berggren et al. focused on the correlations between GWG and maternal accrual of lean and fat mass in 49 overweight/obese pregnant women [15]. Inadequate GWG, defined as ≤ 5 kg weight gain, was associated with significantly lower maternal lean body mass accrual. Furthermore, the changes in body composition accompanying GWG varied by IOM guideline adherence. Women with excess GWG accrued weight reflecting 60% lean mass and 40% fat mass, while those adhering to guidelines accrued weight as 96% lean mass and only 4% fat mass. Those who had inadequate weight gain lost fat mass and accrued lower lean mass. The authors speculated that the 1.6 kg difference in lean mass accrual in mothers with inadequate gain may be the link to explain why the infants born to these mothers were SGA. The authors emphasized that appreciating body composition changes associated with GWG is critical to understanding the metabolic impact of adherence or noncompliance with IOM GWG guidelines. In particular, excess fat mass accumulation secondary to excess GWG may be the driver of adverse metabolic complications both for the mother and the infant. Their data clearly demonstrated that excess GWG reflected fat and not lean mass accrual. Excess GWG as fat mass is a significant factor in postpartum weight retention and likely impacts pregravid weight status prior to a subsequent pregnancy [34]. Focusing discussions

solely on the broad category of GWG without inclusion of maternal and fetal alterations in body composition limits our understanding of the long-term clinical consequences of non-compliance to the IOM GWG guidelines [15].

Secondary to insufficient available data, the IOM 2009 guidelines did not include nor support a specific lower limit of weight gain for the specific classes of obesity. They determined that insufficient evidence was available to ascertain whether the appropriate physiologic, metabolic, and endocrine changes associated with normal pregnancy would occur in the face of obese/overweight women who lose or fail to gain the minimum 5 kg during gestation. They concluded that secondary to caloric insufficiency, weight loss or low weight gain in obese women may have long-term consequences for the neurologic development of the infant. There was not sufficient evidence to identify all potential adverse outcomes [35, 36].

To summarize, best clinical practice related to GWG should support the IOM 2009 guidelines. At this time, weight loss and lifestyle interventions can be most safely addressed either before or after gestation in the best long-term health interest of the mother and child [15, 27, 37].

Recommendations for Management of Maternal Obesity: General

- Every pregnant woman, but in particular those who enter pregnancy at an overweight or obese BMI, should be seen by a social worker in addition to their obstetrician and/or primary health care provider. The social worker can assess socioeconomic and environmental factors that may adversely impact an optimal pregnancy outcome. Referral to specific food assistance programs such the Women's, Infants and Children's program (WIC) [<http://www.fns.usda.gov/wic/women-infants-and-children-wic>] and the Supplemental Nutrition Assistance Program (SNAP) [<http://www.fns.usda.gov/snap/supplemental-nutrition-assistance-program-snap>] may be warranted.
- A nutrition assessment conducted by a registered dietitian/nutritionist is also critical to understanding nutrition risk. Nutrition risk assessment should include adequacy of nutrient intake, cultural and religious practices, chronic diseases with nutritional implications, weight stability, history of dieting practices or eating disorders, meal patterns, food allergies and dietary restrictions, cravings, aversions, use of pica (consumption of non-food items such as toilet paper, ice, etc.), alcohol intake, tobacco use, use of dietary supplements, and intake of sugar-sweetened beverages [38].
- Studies have shown that when too much nutrition advice is offered at one sitting or is conflicting or unclear, mothers become confused and this becomes a barrier to adherence [39]. Therefore, after a dietary assessment of the mother's current dietary practices, identify high-priority nutrition changes and avoid trying to recommend achieving a comprehensive dietary overhaul [39].

- The 2015 clinical management guidelines from the ACOG indicated that weight management medications are not recommended during pregnancy nor during the time of conception because of concerns regarding adverse effects and safety [31].
- Under the guidance of clinical exercise physiologists, or physical therapists and/or occupational therapists, obese and overweight pregnant women should be encouraged to follow an exercise regimen, unless medically contraindicated [31].

Recommendations for Maternal Nutrient Needs

Energy

Energy recommendations are based upon resting metabolic rate (RMR), the thermic effect of food (TEF), physical activity, and the deposition of maternal tissues and fetal growth during pregnancy. Current energy guidelines from the IOM are based on trimester and the mother's preconception weight. For the overweight/obese mother, no additional calories are recommended during the first trimester, an additional 450 kcal/day during the second trimester, and 350 additional kcal/day during the third trimester [40]. Considerable individual variability exists, and ultimately the best assessment of adequate energy intake is to monitor GWG [41, 42].

Macronutrient Recommendations

The IOM recommendation for an acceptable macronutrient distribution range for non-pregnant and pregnant females is identical: 10–35% of total calories from high-quality, lean protein, 45–65% of total calories from high-quality carbohydrates, and 20–35% of calories from fat. For fat type, the emphasis is placed on sources of the essential fatty acids linoleic and α -linolenic acid as well as choline [42]. The amounts of essential fatty acids available to the fetus are dependent on the maternal diet and should include 13 g/day of omega 6 fatty acids and 1.4 g/day of omega 3 fatty acids. Omega 6 fatty acids are plentiful in the American diet and can easily be found in oils, nuts, and seeds, while long-chain omega 3 fatty acid-containing food sources include seafood—particularly fatty fish such as salmon, tuna, sardines, anchovies—and some plant sources such as walnuts and flax seeds [43, 44].

The Food and Drug Administration (FDA) recommends that pregnant women consume 8–12 oz. of fish weekly including salmon, shrimp, pollock, tuna (light), catfish, and cod. [<http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm>]

Choline recommendations of 450 mg daily during pregnancy could be met from no- and low-fat milk and dairy products (~40 mg/8 oz.), eggs (126 mg/egg), peanuts (20 mg/1 oz.), spinach (171 mg/cup), mushrooms (157 mg/cup), and tofu (100 mg/3 oz.) [40].

Protein

High-quality, lean dietary protein is required for fetal development, maternal and placental tissue, and to support the expansion of blood volume, breast tissue, and uterine development. Daily protein recommendations for pregnant women are increased from the non-pregnant state of 0.8 g/kg of body weight to 1.1 g/kg of body weight [42]. It is most critical to obtain all necessary essential amino acids from daily dietary protein, and at-risk populations would include vegans, mothers with excessive nausea and vomiting, and those experiencing food insecurity [42].

Micronutrients

Nutrient reference guidelines, called Dietary Reference Intakes (DRIs), have been established by the IOM for healthy individuals from infancy through age 70 years, and include recommendations during pregnancy and lactation [42]. Dietary recommendations for total daily calories, essential micronutrients, and important food components such as dietary fiber are included in this report. Tables of DRI values and the evidence to support these recommendations are available online at <http://www.iom.edu/dri>. All micronutrient recommendations are increased for pregnant versus non-pregnant females >19 years of age, except for vitamins E, K, and D. No reports of vitamin E deficiency in pregnancy were available to the IOM, therefore recommendations did not change for pregnancy. Vitamin K recommendations were based on observations of adequate intake at the observed median values, so recommendations remained the same for non-pregnant and pregnant women. Lastly, vitamin D recommendations during pregnancy were not changed; however, individuals with a high BMI are recognized as a population at risk for deficiency secondary to the sequestration of the vitamin in adipose tissue [42]. Accordingly, vitamin D status using 25-OH-D3 should be assessed in obese and overweight pregnant women, with the goal of achieving plasma levels greater than 20 nmol/l [45].

During pregnancy, most health care providers will recommend a prenatal vitamin and mineral supplement to ensure adequacy of these micronutrients. The IOM micronutrient recommendations are based on the associated micronutrient needs of the growing fetus and maternal needs, and not the mother's preconception BMI.

Iron

Increased iron needs are necessary for fetal and placental tissue production, as well as the increased production of hemoglobin during pregnancy. Since iron-deficiency anemia increases the risk for adverse outcomes of pregnancy, the CDC recommends screening for iron adequacy during each trimester [46]. A daily dietary supplement of iron is usually provided to women during their first trimester at a level of 30 mg/daily if hemoglobin measures were normal during their preconception assessment, or 60–100 mg daily for those who present with low hemoglobin levels [46].

Iron supplements are often associated with gastrointestinal side effects including constipation and possibly nausea. Stool softeners and dietary fiber may help with the constipation, while nausea may be reduced if the supplement is taken following a meal. Absorption of the iron will be increased with concurrent consumption of a vitamin C source and avoidance of taking the iron supplement at the same time as consuming a calcium source [46].

Dietary Fiber

The recommendation by the IOM for dietary fiber during pregnancy is 28 g/day. Advice should be given to focus on whole-grain carbohydrates; high-fiber cereals; whole fruits, vegetables, legumes, nuts and seeds; and increase ingestion of non-caffeinated sources of fluids. Fiber supplements containing psyllium such as Metamucil® or Konsyl® or those containing methylcellulose such as Citrucel® can be safely taken upon physician approval. Emphasizing consumption of dietary fiber will assist in the management of constipation experienced by about 50% of women during pregnancy, and may aid in maintenance of blood glucose control [47].

Conclusion

The ideal management of obesity during pregnancy begins prior to a planned pregnancy. There should be screening and treatment as necessary for metabolic disease such as hypertension, glucose intolerance, and hyperlipidemia. While optimizing pre-pregnancy weight is the ideal, there are data to suggest that even as little as a 5% decrease in weight in obese individuals can improve metabolic function [31]. An appropriate diet or healthy eating pattern as described previously is the cornerstone for management of obesity during pregnancy, with consideration given to micronutrient supplements as necessary. Regular exercise such as walking 30 min a day should be encouraged. Notably, the issues of obesity during pregnancy extend beyond the nine months of gestation, and management should be recognized as a lifelong process for the short- and long-term health of the mother and her offspring.

Hence, an interdisciplinary approach with health care professionals that include physicians, RNs, RDs, PTs OTs, and social workers is integral to weight management during pregnancy and the prevention of future metabolic problems.

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Pregnancy and Weight Loss Surgery

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Keywords Bariatric surgery · Weight loss surgery · Gastric bypass · Sleeve gastrectomy · Gastric band · Lap Band · Biliopancreatic diversion · Duodenal switch · Pregnancy · Nutrition

Key Points

- The prevalence of severe obesity continues to increase with a corresponding rise in bariatric surgery.
- After bariatric surgery, patients may suffer from nutritional deficiencies due to decreased oral intake or malabsorption.
- Multiple types of bariatric operations are performed around the world, with sleeve gastrectomy being the most common one in the USA as of 2018.
- Female bariatric patients are generally counseled to avoid pregnancy during the first year or more after surgery due to a theoretically increased risk of nutrition-related problems.
- Post-bariatric nutritional deficiencies may include macronutrients or micronutrients.
- An understanding of post-bariatric surgery nutrition recommendations is important for management of the pregnant bariatric surgery patient.

Introduction

As of 2012, more than 1 in 3 adults were obese, defined as a body mass index of 30 kg/m² or more. More than 2 in 3 adults were either overweight or obese. Current projections by the Centers for Disease Control and Prevention (CDC) suggest that 1 in 3 adults could have diabetes by 2050 [1].

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The single intervention with demonstrated long-term efficacy for the severely obese is bariatric surgery. A consensus statement from the National Institutes of Health (NIH) in 1991 recognized bariatric surgery as a safe and effective treatment option for the severely obese patient [2]. Following the publication of this report, the national interest in bariatric surgery increased dramatically. In 2014, it was estimated by the American Society for Metabolic and Bariatric Surgery that more than 193,000 bariatric operations were performed in the United States [3]. Of all bariatric operations, the most common type was sleeve gastrectomy (SG, 51.7%) followed by Roux-en-Y gastric bypass (RYGB, 26.8%). Adjustable gastric band (Lap-Band) comprised less than 10% of all bariatric procedures by 2014 [3].

This chapter addresses the indications for bariatric surgery, the types of surgical procedures available, and the impact of bariatric surgery on pregnancy. Additionally, we review the common side effects and nutritional sequelae of bariatric surgery. Finally, we address the nutritional recommendations for pregnant women who have undergone bariatric procedures.

Considerations for Bariatric Surgery

Bariatric surgery is reserved for individuals who are severely obese as defined by body mass index, or BMI. The BMI is calculated by dividing a patient's weight in kilograms by the square of their height in meters. Alternatively, BMI can be calculated by taking the patient's weight in pounds and dividing it by the square of their height in inches, then multiplying by 703. BMI is measured in units of kg per meters squared (kg/m^2). A BMI between 18 and 25 kg/m^2 is considered normal. Individuals are considered candidates for bariatric surgery when their BMI is greater than 40 kg/m^2 , or greater than 35 kg/m^2 with one or more comorbidities including severe hypertension, obstructive sleep apnea, or diabetes. For most patients, this BMI corresponds to being approximately 45 kg (100 lbs) or more above ideal body weight [4].

Types of Bariatric Surgery

A number of different bariatric procedures are currently performed in the United States.

Roux-En-Y Gastric Bypass

Roux-en-Y gastric bypass (RYGB) has historically been considered the “gold standard” bariatric operation, and was the most common bariatric procedure performed in the United States until 2013 (Fig. 1). In the RYGB, a surgical stapler is used to

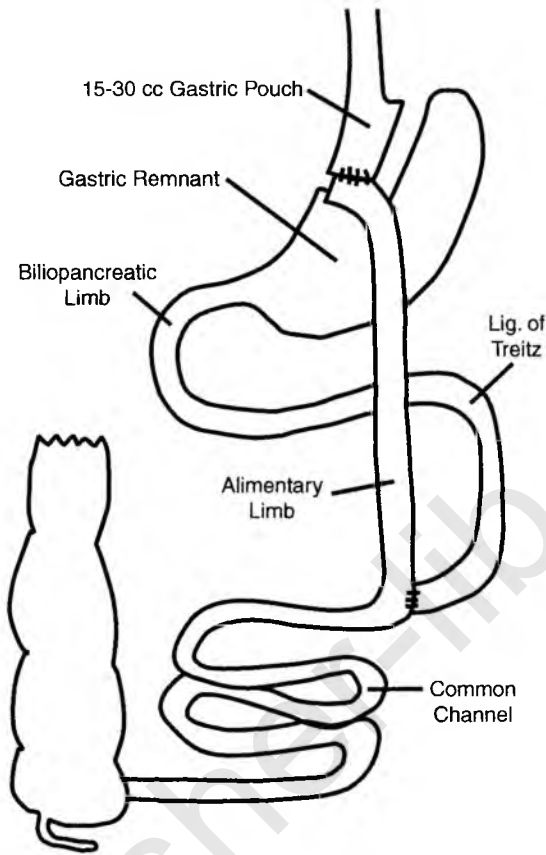


Fig. 1 Diagram of the Roux-en-Y gastric bypass operation. (Image ©2005 Daniel M. Herron, reprinted with permission)

divide the stomach into a small upper pouch and a large gastric remnant. The upper pouch, only 15–30 ml in volume, causes the patient to feel full after eating a small meal. The small intestine is reconnected in a Y shape to the gastric pouch in such a manner that the ingested food bypasses the stomach, duodenum, and proximal jejunum. In addition to the volume restriction caused by the small pouch, the RYGB causes weight loss by altering both absorption and levels of hormones involved in weight maintenance, such as insulin and ghrelin [5].

Adjustable Gastric Band

The adjustable gastric band (AGB) was almost as commonly performed as the RYGB as recently as 2011, but dropped in popularity due to its limited efficacy and high incidence of reoperation due to inadequate weight loss, mechanical

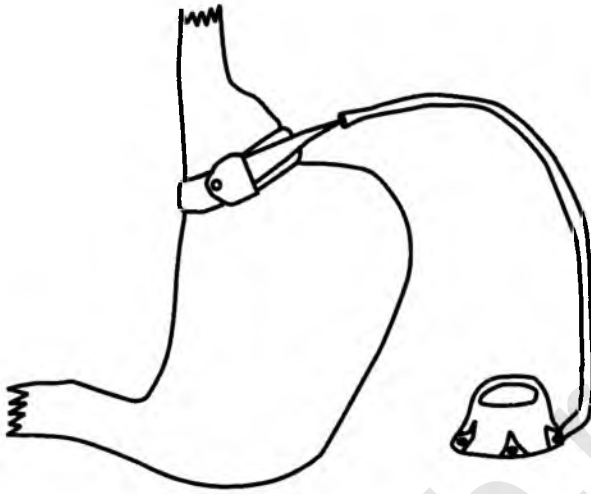


Fig. 2 Diagram of the adjustable gastric band. (Image ©2005 Daniel M. Herron, reprinted with permission)

malfunction, or other complication (Fig. 2) [3]. In this operation, commonly referred to as the Lap-Band (Apollo Endosurgery, Austin, TX), a small adjustable ring made of silicone rubber is wrapped around the upper portion of the stomach, creating a pouch of 15–20 ml volume [6].

The band is connected, via a thin flexible tube, to an access port placed underneath the skin on the abdominal wall. By injecting or withdrawing saline from the access port, the band can be tightened or loosened and the amount of restriction adjusted. Unlike the RYGB, the AGB does not involve any division or reconnection of the stomach or intestines.

Vertical Banded Gastroplasty

Vertical banded gastroplasty, also known as VBG or “stomach stapling,” was at one time the most common bariatric operation, but has essentially disappeared from clinical practice due to its poor long-term results [7]. Like the adjustable gastric band, the VBG serves to decrease the volume of food that a patient can eat at one sitting. Unlike the gastric band, the VBG cannot be adjusted. While VBG is no longer performed, many patients with a history of “stomach stapling” in the 1980s or 1990s may still be encountered clinically.

Sleeve Gastrectomy

In 2013, the sleeve gastrectomy (SG) eclipsed the RYGB to become the most popular bariatric procedure performed in the USA (Fig. 3) [3]. It was originally performed as the first stage of a two-stage duodenal switch procedure, but was found to produce sufficient weight loss that it could serve as a stand-alone procedure [8]. It has now become the main surgical treatment option for severely obese patients in the USA and many other countries [9]. The popularity of SG was shown in a study which sent questionnaires to the heads of the 50 member societies of the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) [10]. The results showed that SG comprised 0.0% of the global total number of bariatric procedures in 2003, 5% in 2003, and 28% in 2011. As of 2014, sleeve gastrectomy comprises 51.7% of all bariatric operations performed in the USA [3].

Part of the reason for the popularity of the SG is that the operation itself is technically straightforward. The surgeon removes approximately two-thirds of the left side of the stomach, resulting in a smaller stomach that is tube- or sleeve-like.

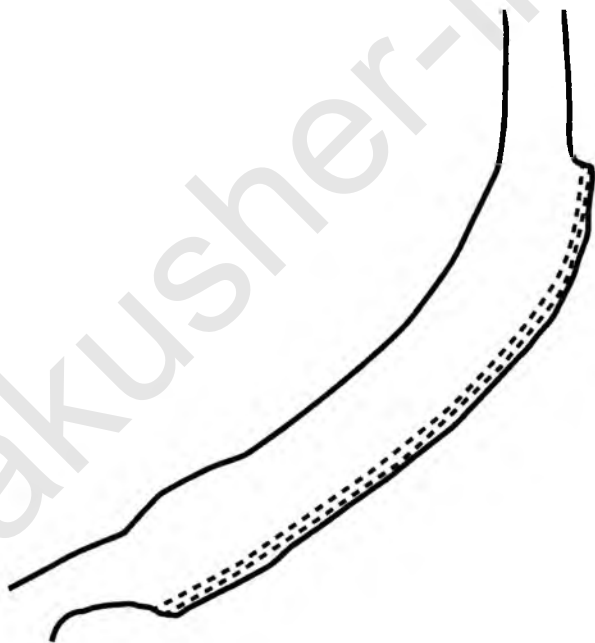


Fig. 3 Diagram of the sleeve gastrectomy. (Image ©2005 Daniel M. Herron, reprinted with permission)

Because the operation is almost always performed via laparoscopic approach, the procedure is commonly referred to as laparoscopic sleeve gastrectomy (LSG).

In this operation, the patient is placed under general anesthetic on a split-leg operating table [11]. Approximately five laparoscopic trocars are used to gain access to the abdominal cavity. The surgeon mobilizes the entire left side, or “greater curvature” of the stomach, up to the junction of the stomach and the esophagus. The size of the sleeve gastrectomy is calibrated by placing a sizing tube or “bougie” through the patient’s mouth down into the stomach. A linear surgical stapler is then placed adjacent to the bougie and serially fired until the left side of the stomach is completely separated. The transected stomach is then removed through a 15 mm trocar site. Some surgeons may use staple-line reinforcements or oversewing suture to potentially decrease the risk of bleeding or leakage from the staple line. An intra-operative leak test may be performed either by instilling air or methylene blue dye into the banana-shaped stomach and looking for extravasation. Some surgeons feel endoscopy may be particularly helpful as it can also help to visualize leaks and intragastric bleeding. Finally the trocars are removed and the larger trocar sites are closed with suture. The patient is typically kept in the hospital for one or two nights. Follow-up evaluations are performed within the first month, then several times during the first year and annually thereafter [11].

Historically, SG has been thought to cause weight loss by restricting energy intake due to reduced gastric capacity. However, some studies suggest that SG also causes weight loss via hormonal modulation. These mechanisms are not fully understood, but it is thought that SG causes faster gastric emptying and thus faster satiety [12]. A reduction in hunger drive may also be because SG resects the ghrelin-secreting cells lining the fundus [13]. Therefore SG appears to cause weight loss by neurohormonal pathways as well as by gastric restriction.

Because the SG operation is technically simple and relatively non-invasive, it can be used on super-obese patients where a more complex operation like RYGB might prove to be too technically difficult [8]. If the patient has not achieved sufficient weight loss (usually 50 kg or more) after 1 year or more, a more extensive operation like the RYGB or duodenal switch may be performed as a “second stage.”

Other reasons for the popularity of the SG are that it avoids foreign bodies, immediately restricts caloric intake, and requires only a short in-patient stay [14]. The SG also requires a relatively short operation time [15]. Also, unlike gastric banding, no adjustments are required after the initial surgery. SG is also suitable for high-risk patients, such as patients with anemia, Crohn’s disease, or other conditions, because it does not involve an intestinal bypass. A further advantage of SG is that it successfully resolves obesity comorbidities. A 2016 study from Israel found that diabetes was resolved in 79% of patients undergoing SG, hypertension was resolved in 85%, and obstructive sleep apnea in 98% [16].

SG has a low incidence of postoperative complications and fewer complications than other bariatric procedures [17]. The surgical morbidity rate of SG is around 6%

[18]. Furthermore, SG seems to be a safe and effective option for morbidly obese women who want children, according to a study examining 13 pregnancies in patients who had lost weight due to an SG [19]. The study found that all pregnancies went well: no baby died or had congenital anomalies, and no mother developed pregnancy-induced hypertension or diabetes.

However, the SG does have disadvantages. One disadvantage of the procedure is its irreversibility [11]. Once the left side of the stomach has been removed, it cannot be put back into place. Another disadvantage is that a relatively long staple line is required, which can potentially lead to leaks or bleeding.

Biliopancreatic Diversion with Duodenal Switch

The least common and most complex bariatric operation performed in the United States is the biliopancreatic diversion with duodenal switch (BPD-DS, Fig. 4) [20]. The BPD-DS consists of an SG combined with the bypass of a substantial portion

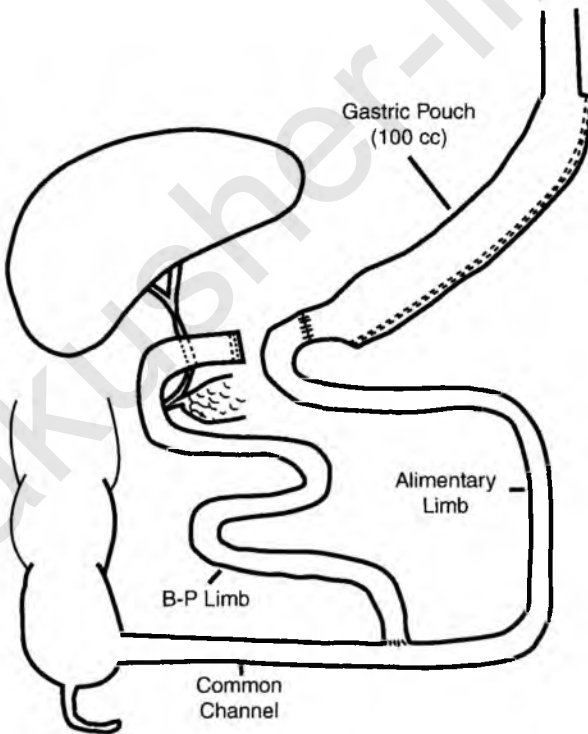


Fig. 4 Diagram of the biliopancreatic diversion with duodenal switch (BPD-DA). (Image ©2005 Daniel M. Herron, reprinted with permission)

of the small intestine. The first portion of the duodenum is divided and reconnected to the distal 250 cm of small intestine. Additionally, bile and pancreatic secretions are diverted to the distal ileum, the BPD-DS results in moderate volume restriction and significant malabsorption. While providing the best long-term weight loss of any bariatric operation, the BPD-DS causes the most nutritional disturbance.

Weight Loss After Surgery and Postoperative Recommendations for Pregnancy

The rate of weight loss after surgery varies with the type of procedure. A large meta-analysis of surgical interventions for weight loss reported a mean excess weight loss regardless of operation of 61.2% [21]. Specifically, excess body weight loss was 47.5% for patients who underwent AGB, 61.6% for those who underwent RYGB, and 70.1% for those who had BPD-DS. Another study with three-year weight outcomes from a bariatric surgery registry in a large integrated healthcare system showed excess body weight loss of 37% for patients who underwent ABG, 66.5% for those who underwent RYGB, and 65% for those who had SG [22]. In a Korean study, 12 women saw their mean BMI fall from 35.1 ± 3.5 to 24.9 ± 2.3 kg/m² after undergoing an SG procedure [19]. Another study found patients lost 56% of excess weight on average, 1 year after their SG surgery [23].

With the RYGB and BPD-DS, the most rapid weight loss occurs during the first 3 weeks after surgery, when patients typically lose one pound per day or more. The rate of weight loss gradually decreases until weight stabilizes, about 12–18 months after surgery [24].

Studies into SG have reported a mean excess weight loss of between 40% and 60% at 1 year and between 50% and 83% at 5 years [23]. Weight loss after AGB occurs at a slower rate, but may continue for 2–3 years after surgery. Most bariatric surgeons recommend that female patients avoid pregnancy for a period of 18 months or more after their operation or until their weight has stabilized.

Nutrition Deficiencies After Weight-Loss Surgery

Deficiencies in vitamins and other nutrients are common after bariatric surgery, particularly with RYGB and BPD-DS, since these operations result in decreased intestinal surface area and bypass the duodenum (Fig. 5). Since BPD-DS results in more significant malabsorption than does RYGB, there are more nutrient deficiencies reported among BPD-DS patients.

Although not as prevalent, nutritional deficiencies have also been reported after AGB and SG, primarily because of decreased food intake and the avoidance of certain nutrient-rich foods because of individual intolerances. The risks of nutrient deficiency are lower with SG because the procedure leaves intestinal absorption

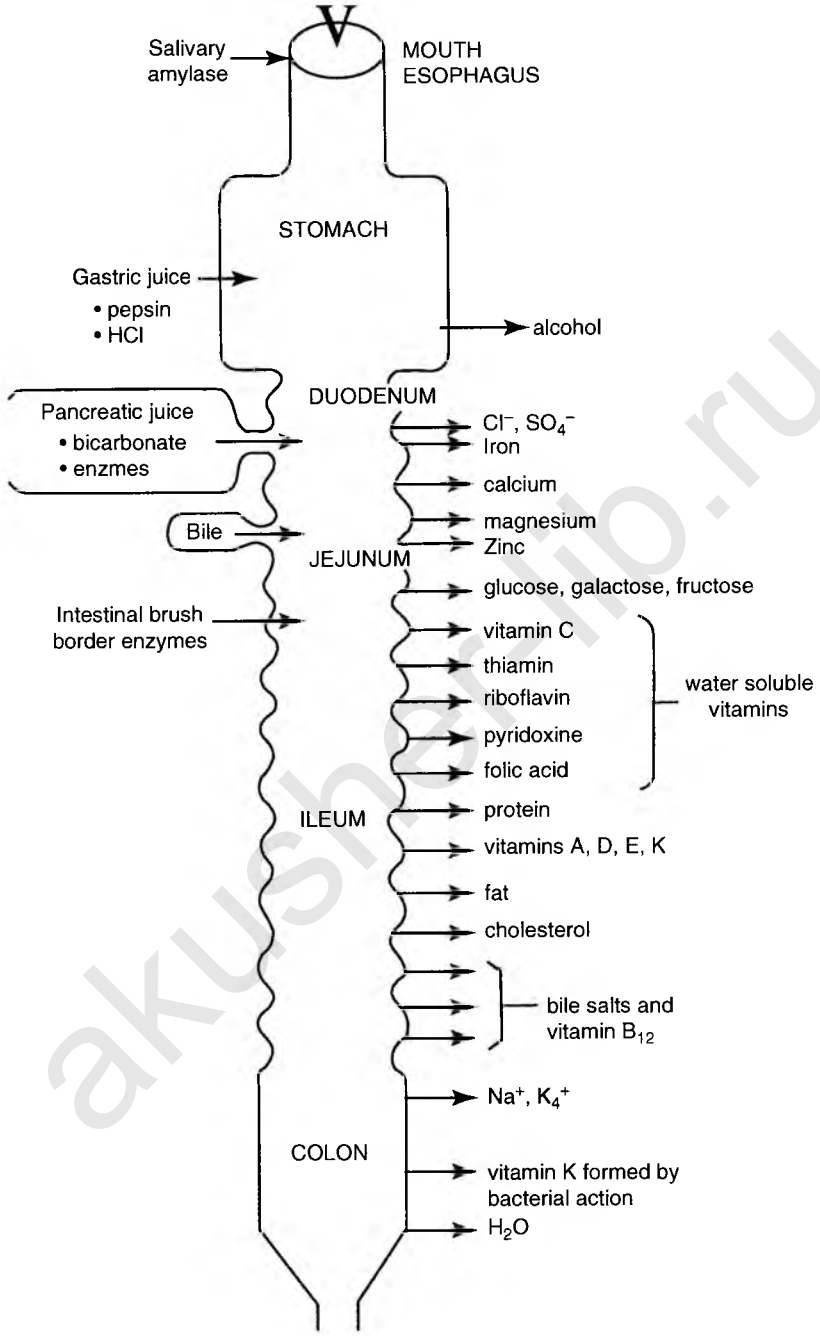


Fig. 5 Sites of absorption of nutrients within the gastrointestinal tract. Adapted from: Mahan and Escott-Stump: Krause's Food, Nutrition and Diet Therapy, 9/e, p 13, ©1996, with permission from Elsevier

capabilities unaffected, unlike bariatric interventions involving an intestinal bypass [25]. One such study found the most common deficiency after SG surgery is vitamin D, since most of the bariatric patients had vitamin D deficiency pre-operatively [26]. Some studies have even found that SG does not cause deficiencies. For example, a study by Kehagias et al. found no vitamin or mineral deficiencies in 30 patients 3 years after SG surgery, even though the patients were not taking supplements [27]. Another study found no iron deficiency in patients 1 year after SG surgery [28]. The differences between results of studies could be due to methodological factors. However, the data from several studies does imply that SG has potential nutritional consequences. A study found that diets of post-surgery SG patients are lower in iron, phosphorus, magnesium, and calcium than the current intake recommendations [26]. This could be because of decreased food intake and an individual preference for nutrient-poor foods.

In order to better understand the postoperative nutrition needs for pregnant women who have had bariatric surgery, it is important to first understand the nutritional deficiencies that commonly accompany such procedures. The main deficiencies reported among postoperative patients are protein, iron, vitamin B12, folate, calcium, vitamin D, and fat-soluble vitamins [29]. Below is a brief review of studies that have been carried out, as well as the assessments that are recommended as a check for nutrient deficiencies following bariatric surgery.

- *Protein.* In a prospective randomized study of patients with a BMI greater than 50 kg/m², 13% of the patients who underwent distal RYGB experienced protein deficiency 2 years after surgery [30]. Protein deficiency occurred more frequently after BPD-DS than RYGB due to the more severe malabsorption caused by this operation. In SG such protein deficiencies are typically nonexistent or mild. It is recommended that total serum protein and albumin be assessed on a regular basis after bariatric surgery to measure protein stores, typically 4, 8, and 12 months after surgery, then annually.
- *Iron.* In a study of RYGB patients before surgery and up to 5 years after the procedure, iron deficiency was identified in 26% of patients preoperatively, in 39% at 4 years postoperatively, and in 25% of those 5 years postoperatively [31]. Damms-Machado et al. performed a micronutrient analysis on 54 obese patients before and after SG surgery, and found that 1 year after the procedure, the patients on average had modestly reduced levels of iron that caused or exacerbated iron deficiencies [32]. The anatomic changes resulting from RYGB reduce the exposure of iron-containing food to the acidic environment in the stomach, which is required for the release of iron from protein and conversion into its absorbable ferrous form [33]. In another study of SG patients, anemia was found preoperatively in 5% of patients, and 20% had an iron deficiency with low serum ferritin level. One year after SG, the number of the affected patients with preoperative iron deficiency had not significantly changed while the ferritin level concentration was increased, possibly due to oral supplementation [34]. Symptoms of iron-deficiency anemia may include enteropathy, dysphagia, koilonychia, fatigue, and palpitations. It is recommended that hemoglobin, hematocrit, iron,

ferritin, and total iron binding capacity be evaluated for diagnosis of iron deficiency or anemia.

- **Vitamin B6 (pyridoxine).** Another finding of the study by Damms-Machado et al. was that post-surgery SG patients also had modestly reduced levels of vitamin B6. A vitamin B6 deficiency causes various problems including seborrheic dermatitis, glossitis, and cheilitis, and may contribute to depression [35]. The recommended dietary allowance for vitamin B6 is 1.3 mg for adults.
- **Vitamin B12 (cobalamin) and folate.** Deficiencies of vitamin B12 and folate are common in bariatric surgery patients. Symptoms of deficiency pernicious anemia (due to absence of intrinsic factor) include megaloblastic anemia, tinnitus (ringing in ear), numbness and paresthesia (tingling or prickly feeling) in extremities, changes in mental status, and sore tongue with a smooth and beefy red appearance. Halverson studied patients 1 year after RYGB and found 33% of patients had a vitamin B12 deficiency and 63% had a folate deficiency [36]. As with iron digestion after RYGB, the absence of an acidic environment prevents the release of vitamin B12 from food [31]. In addition, intrinsic factor (IF), secreted from parietal cells of the stomach, is responsible for the absorption of vitamin B12. Therefore, after bariatric surgery, inadequate IF secretion or function is a possible mechanism for vitamin B12 deficiency [37]. Vitamin B12 deficiency is less common after SG because the procedure involves resection of about 70–80% of the stomach, which leads to a decrease in the number of parietal cells, and consequently a decrease in the production of intrinsic factor (IF). The storage of IF is in the liver so vitamin B12 deficiency may not manifest until 5 years after surgery because a large amount of IF is stored in the liver [38]. Nonetheless, it is recommended that vitamin B12 and folate be assessed regularly because some symptoms of deficiency may be irreversible. Blood levels of >300 pg/ml for B12 are considered normal.
- **Calcium and vitamin D.** Calcium and vitamin D are usually assessed together since vitamin D promotes the intestinal absorption of calcium. Brolin et al. found a 10% incidence of calcium deficiency and 51% incidence of vitamin D deficiency in patients who had distal RYGB [30]. A study by Gehrler et al. also found that SG patients presented lower rates of vitamin D deficiency, and Moizé et al. found that vitamin D is the most common deficiency after SG surgery [25, 26]. Parathyroid hormone (PTH) levels may be a more sensitive indicator of calcium deficiency [33]. If PTH is elevated, then calcium deficiency is presumed. Symptoms of calcium deficiency are leg cramping, hypocalcemia, tetany, neuromuscular, hyperexcitability, and osteoporosis. As for vitamin D, it is important to check 25(OH) vitamin D levels rather than 1,25(OH)₂ vitamin D. Although the normal range of vitamin D is variable depending on the lab, it is usually recommended that serum 25(OH) vitamin D should be >30 ng/ml.
- **Other fat-soluble vitamins: A, E, K.** Malabsorption of these vitamins is most commonly seen after BPD-DS. Slater et al. studied 170 patients following BPD and BPD-DS and reported that 69% were deficient in vitamin A and

68% were deficient in vitamin K 4 years after surgery [39]. Dolan et al. showed that 5% of patients had low levels of vitamin E an average of 28 months after BPD and BPD-DS [40]. Therefore, vitamin A, vitamin E (tocopherol), and INR (the International Normalized Ratio, used to measure clotting and indirectly assess vitamin K deficiency) should be assessed at least annually.

Common Postoperative Problems

In addition to nutrient deficiencies after bariatric surgery, there are other common side effects that are worth mentioning because they may be confused with symptoms of pregnancy.

- *Vomiting.* Emesis may occur after surgery if the patient eats too much at one time, eats too quickly, or does not chew solid food thoroughly. In an RYGB patient, food that is not chewed well may get stuck in the narrow anastomosis between the stomach pouch and jejunum; in an SG patient it may get caught in the narrowest part of the sleeve. Scarring and stricture may also narrow the stomach and lead to vomiting. Excessive vomiting in patients who have had the AGB requires removal of some or all of the saline from their band to reduce the degree of restriction [41]. It is important to correct the problem because persistent vomiting may lead to malnutrition and dehydration, which are harmful during pregnancy. At study of 30 patients found that during the first 6 months after SG surgery, around 20% of the patients had acid regurgitation, heartburn, or vomiting [27]. However, most of the time these symptoms were not severe. Furthermore, the symptoms disappeared in all patients after the first postoperative year.
- *Constipation/Diarrhea.* Constipation may occur because postoperative patients focus on high-protein foods as a dietary mainstay and reduce their overall quantity of food intake, so their fiber intake may be suboptimal. If the patient is not drinking an adequate amount of fluid, then this may exacerbate the constipation. In addition, the iron that is recommended for bariatric patients and for pregnancy is also known to cause constipation. A stool softener or fiber supplement can be suggested. On the other hand, sometimes patients complain of diarrhea or steatorrhea which can happen after malabsorptive procedure like BPD-DS. The cause might be ingestion of a low-fiber or high-fat diet. Diarrhea is also possible after sleeve gastrectomy if a patient eats and drinks at the same time, pushing the food through the narrow stomach too quickly.
- *Dumping syndrome.* This occurs after RYGB when there is consumption of simple sugars. Symptoms may vary and are commonly classified as either “early dumping” or “late dumping” based on whether they occur 20–30 min after eating (early) or 1–3 h after eating (late). Early dumping is felt to be caused by physical distension of the stomach pouch or intestine and may include gastrointestinal symptoms (abdominal pain, cramping, diarrhea, bloating, nausea, and vomiting)

or vasomotor symptoms (flushing, palpitations, tachycardia, hypotension, lightheadedness). Late dumping is felt to be neurohumorally mediated and may include symptoms of hypoglycemia such as sweating, palpitations, hunger, weakness, tremor, and syncope. Dumping syndrome may be averted by instructing patients to avoid concentrated sweets. Importantly, when screening for gestational diabetes mellitus (GDM) during pregnancy, a glucose tolerance test will likely cause dumping syndrome. An alternative approach to assess for GDM would involve measuring fasting serum glucose periodically, since an elevation usually correlates with elevated postprandial blood glucose [42]. The overall risk of GDM is significantly lower in bariatric patients than in morbidly obese women. Dumping syndrome is common with RYGB but is less likely to occur with SG because it preserves the pylorus.

- *Gastroesophageal reflux disease (GERD)*. Gastroesophageal reflux occurs when stomach contents flow back up into the esophagus, which can lead to bleeding, ulcers, and if longstanding, Barrett's esophagus and esophageal dysplasia and cancer. Several studies have investigated the impact of SG on GERD, but there is no consensus as to whether SG increases or decreases it [43]. While a number of studies suggest that SG increases GERD [44–46], a similar number support the opposite finding [47–49]. One way SG may affect reflux symptoms is by increasing pressure in the lower esophageal sphincter [50]. Further high-quality studies are needed to clarify this problem.

Preconception Care

The best pregnancy is a planned pregnancy, especially after bariatric surgery, because the patient is able to take preventive measures against postnatal nutrient deficiencies. In addition to meeting with their obstetrician, women who have undergone a bariatric operation should schedule a follow-up visit with their bariatric surgeons and dietitians. At this risk, the surgeon will check a complete laboratory assessment for nutrient status. If any levels are low, then there is adequate time to correct them. Deficiencies in iron, calcium, vitamin B12, and folate can result in maternal complications, such as anemia, and in fetal complications, such as neural tube defects. Even if all lab values are normal, the patient should be encouraged to continue her bariatric prenatal supplement regimen.

Assessments should be carried out before becoming pregnant and frequently (every 2–3 months) during gestation, especially if deficiencies were present initially. In addition to reviewing blood work, the dietitian will ensure the patient is eating an adequate amount of protein, drinking enough fluid, and eating a healthy diet. The main goals of medical nutrition therapy during pregnancy are to facilitate adequate weight gain to promote fetal growth and development, to provide appropriate vitamin and mineral supplementation to prevent or correct deficiencies, and to assess nutrition educate on needs.

Standard Supplement Recommendations

Dietary supplementation before and during pregnancy should be based on laboratory findings as well as the type of bariatric surgery. General practice includes adding a prenatal vitamin to the current supplement regimen for the bariatric surgery, not giving it in lieu of the standard postoperative regimen. Patients should be monitored with regular micronutrient analyses to ensure their individual needs are met.

The standard prenatal vitamin contains 1 mg of folic acid, which is sufficient to reduce the risk of neural tube defect in the fetus (1 mg of folic acid per day should be taken prior to pregnancy for maximum benefit). For RYGB, sleeve gastrectomy, and BPD-DS, it is important that the calcium source be citrate because citrate does not require an acidic environment in order to be broken down. It is best that vitamin B12 be taken sublingually in crystalline form for better absorption [33]. When prescribing iron, ferrous fumarate is best tolerated [51]. Heme iron is another form of iron that tends to be better utilized by the body and less constipating. For all patients who take iron and calcium, to maximize absorption the two should not be taken at the same time. Ideally, they should be spaced apart by at least 2 h. If BPD-DS patients are compliant with taking fat-soluble vitamins but remain deficient in vitamin A, then additional vitamin A should be given as beta-carotene, since vitamin A may have teratogenic potential [52]. SG patients may benefit specifically from supplements for vitamin D, protein, iron, vitamin B12, vitamin B6, and folate [12]. While general recommendations are given below (Table 1), each patient should be treated as an individual and may require a slightly different regimen.

Table 1 Standard supplementation regimens for bariatric procedures

Procedure	Supplement and dose
Laparoscopic adjustable gastric banding	Prenatal vitamin with iron
	Calcium citrate plus vitamin D: 1200 mg/day
Sleeve Gastrectomy	Prenatal vitamin with iron
	Calcium citrate plus vitamin D: 1200 mg/day
	Sublingual B12 500 mcg/day or 1000 mcg 3×/week
	Additional iron: Based on blood work
Roux-en-Y gastric bypass	Prenatal vitamin with iron
	Calcium citrate plus vitamin D: 1500 mg/day
	Sublingual B ₁₂ : 500 mcg/day or 1000 mcg 3×/week
	Elemental iron: 300 mg/day (ferrous and polysaccharides complex or 60 mg heme iron)
Biliopancreatic diversion with duodenal switch	Prenatal vitamin with iron
	Calcium citrate plus vitamin D: 2000 mg/day
	Sublingual vitamin B12: 500 mcg/day or 1000mcg 3×/week
	Iron: 320 mg four times a day 60 mg heme iron
	Fat-soluble vitamins A,D,E,K: three times a day

Protein Recommendations

Protein is the most important macronutrient for the bariatric patient. For this reason, patients should be instructed to consume protein at the beginning of a meal to ensure adequate intake if the patient becomes sated prematurely. During pregnancy, protein needs are 1.1 g/kg/day. There are no published protein guidelines for bariatric patients during pregnancy. Therefore, protein recommendations may vary among institutions. Our program recommends 60–80 g/day for the RYBG and sleeve gastrectomy, 80–120 g/day for the BPD-DS, and 0.8–1 g/kg/day of adjusted body weight for AGB in non-pregnant women. Each pregnant bariatric patient should be encouraged to meet the upper end of the protein range specified for her type of surgery. If needed, protein intake may be supplemented with sugar-free protein shakes.

Patients are instructed to avoid pregnancy during the first year after surgery, since this is the period of most rapid weight loss. If there is an unplanned pregnancy during this time, protein requirements should be increased to 1.5 g/kg/day of ideal body weight.

Calorie Recommendations and Weight Gain During Pregnancy

Calorie recommendations for the pregnant bariatric patient include approximately 300 kcal/day above maintenance guidelines for bariatric surgery in the second and third trimesters. As with protein, calorie recommendations may vary between institutions. Typically, 1 year after surgery, individuals consume approximately 1200 kcal/day, so this would result in a caloric recommendation of 1500 kcal/day for pregnant bariatric patients. These are general guidelines, and each patient should be monitored for appropriate weight gain during pregnancy to ensure she is getting adequate caloric intake.

Weight gain during pregnancy after bariatric surgery is variable, as with any pregnancy. There are no published guidelines for pregnancy weight gain in bariatric patients. Therefore, the guidelines set forth by the Institute of Medicine should be used (Table 2) [53]. The postoperative BMI should be used to determine the appropriate weight category. Even when weight gain is normal and expected during preg-

Table 2 Recommended weight gain for different BMI categories

Weight category	Recommended weight gain (lb)
Underweight: BMI <19.8	28–40
Normal weight: BMI 19.8–25	25–35
Overweight: BMI 26–29	15–25
Obese: BMI >29	15

nancy, some patients may have an emotional response to this gain since they worked so hard to lose weight. It should be reinforced to patients that pregnancy is not a time to lose weight. Inadequate weight gain can result in intrauterine growth retardation and fetal abnormalities [33]. Patients may also be nervous about losing their pregnancy weight after the birth of their infants. It may be helpful to refer the patient to a psychologist to help sort out these issues.

Other Recommendations During Pregnancy

General pregnancy recommendations should be stressed to the bariatric patient, such as avoiding alcohol, drugs, and undercooked meat, as well as increasing intake of omega-3 fatty acids and avoiding fish that are high in mercury. Patients should be advised to do the following:

- *Eat slowly and chew very well.* It is best to try to take a half hour to eat each meal. If the patient does not stop eating when she is full, then there is an increased chance that vomiting will follow. This may lead to malnutrition and dehydration.
- *Do not skip meals.* Have three to five small, protein-rich meals every day. Skipping meals may lead to malnutrition.
- *Avoid concentrated sugars.* RYGB patients may experience dumping syndrome. For patients with SG and AGB it is important to avoid concentrated sugars because they are high in calories and will contribute to excessive weight gain.
- *Limit fat intake.* Fat is high in calories, and like sugar, will contribute to excess weight gain. Some patients may also experience nausea after eating a high fat meal.
- *Maintain adequate hydration.* The patient should drink six to eight 8-ounce, non-caloric, noncarbonated, non-caffeinated drinks per day. Patients should avoid drinking 15 min before or during meals and for 45 min after meals. Drinking immediately before a meal may cause the stomach pouch to fill up with fluid, and there will not be room to eat an adequate amount of protein. Drinking during the meal may cause the food to move quicker through stomach, and therefore decrease a feeling of fullness. Drinking within 45 min after eating may cause vomiting because there will not be any room for the fluid with all the food that was eaten.
- *Increase intake of fiber* to prevent or treat constipation.

Outcomes of Pregnancy After Weight Loss Surgery

A number of published studies have addressed the issue of outcomes after bariatric surgery. One of the largest studies to date evaluated the perinatal outcome of 159,210 deliveries occurring in Israel between 1988 and 2002. Of these deliveries, 298 were

from women who had previously undergone bariatric surgery [54, 55]. Although there was a higher rate of caesarean delivery in the bariatric surgery group (25.2 vs. 12.2%), no difference was found in perinatal mortality, congenital malformations, and Apgar scores at one and 5 min.

Few studies have been published to date regarding the outcomes of pregnancy after SG [56]. A 2015 study from France found only that women who remain obese after SG are at increased risk of adverse perinatal outcomes, including lower birth weight and lower gestational age at birth. The risk of preterm delivery was also increased.

Conclusion

It is important for the obstetrician and bariatric surgeon to work together to care for the bariatric surgery patient. In addition, the patient will benefit from attending bariatric surgery support groups where she can share her experiences, ask for advice, and help others with the challenges they encounter. Encourage the bariatric patient to attend these support groups because they will find help in dealing with nutrition before and after pregnancy.

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Preeclampsia

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Keywords Preeclampsia · Eclampsia · Hypertensive disorders of pregnancy · Gestational hypertension

Key Points

- Preeclampsia is a multi-organ disease that is specific to pregnancy
- There are no well-established methods of primary prevention for preeclampsia
- 2013 World Health Organization recommendations advise calcium supplementation in populations where calcium intake is low, however, low dietary intake is considered an uncommon occurrence in the US due to fortification of many foods with calcium
- The American College of Obstetricians and Gynecologists and the United States Preventive Services Task Force recommend aspirin prophylaxis in women with certain risk factors for the development of preeclampsia
- Diets high in fiber and potassium may reduce the risk of preeclampsia
- Diets high in calories, sucrose, and polyunsaturated fatty acids may increase the risk for preeclampsia

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Introduction

Preeclampsia is a multi-organ disease that occurs after 20 weeks gestation and is characterized by the development of hypertension and either proteinuria or other evidence of end-organ effects [1]. It is specific to pregnancy and complicates 5–7% of pregnancies [2]. It falls into the larger category of hypertensive disorders of pregnancy, which is addressed briefly within this chapter. The exact etiology or pathophysiology of this disorder is poorly understood, however, it is thought to involve both poor placentation and the subsequent consequences of relative placental hypoxia, resulting in a cascade of events that culminates in the recognized clinical manifestations of the disease [1]. Additionally, there are no well-established methods of primary prevention or reliable and cost-effective screening, though new research focuses on biomarkers that may be useful for screening in the future [3]. Preeclampsia is associated with increased maternal mortality and morbidity including placental abruption, acute renal failure, cerebrovascular and cardiovascular complications, and disseminated intravascular coagulation [4], as well as fetal/neonatal morbidity and mortality caused by intrauterine growth restriction, abruption, and prematurity.

Hypertensive Disorders of Pregnancy

Complications from hypertension are a leading cause of pregnancy-related deaths, ranking third behind hemorrhage and embolism [4]. Hypertensive disorders that may be found during pregnancy include chronic hypertension, preeclampsia, eclampsia, preeclampsia superimposed on chronic hypertension, and gestational hypertension [5].

Chronic hypertension is hypertension that exists outside of the pregnancy. As such, it will predate the pregnancy, be documented prior to 20 weeks gestation, or will still be present 12 weeks after delivery [5]. Treatment of mild-to-moderate chronic hypertension during pregnancy has not been shown to prevent preeclampsia and has shown no proven fetal benefit [6–8].

Preeclampsia is the onset of hypertension with proteinuria or other evidence of end-organ effects that occurs after 20 weeks of pregnancy. Eclampsia, which occurs in less than 1% of women with preeclampsia [2], is the new onset of seizures during preeclampsia.

If a patient has chronic hypertension but develops new or worsened proteinuria or other evidence of end-organ effects, this is preeclampsia superimposed on chronic hypertension [9].

Gestational hypertension, previously termed “pregnancy induced hypertension,” [5] is hypertension that develops in the absence of proteinuria or other end-organ effects. Gestational hypertension develops after 20 weeks of pregnancy and blood pressure returns to normal within 12 weeks of delivery [9].

Diagnosis of Preeclampsia

Historically, both proteinuria and hypertension after 20 weeks of gestation were required for a diagnosis of preeclampsia. Our current understanding of the pathophysiology and clinical manifestations suggests that gestational hypertension and preeclampsia exist along a continuum of disease, such that proteinuria need not be present if other evidence of end-organ effects can be demonstrated. This includes new onset of thrombocytopenia, impaired liver function, renal insufficiency, pulmonary edema, or cerebral or visual disturbances [1]. The diagnostic criteria for preeclampsia are presented in Table 1. Blood pressure should be measured with an appropriately sized cuff, with the patient in an upright position [10]. Edema and blood pressure elevations above the patient's baseline are no longer included in diagnostic criteria [5, 9].

In preeclampsia with severe features, blood pressures are higher and/or signs or symptoms are present indicating end organ damage. The diagnostic criteria for preeclampsia with severe features are also presented in Table 1.

Although 24-h urine collection is the gold standard for measuring proteinuria, a random urinary protein-to-creatinine ratio can rule out significant proteinuria if the ratio is less than 0.19 [11]. The urine protein-to-creatinine ratio using the 0.19 cut-off has a sensitivity of 90%, specificity of 70%, and a negative predictive value of 87% [11]. Likewise, a random urinary protein-to-creatinine ratio of 0.3 or higher can be used to rule in preeclampsia when expediency precludes collection of a 24-h urine [1].

Pathophysiology and Risk Factors

The etiology of preeclampsia remains poorly understood. Multiple theories have been proposed regarding the pathophysiology, and no single causal factor has been found, however most current models describe a two-stage process with abnormal placentation causing poor uteroplacental perfusion, and thus oxidative stress. This

Table 1 Diagnostic criteria for preeclampsia with and without severe features [1]

	Gestational HTN	Preeclampsia	Preeclampsia with severe features (at least one of the below must be present)
Blood pressure (on 2 occasions at least 4 h apart)	$\geq 140/90$	$\geq 140/90$	$\geq 160/110$
Proteinuria	Absent	Present or absent	Present or absent
Platelet count	Normal	Normal	$< 100 \text{ K}/\mu\text{L}$
Liver function	Normal	Normal	Transaminases twice normal
Renal function	Normal	Normal	Creatinine doubled or $> 1.1 \text{ mg/dL}$
Cerebral function	Normal	Normal	Headache or visual disturbances
Edema	Normal	Normal	Pulmonary edema

in turn mediates inflammatory response, endothelial dysfunction, and lack of modulation of angiogenic and antiangiogenic factor production/activity [12]. Other mediators may include genetic factors such as maternal thrombophilias [13] and leptin receptor gene differences [14], as well as paternal influences [15]. Immunologic factors such as major histocompatibility complex molecules and natural killer receptors are also under investigation regarding their relationship to the development of preeclampsia [16].

Although hypertension and either proteinuria or other evidence of end-organ effects are the criteria by which preeclampsia is diagnosed, the pathophysiologic changes associated with preeclampsia affect virtually every organ system. Microthrombi occur from activation of the coagulation cascade [17], as well as systemic vasospasm and decreased blood flow to organs [18, 19]. Perfusion is further compromised by vascular hemoconcentration and third-spacing of intravascular fluids [20].

Newer research explores the possibility of using biomarkers to assess risk of the development of preeclampsia. One such investigation has evaluated the ratio of soluble fms-like tyrosine kinase 1 (sFLT1) to placental growth factor (PlGF), suggesting that a low maternal ratio may have a negative predictive value of 99.3% for the development of preeclampsia within 1 week [1].

Risk factors for preeclampsia are presented in Table 2 [1]. Note that young maternal age is no longer considered a risk factor, as this was not supported by a systematic review [21]. Women with preeclampsia should be counseled about the increased risk of recurrent preeclampsia in future pregnancies. The recurrence rate may be as high as 40% in nulliparous women with preeclampsia before 30 weeks gestation, and even higher in multiparous women [5]. A systematic review of controlled studies found an odds ratio of 7.19 for recurrence of preeclampsia among 24,620 women with preeclampsia in a previous pregnancy [22].

Table 2 Risk factors for preeclampsia [1]

Increased maternal age (>40 years old)
Nulliparity
Multiple gestation
Preeclampsia in a prior pregnancy
In vitro fertilization
Family history of preeclampsia
Elevated body mass index
Certain medical conditions:
Chronic hypertension
Chronic renal disease
Antiphospholipid syndrome
Systemic lupus erythematosus
Diabetes mellitus

Prevention and Nutrition

There are no well-established methods of primary prevention for preeclampsia, although numerous supplements have been studied regarding their ability to impact its occurrence. Thus far, randomized controlled trials do not support routine prenatal supplementation with magnesium [23], omega-3 fatty acids [24], or antioxidants (vitamins E and C) [25] to prevent preeclampsia. However, calcium and aspirin may have a role in preventing preeclampsia in certain subpopulations, though the optimal treatment regimens will require further research.

Calcium supplementation in high-risk women and in women with low dietary calcium intake reduced the risk of hypertension and preeclampsia [26]. Also, calcium supplementation has been shown to decrease the incidence of neonatal mortality and severe maternal morbidity due to hypertensive disorders when given to normotensive nulliparous women [27]. The 2013 World Health Organization recommendations advise supplementation with 1.5–2 g per day of elemental calcium beginning at 20 weeks gestational age in populations where calcium intake is low [28]. However, low dietary intake is considered an uncommon occurrence in the United States due to fortification of many foods with calcium.

Low-dose aspirin was shown to have small to moderate benefits for prevention of preeclampsia within certain groups of women. A Cochrane analysis demonstrated that in women at increased risk for preeclampsia, 72 women would need to be treated with low-dose aspirin to prevent one case of preeclampsia [29]. However, in the subgroup of women at highest risk for preeclampsia (because of histories of previous severe preeclampsia, diabetes, chronic hypertension, renal disease, or autoimmune disease), only 19 would need to be treated with low-dose aspirin to prevent one case of preeclampsia [27, 29]. The 2013 American College of Obstetricians and Gynecologists (ACOG) Task Force on Hypertension in Pregnancy recommends initiation of aspirin in the late first trimester for women with a history of prior delivery for preeclampsia at less than 34 weeks gestational age or preeclampsia in more than one prior pregnancy [1]. In 2014, the United States Preventive Services Task Force (USPSTF) published recommendations for aspirin prophylaxis in pregnant women with multifetal gestations, chronic hypertension, type 1 or 2 diabetes, renal or autoimmune disease, or the presence of multiple risk factors from a group of characteristics thought to confer moderate risk (nulliparity, BMI >30, mother or sister affected by preeclampsia, age ≥ 35 years, etc.) [30]. A cost-benefit analysis comparing the USPSTF and ACOG Task Force approaches to aspirin prophylaxis showed a 3.83% versus 4.17% rate of preeclampsia (compared to 4.18% background rate), with 23.5% versus 0.35% of pregnant women receiving aspirin, respectively [31].

Research continues regarding possible nutritional interventions for preeclampsia. While larger studies that are more reliable are needed to confirm results, diets high in fiber and potassium may reduce the risk of preeclampsia [32, 33]. Additionally, diets high in calories, sucrose [34], and polyunsaturated fatty acids may increase the risk for preeclampsia [35].

Management of Preeclampsia

Childbirth is the cure for preeclampsia, as the disease process usually resolves within days of delivery. Delivery is always preferable from the perspective of maternal health. However, decisions on induction of labor or cesarean delivery must include a consideration of prematurity-related neonatal risks and the severity of the preeclampsia. Women with gestational hypertension and preeclampsia without severe features should be carefully followed until they are close to term and delivered at 37 weeks [1, 36]. Women with preeclampsia with severe features may be expectantly managed until 32–34 weeks, or delivered sooner based on maternal and fetal status [37]. Women with preeclampsia need to have regular surveillance of the fetus with nonstress testing and amniotic fluid volume assessment. Blood work should be checked periodically to detect renal or hepatic involvement, hemolysis, or thrombocytopenia.

The hypertension of preeclampsia only warrants treatment if the systolic blood pressure is above 160 mm Hg or the diastolic blood pressure is above 110 mm Hg [5]. If these pressures occur at 37 weeks or greater gestational age, the blood pressure may be managed with intravenous hydralazine or labetalol until delivery [38]. In addition, oral nifedipine has emerged as an effective therapy for acute control of blood pressure in labor [39]. Women with preeclampsia with severe features undergoing expectant management may have their blood pressure controlled with oral labetalol, methyldopa, or nifedipine [5]. Magnesium sulfate is the drug of choice for the prevention and treatment of eclamptic seizures [40]. All women with preeclampsia with severe features need intravenous magnesium in labor and for 24 h postpartum [41]. The routine use of magnesium sulfate in women with preeclampsia without severe features is no longer recommended, as 400 women may need to be treated to prevent one eclamptic seizure [42]. However, women without severe features must be observed carefully for the development of signs and/or symptoms consistent with progression to severe disease.

Neonatal morbidity and mortality are due to the risk of prematurity, uteroplacental insufficiency, or placental abruption. An ultrasound for estimated fetal weight should be performed at the time of diagnosis to evaluate for possible intrauterine growth restriction secondary to uteroplacental insufficiency [5]. If delivery is required prior to term, the birth should occur at an institution with a neonatal intensive care unit capable of caring for infants at the anticipated gestational age. Placental abruption is an unpredictable event which can lead to fetal death or morbidity, and the incidence is decreased with the use of magnesium sulfate [40].

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US Hispanics and Preterm Births

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Keywords Health disparities · Hispanics · Preterm births · Risk factors · Vitamin D deficiency

Key Points

- Preterm birth is a major public health problem in the USA.
- Hispanic women are at a high risk of delivering prematurely.
- The rate of preterm birth is highest for infants born to women of Puerto Rican descent.
- Vitamin D deficiency, a risk factor for preterm delivery, is prevalent among Hispanic women.
- Further research is needed to better understand how vitamin D deficiency may increase the risk of premature birth among Hispanic women.

Introduction

Preterm birth, defined as birth before 37 weeks of pregnancy [1], is recognized as the greatest contributor to infant death in the USA and globally, with most preterm-related deaths occurring among babies born very preterm, before

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32 weeks [1]. Preterm birth is the leading obstetric problem negatively impacting the health of both mothers and babies in the USA [2]. In 2007, the Institute of Medicine reported that the annual cost associated with premature births in the USA was \$26.2 billion [3]. Despite medical advances, the incidence of preterm birth has increased in the USA for decades and only recently has started to slightly decrease.

While rates of preterm birth have been declining nationally for the past 12 years, in 2014, preterm births affected about one out of every ten infants born in the USA [4]. According to data from National Center for Health Statistics (NCHS) natality files, in 2014, the preterm birth rate was 9.57%, compared to 9.62% in 2013 (Fig. 1). During 2011–2013 in the USA, preterm birth rates were the highest for Black infants (16.5%), followed by Native Americans (13.4%), Hispanics (11.5%), Whites (10.3%), and Asians (10.1%) [4, 5]. Among US Hispanics, in 2014 preterm births were highest among Puerto Rican infants [4, 6].

The purpose of this chapter is to present the epidemiology of prematurity and related indicators among US Hispanics. The association between vitamin D deficiency and adverse pregnancy outcomes will be explored as a potential mechanism for the relatively high prevalence of prematurity among Hispanic women.

Population Growth and Preterm Births Among Hispanics

According to the US Census Bureau, Hispanics are the largest and fastest growing racial/ethnic minority group in the USA. It is predicted that the Hispanic population will more than double, from 53.3 million in 2012 to 128.8 million in 2060 [7]. By 2020, the Census Bureau projects that there will be more than 13.8 million Hispanic

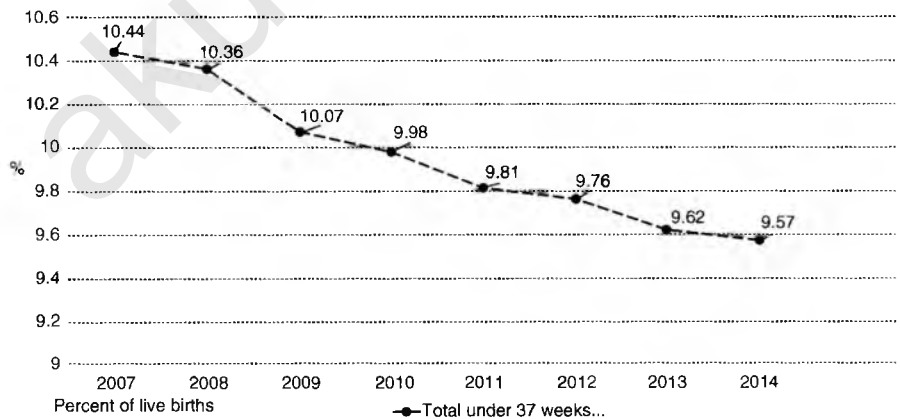


Fig. 1 Distribution of live births: United States, 2007–2014. Source: CDC, NCHS. National Vital Statistics

women of childbearing age (15–44 years) in the USA, up from more than 11.8 million in 2010 [2, 7]. The US Hispanic population is made up of heterogeneous subgroups from different cultures, including people of Mexican descent, Central/South American, Puerto Rican, Cuban, Dominican, and others. According to a 2014 March of Dimes report, nearly 105,000 Hispanic infants are born preterm annually, accounting for one out of four preterm births in the USA [2].

Fig. 2 outlines the most recent data in the USA for preterm births, by Hispanic origin and by race for mothers of non-Hispanic origin (2012–2014). The gap between non-Hispanic White and Hispanic preterm births has been increasing since 2005 [2]. Within the Hispanic population, rates of preterm birth in 2014 were highest for infants born to women of Puerto Rican descent (11.0%) and lowest for infants born to women of Central and South American descent (8.5%) [4].

Prematurity is a major contributor to infant mortality, and preterm-related causes accounted for more than 35% of infant deaths in the USA in 2010 [2]. Among US Hispanics, Puerto Rican infants have the highest infant mortality rates due to preterm-related conditions [8]. In 2010, 34.7% of Hispanic infant deaths were due to preterm-related causes and varied by Hispanic origin. Indeed, 32.8% of infant deaths were due to preterm-related causes among Central-South Americans, 34.0% among Mexicans, and 41.6% among Puerto Ricans [2].

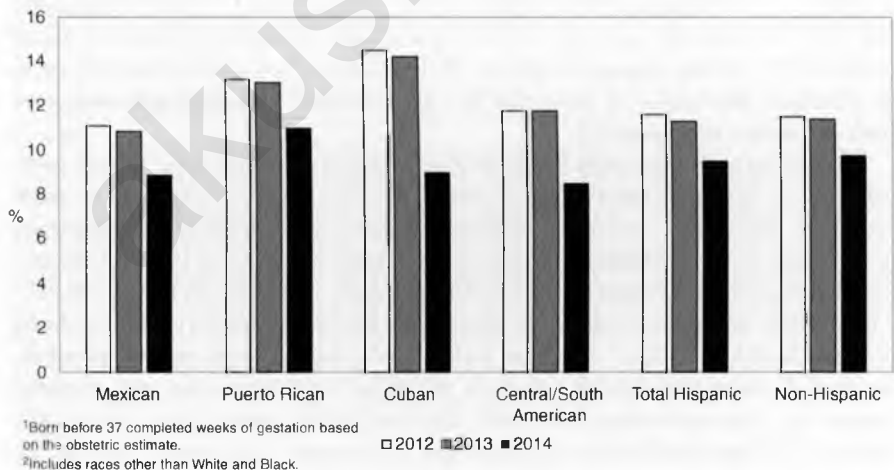


Fig. 2 Preterm births (born before 37 completed weeks of gestation based on the obstetric estimate) prevalence by Hispanic origin of the mother, and by non-hispanic origin (includes races other than White and Black), US, 2012–2014. Source: National Vital Statistics Reports

Risk Factors

While the specific causes of spontaneous preterm labor and delivery are largely unknown, research indicates that they are likely due to a complex interplay of multiple risk factors, as opposed to any single isolated risk factor [5]. Well-established risk factors of preterm birth include very young or advanced maternal age, lower parity, Black and Hispanic race and ethnicity, low pre-pregnancy body mass index, smoking, alcohol, substance use, high stress levels, single marital status or marital strain, depression, maternal sexually transmitted infections, lower self-esteem, and inadequate social support [9–15]. This section will elucidate demographic characteristics, medical conditions, and behavioral risk factors for preterm birth among Hispanic women.

Maternal Demographic and Socio-Economic Characteristics

Hispanic women of childbearing age are more likely to experience demographic and socio-economic risk factors for preterm birth and other adverse outcomes than non-Hispanic White women [2]. Maternal age is a risk factor of preterm birth. Women younger than 17 or older than 35 years of age are at higher risk [16]. Studies have found that young adolescents (younger than 16 years of age at the time of their last menstrual period), especially those of young gynecological age (within 2 years of menarche), have a twofold greater risk for preterm delivery compared with the risk for older women (ages 18–29 years) [1, 17]. This risk decreases with an increase in the age of adolescent mothers [17]. In 2012, Hispanic mothers were three times as likely as non-Hispanic White mothers to be younger than 17 years of age (1.8% and 0.6%, respectively) [2]. It is not known at present whether the increased risk of preterm birth among young adolescents is due to their biological immaturity or to an increased prevalence of other risk factors associated with their generally poor socio-economic condition [1].

Mothers experiencing high levels of psychological or social stress during pregnancy are at significant risk for preterm birth [18–20]. Long-term exposure to socio-economic challenges, including residence in socio-economically disadvantaged neighborhoods, is detrimental to maternal reproductive health and is one of the factors that contribute to more adverse birth outcomes, including preterm birth [21–23]. Multiple determinants across the lifespan need to be considered when examining perinatal health outcomes [3]. These include distal factors (e.g., genetic, physical, and social environments) that affect an individual's predisposition and proximal factors (e.g., biomedical and behavioral) that have a direct impact on an individual's health [3]. These risk factors are connected to a woman's life course through the transition from preconception and interconception to pregnancy [3]. According to data from 38 states and the District of Columbia, in 2012, Hispanic mothers were four times more likely than non-Hispanic White mothers to have completed less

than 12 years of high school (36.6% and 8.9%, respectively) [2]. In addition, Hispanic women aged 15–44 were more than twice as likely to be without health insurance compared to non-Hispanic White women (36.1% and 15.0%, respectively).

Medical and Pregnancy Conditions

A number of maternal medical conditions are associated with an increased risk of preterm birth, including multi-parity, infections, chronic hypertension, pre-gestational diabetes mellitus, gestational diabetes mellitus, and hypertensive disorders of pregnancy, among others [3]. A history of low birth weight (LBW), preterm birth, stillborn birth or neonatal death, and other complications are also associated with increased risk of preterm birth and shortened length of gestation [3]. Table 1 outlines the medical risk factors among women aged 18–44 in the year 2012. Medical risk factors associated with poor birth outcomes also vary by maternal race/ethnicity [2]. Hispanic women of childbearing age report significantly higher rates

Table 1 Biomedical risk factors among US women 18–44 years

Risk factor	Percent (95% confidence interval)
<i>Obesity</i>	
Hispanic	27.8 (26.0–29.5)
White	22.0 (21.4–22.7)
Black	39.7 (37.8–41.7)
<i>Diabetes</i>	
Hispanic	3.9 (3.2–4.5)
White	2.7 (2.5–2.9)
Black	4.6 (3.8–5.4)
<i>Pregnancy-related diabetes</i>	
Hispanic	4.2 (3.5–4.9)
White	2.4 (2.1–2.6)
Black	2.5 (2.0–3.1)
<i>Hypertension</i>	
Hispanic	8.5 (7.5–9.4)
White	10.4 (9.9–10.9)
Black	18.2 (16.9–19.6)
<i>Pregnancy-related hypertension</i>	
Hispanic	4.3 (3.5–5.0)
White	2.8 (2.6–3.0)
Black	4.1 (3.4–4.9)

White and Black categories exclude Hispanics

Source: Centers for Disease Control and Prevention, Behavioral Risk Factor Surveillance System, 2011 (for Hypertension and Pregnancy only) and 2012 [2]

of obesity, diabetes, pregnancy-related diabetes, and pregnancy-related hypertension compared to non-Hispanic White women [2].

Pre-pregnancy body mass index (BMI) has been investigated as a factor contributing to preterm birth risk in several studies [24–29]. Low maternal pre-pregnancy weight and body mass index (BMI) have consistently been associated with preterm birth [3]. The relationship between low pre-pregnancy BMI and spontaneous preterm birth is consistent among urban Hispanics [30, 31]. Studies have also found an increased risk of preterm birth associated with elevated BMI, specifically obesity [24]. Shaw et al. found that increased relative risks and preterm birth at 20–23 weeks among class III obese women compared normal weight women were 6.29 [95% confidence interval (CI) 3.06, 12.9], 4.34 [95% CI 2.30, 8.16], and 4.45 [95% CI 2.53, 7.82] for non-Hispanic Whites, non-Hispanic Blacks, and Hispanics, respectively [24]. Salihu et al. conducted a birth records study in Florida to examine the association between prematurity and obesity subtypes across three racial/ethnic groups [29]. Among Hispanic women, the adjusted risk of prematurity increased with increasing BMI [29].

Behavioral Factors

A report by the Hispanic Health Council, in Hartford, Connecticut, documents that Hispanic women are more likely to seek prenatal care late during their pregnancies compared to non-Hispanic Whites (20% and 8%, respectively) [32]. Delayed or inadequate use of prenatal care is a risk factor of preterm birth. Among Hispanic births in 2012, 69.0% occurred to women who received early prenatal care (in the first pregnancy trimester), compared to 78.9% of non-Hispanic White women [2].

Partridge et al. conducted a population-based cohort study of all deliveries in the USA between 1995 and 2002 using the Centers for Disease Control and Prevention's Linked Birth-Infant Death and Fetal Death data [33]. The researchers found a greater risk of prematurity when prenatal care was inadequate (adequate prenatal care (PNC) as defined by the Adequacy of Prenatal Care Utilization (APNCU) index [34], OR 3.75 [95% CI 3.73–3.77]) [33]. Over the eight-year span, the proportion of mothers receiving inadequate prenatal care was greatest among women under 20 years of age who were Black non-Hispanic or Hispanic, who were not married, had less than 12 years of education, had three or more prior live births, and who smoked or drank alcohol during the pregnancy [33].

Despite overall decreased smoking in recent years, in 2009 about 19% of women of reproductive age were smokers, and about 10% of women reported smoking during pregnancy in 2011 (25 states) [1]. In 2012, about 1 in 10 Hispanic women of childbearing age reported smoking some days or every day [2]. Smoking during pregnancy is associated with 5–8% of preterm births [1]. Similarly, alcohol use during pregnancy has adverse effects on birth outcomes, especially among heavy drinkers. In 2012, nearly 12% of Hispanic women of childbearing age reported binge drinking (11.7%), and 3.0% reported heavy drinking [2]. Even moderate levels of

alcohol consumption during pregnancy may have adverse birth outcomes, as studies have found that women who have more than one drink per day, on average, have an increased risk of preterm birth [3].

Acculturation

Among Hispanics, acculturation (the process by which immigrants adopt the attitudes, values, customs, beliefs, and behaviors of a new culture) [35] is significantly associated with health-related behaviors [36]. Therefore, studies have suggested that when studying immigrant populations and risk of adverse perinatal outcomes, acculturation should be taken into consideration [37, 38]. The role of acculturation on infant birth weight has been examined in Hispanic populations.

Cervantes et al. found that (a) US-born Mexican women had similar risk of LBW and preterm infants as non-Hispanic White women, and (b) Mexican-born women had significantly lower risks of experiencing both outcomes than non-Hispanic Whites. Immigrant Mexican women had a significantly lower risk of both LBW [adjusted odds ratio (AOR): 0.78, 95% confidence interval (CI) 0.66–0.91] and preterm births (AOR: 0.75, 95% CI 0.65–0.86) and were at 28% and 33% lower risks, compared with non-Hispanic White women, of delivering an LBW infant or a premature infant, respectively [39].

The “Hispanic epidemiologic paradox” includes the observation that despite socio-economic disadvantages, Hispanic mothers in the USA have a similar or lower risk for delivering an infant with LBW compared to non-Hispanic White mothers [40]. Researchers have attempted to explain this paradox, with one hypothesis being the “Healthy Migrant” effect. This hypothesis suggests that Hispanic women who migrate to the USA are the healthiest in their communities and consequently, give birth to healthier babies [41]. This is supported by a study conducted by Landale et al. that showed that Puerto Rican women who migrated to the USA had lower risk of infant mortality than non-migrant Puerto Rican women [42]. Similarly, a study conducted by Engel et al. with a national sample of 127,818 Puerto Rican women found that island-born women had lower odds of LBW (OR 0.94 [95% CI 0.89, 0.97] and small for gestational age (SGA) (or 0.93 [95% CI 0.89, 0.97] than women born on the mainland [43].

Another theory that may help explain the paradox suggests that ingrained Hispanic cultural traditions such as *marianismo* (a cultural value that denotes the gender role expectations of Hispanic women) [44] are protective against the adverse conditions that Hispanics experience [41]. Adherence to these cultural traditions combined with support from family and friends is believed to protect Hispanic mothers against poor birth outcomes [41].

The paradox of favorable birth outcomes, despite social disadvantages, among some immigrant groups and the increased rates of preterm birth with increasing length of residence in the USA have been attributed, in part, to the loss of cultural resiliency factors with increasing acculturation [3]. This suggests that research on

disparities in the rates of preterm birth needs to pay more attention to protective cultural factors, including the structure of social networks and spirituality [3].

Despite these advantages, the literature suggests that as Hispanic immigrant women stay longer in the USA, they modify their own culture to adapt to the US culture and they gradually lose the advantage they have for better birth outcomes [45]. As Hispanics are exposed to US culture, they may obtain both positive and negative values and behaviors [46]. Indeed, the rates of preterm birth in the USA have been found to be influenced by acculturation through exposure to and adoption of US behaviors and cultural beliefs [47, 48].

Evidence has shown that acculturation of Hispanics into the US culture has adversely affected the biological mechanisms that maintain pregnancy, particularly the progesterone and estriol balance, thus increasing the risk of preterm birth [45, 46]. Ruiz et al. examined the Hispanic acculturation paradox by identifying the effect of acculturation on serum progesterone and estriol levels, the progesterone/estriol ratio, and preterm birth [46]. Progesterone and estriol are key reproductive hormones in pregnancy, with both hormones being important in the process of parturition [46]. The researchers found that Hispanic women who were more acculturated (i.e., proficient in English) had four times the risk of preterm birth (AOR: 4.03, 95% CI: 1.44–11.25), and the lowest quartile of the progesterone/estriol ratio (AOR: 2.93, 95% CI: 1.25–6.89) [46]. English proficiency was significantly associated with a decrease in progesterone/estriol ratio and an increased risk in preterm birth. This finding is consistent with the Hispanic paradox, whereby more acculturated individuals exhibit poorer health outcomes [45]. Wommack et al. investigated the potential relationships among preterm birth, acculturation, and inflammatory markers and found that low or negligible interleukin-10 levels became increasingly predictive of preterm birth the longer the Hispanic women had lived in the USA [47]. Interleukin-10 is an anti-inflammatory cytokine that serves as protective factor for preterm birth [47, 49, 50]. A recent review by Abraído-Lanza et al. suggests that greater attention should be paid to areas of research that cross disciplinary boundaries and offer overlapping and yet distinct ways to conceptualize and identify determinants of health in Hispanic populations, including the life course cross-cutting approach [51]. For example, Fox et al. propose a biological life course perspective suggesting that the effects of acculturation can be biologically transmitted from mothers to offspring by fetal programming [52]. That is, poorer health among second-generation Hispanics may result from fetal exposures to intrauterine biological conditions resulting from the mother's degree of acculturation [52]. The intergenerational biological transmission could be the consequence of gestational stress processes (e.g., higher concentrations of stress-related hormones such as cortisol), maternal health-related behaviors (e.g., poor diet), or psychosocial processes (e.g., increased depression, decreased social support) occurring during pregnancy, which are related to acculturative processes and create vulnerabilities for children [51, 52]. The authors acknowledge that postnatal factors (e.g., parental behaviors or socialization practices) may also determine the health of subsequent generations; however, they assert that fetal programming provides a feasible, alternative explanation for the declining health observed among second-generation Hispanics [51, 52].

In striking contrast to the studies above, a recent study conducted with Puerto Rican women in Massachusetts found that low acculturation was associated with lower gestational age and birthweight and a possible increased risk of adverse birth outcomes [37]. Women who preferred to speak Spanish ($\beta = -0.39$, $SE = 0.2$, $p = 0.02$) and who were first generation in the USA ($\beta = -0.33$, $SE = 0.1$, $p = 0.02$) had significantly lower gestational ages than women who preferred English or who were later generation, respectively [37]. Similarly, women who were first generation had babies who weighed 76.11 g less ($SE = 35.2$, $p = 0.03$) than women who were of second or later generation [37]. In this study, acculturation was measured directly via the Psychological Acculturation Scale (psychological acculturation), a 10-item bi-dimensional instrument that measures psychological attachment to and belonging within the Anglo-American and Latino/Hispanic cultures, a predictor of cultural behaviors and preferences [37]. Puerto Ricans have distinct migration patterns, culture, and history from other Hispanics, set apart primarily by the fact that they possess US citizenship [37]. As such, Puerto Ricans are technically internal migrants when moving to the continental USA, and their experiences as “immigrants” may not be the same as other Hispanics in the USA [37]. Since the rate of preterm births among Hispanics in the USA is significantly higher among Puerto Ricans, there is a need for more research in this area, focusing on the acculturative differences among Hispanics in the USA. Future studies should utilize prospective designs that include measures of acculturation, nativity, and ethnicity when studying health disparities in birth outcomes [37].

Vitamin D Deficiency as a Risk Factor of Premature Delivery

Since its discovery a 100 years ago, vitamin D has emerged as one of the most debated nutrient and prohormones of the twenty-first century [53]. Vitamin D is a prohormone that is either ingested or is produced photo-chemically in the skin [54]. Dietary vitamin D and cutaneous vitamin D₃ bind to vitamin D binding protein (DBP) and are transported to the liver, where they are metabolized to form 25(OH)D [54]. The latter is the major circulating vitamin D metabolite, and is widely recognized as the best marker of vitamin D nutritional status [54]. Vitamin D and its receptor are active in the human placenta and immune modulation, suggesting a causative role for vitamin D deficiency in preeclampsia [55].

According to the American College of Obstetrics and Gynecology and the Institute of Medicine (IOM) the current vitamin D Estimated Average Requirement (EAR) during pregnancy is 400 IU/day, the Recommended Dietary Allowance (RDA) is 600 IU/day, and the tolerable upper intake limit (UL) is 4000 IU/day [53, 56].

Vitamin D deficiency (<50 nmol/L) is estimated to affect about 38% of US reproductive-aged women and 28% of US pregnant women [57]. Vitamin D deficiency is common during pregnancy [58]. Among pregnant women, vitamin D deficiency varies significantly by racial and ethnic groups, ranging from 13% of

non-Hispanic White women to 80% among non-Hispanic Black women [57]. Women who have low levels of vitamin D may be at higher risk for problems during pregnancy, including preterm birth [57].

Vitamin D deficiency is prevalent and is also higher in Hispanic compared with non-Hispanic White women [53, 58, 59]. Scholl et al. conducted a study in New Jersey that included Hispanic women and found a 34.7% prevalence of vitamin D deficiency (<50 nmol/l) [58, 60]. A study conducted by Merewood et al. in Boston that also included Hispanic women found that 22.6% of participants had vitamin D levels <37.5 nmol/l [58, 61]. In a study by Baker et al. in North Carolina that included Hispanic women, the authors found a 33.6% prevalence of vitamin D insufficiency, with 12.4% of participants being vitamin D deficient [58, 62].

Ginde et al. evaluated vitamin D insufficiency in a nationally representative sample of adolescent and adult women of childbearing age [59] and found that Hispanic women had a prevalence of 25(OH)D <75 nmol/L that is similar to non-Hispanic Blacks. Individuals with darker skins, those who cover their skin with clothing for religious or cultural reasons, and those living farther away from the equator during the winter season are at particular risk for vitamin D insufficiency [63, 64]. The absorption of ultraviolet B radiation by skin melanin and consequent reduction of vitamin D synthesis is likely to be a major cause of the observed differences by race/ethnicity [59, 65].

Until recently, there has been a paucity of data from randomized controlled trials to establish clear-cut beneficial effects of vitamin D supplementation or concentration of circulating 25(OH)D during pregnancy and birth outcomes [53]. Nobles et al. investigated the association between vitamin D status in early pregnancy and the risk for subsequent adverse maternal and infant outcomes in an ethnically diverse population at high risk for gestational diabetes mellitus. They also investigated whether these associations differed according to Hispanic ethnicity [58]. Hispanic ethnicity was associated with higher odds of vitamin D insufficiency (OR 2.53; 95% CI 1.49, 4.29) [58]. Among Hispanic women only, higher serum vitamin D levels in early pregnancy were associated with a small increased risk for gestational diabetes mellitus [58]. In this study, in which eight Hispanic women delivered prematurely, early-pregnancy vitamin D insufficiency and deficiency were significantly associated with a lower birth weight, as compared with women with sufficient levels of vitamin D [58].

Wagner et al. conducted post-hoc analyses to examine the relationship between 25(OH)D concentration and preterm birth rates using two combined cohort datasets ($n = 509$), funded by the National Institute of Child Health and Human Development (NICHD, $n = 346$) and the Thrasher Research Fund (TRF, $n = 163$) [53]. Women with serum 25(OH)D concentrations ≥ 40 ng/mL ($n = 233$) had a 57% lower risk of preterm birth compared to those with concentrations ≤ 20 ng/mL [$n = 82$; RR = 0.43, 95% confidence interval (CI) = 0.22, 0.83]. This finding remained practically the same after adjusting for covariates (RR = 0.41, 95% CI = 0.20, 0.86) [53]. Among racial/ethnic groups, there was a 79% lower risk of preterm birth among Hispanic women with 25(OH)D concentrations ≥ 40 ng/mL ($n = 92$) compared to those with 25(OH)D concentrations ≤ 20 ng/mL ($n = 29$; RR = 0.21, 95% CI = 0.06, 0.69); and

a corresponding 45% lower risk among Black women ($n = 52$ and $n = 50$; $RR = 0.55$, 95% $CI = 0.17, 1.76$). Differences by race/ethnicity were not statistically significant when 25(OH)D was included as a covariate, suggesting that the impact on prematurity risk may be mediated by vitamin D levels. When compared to 2009–2011 Charleston County, South Carolina rates, women with serum concentrations ≥ 40 ng/mL in the combined cohort had a 46% lower rate of preterm birth overall ($n = 233$, $p = 0.004$) with a 66% lower rate among Hispanic women ($n = 92$, $p = 0.01$) and a 58% lower rate among Black women ($n = 52$, $p = 0.04$) [53]. These post-hoc analyses support the importance of attaining 25(OH)D blood concentration levels substantially above 20 ng/mL during pregnancy for the prevention of preterm birth.

Conclusion

Preterm birth is a major public health problem in the USA. A 2007 report from the IOM states that the problem of premature deliveries is complex and poorly understood, but that it involves interrelated, biologic, psychologic, and social factors [3].

Hispanic women are at relatively high risk of delivering prematurely, although this risk appears to be exacerbated or modified by multiple factors. This public health challenge deserves strong attention, as nearly 105,000 Hispanic infants are born preterm annually.

Hispanic women of childbearing age suffer from significantly higher rates of obesity and diabetes, and pregnancy-related hypertension compared to non-Hispanic Whites, all previously found to be risk factors for preterm birth. Maternal age, late prenatal care, smoking and drinking status, and acculturation have been identified as risk factors for premature delivery among Hispanics. In addition, among the Hispanic population, the rate of preterm birth is highest for infants born to women of Puerto Rican descent.

Women who have low levels of serum vitamin D may be at higher risk for negative pregnancy outcomes, including preterm birth. Among pregnant women, vitamin D deficiency varies significantly across racial/ethnic groups. Vitamin D deficiency is prevalent and is also higher in Hispanic compared with non-Hispanic White women. More research, especially through prospective cohort studies, is needed to clarify the relationship between vitamin D deficiency and poor pregnancy outcomes. Further research should focus on defining optimum 25-hydroxy vitamin D levels in pregnancy as well as among various subgroups of the population. Randomized trials are needed to determine whether vitamin D supplementation can improve pregnancy outcomes in Hispanic populations.

Glossary

Acculturation: Process by which individuals whose primary lifestyle has been that of one culture (e.g., Latin American) acquire characteristic ways of living of another culture (e.g., Anglo American). As implied by the definition, acculturation scales typically assume that an individual moves from one cultural orientation to another.

losing the first as the second is acquired. More complex theories of acculturation posit that individuals may simultaneously retain one ethnic identity while also learning the new culture's traditions and values. While the latter conceptualization of acculturation is appealing, it is rarely used in studies.

Adequate prenatal care (PNC): The Adequacy of Prenatal Care Utilization (APNCU) Index attempts to characterize prenatal care (PNC) utilization on two independent and distinctive dimensions—namely adequacy of initiation of PNC and adequacy of received services (once PNC has begun). The index uses information readily available on US birth certificates (month of initial PNC visit, number of visits, and gestational age).

Binge drinking: Pattern of drinking that brings a person's blood alcohol concentration (BAC) to 0.08 grams percent or above. This typically happens when women consume four or more drinks in about 2 h.

Current Smoking: Current smoking is defined as having smoked at least 100 cigarettes in one's life and smoking every day or some days at the time of the survey.

Marianismo: A cultural value that denotes the gender role expectations of Latina women. An important aspect of *marianismo* is the sense of responsibility to the family [66].

This role is based on the emulation of the Virgin Mary in the Catholic religion, and has been referred to as *la madre abnegada*, meaning "self-sacrificing mother" [66].

Obesity: Body Mass Index ≥ 30 kg/m².

Preterm: A birth before 37 weeks of pregnancy.

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Anorexia Nervosa, Bulimia Nervosa, and Binge-Eating Disorder During Pregnancy

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Keywords Anorexia nervosa · Binge-eating disorder · Bulimia nervosa · Compensatory behavior · Purging

Key Points

- Anorexia nervosa (AN), bulimia nervosa (BN), or binge-eating disorder (BED) that occurs before, during, or after pregnancy may impact maternal and fetal outcomes via malnutrition.
- Optimal energy and nutrient intakes, notably folate, B₆, B₁₂, vitamin A, calcium, iron, zinc, and electrolytes, across pregnancy are crucial for women with AN, BN, or BED.
- Screening and assessing for AN, BN, or BED should be routine in prenatal care as these disorders are often unreported.
- Interdisciplinary treatment of AN, BN, or BED before conception is beneficial to preventing a high-risk pregnancy. Identification and intervention of AN, BN, or BED during pregnancy is critical to optimizing maternal and fetal health.

Introduction

During periods of severe caloric deprivation, reproduction becomes a nonessential life function. For example, approximately half of all women of childbearing age experienced amenorrhea during the Dutch Winter Famine of 1944–1945 [1]. Reproduction requires a nutritionally replete woman at conception and the availability of energy, macronutrients, and micronutrients throughout pregnancy. A supply of energy that is balanced to support eumenorrhea, implantation, and growth

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and development of the placenta and other maternal and fetal tissues is critical for optimal pregnancy outcomes. Anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED) represent conditions of energy, macronutrient, and micronutrient imbalances for individuals with such eating disorders.

When occurring before, during, or after pregnancy, such a disorder may impact maternal and fetal outcomes. Treatment prior to conception is ideal; however, screening for eating disorders during pregnancy is important to facilitate early intervention that may optimize maternal and fetal health.

Eating Disorders Defined

The American Psychiatric Association defines AN, BN, and BED based on diagnostic criteria for each eating disorder [2]. Selected features are displayed in Table 1. Very little is known about the incidence and outcomes of other specified or unspecified feeding or eating disorders during pregnancy. Thus, this discussion focuses on AN, BN, and BED.

Anorexia Nervosa

Characterized by substantial voluntary weight loss and persistent low body weight due to self-starvation or extreme energy expenditure (restricting subtype) or binge-eating followed by purging (binge-eating/purging subtype), AN occurs in 0.5–4.3% of the female population [3, 4]. Clinical signs and symptoms of AN include an emaciated appearance, prepubertal features, lethargy, lanugo, alopecia, acrocyanosis, hypothermia, swollen joints, pitting edema, and bradycardia and hypotension. Biochemical evaluation often shows fluid and electrolyte disturbances and hypercarotenemia as well as endocrine and hematologic abnormalities such as hypothyroidism and anemia, respectively. Several cardiovascular irregularities develop along with a host of gastrointestinal complications, particularly in those with the binge-eating/purging type of AN. Osteoporosis and skeletal fractures are common in persons with AN. Some may experience peripheral neuropathy and seizures. Mortality is as high as 20% in women with long-term AN [3].

Bulimia Nervosa

Individuals with BN engage in binge-eating episodes, followed by compensatory behaviors to prevent any increases in body weight. Purging behaviors include self-induced vomiting or self-prescribed use of enemas, laxatives, or diuretics. Nonpurging behaviors include fasting and excessive exercise. Clinically diagnosed BN occurs in 0.9–2.9% of the female population [3, 4]. Clinical features of BN include Russell's sign, dental enamel erosion, dental caries, and enlargement of the parotid glands in

Table 1 Common features of anorexia nervosa, bulimia nervosa, and binge-eating disorder [2]

Feature	Anorexia nervosa (AN)	Bulimia nervosa (BN)	Binge-eating disorder (BED)
Body weight	<ul style="list-style-type: none"> • Habitually extreme low weight for age, sex, life stage, and/or health status • Intense fear of weight gain 	<ul style="list-style-type: none"> • Generally normal weight • Weight fluctuations 	<ul style="list-style-type: none"> • Generally normal weight, overweight, or obese
Eating pattern	<ul style="list-style-type: none"> • Restricting • Binge-eating/purging 	<ul style="list-style-type: none"> • Recurrent binge-eating with compensatory behavior (\geq once per week for ≥ 3 months) • During a binge episode, larger than typical quantity of food intake within 2 h • Sensation of no control over intake during binge-eating episode 	<ul style="list-style-type: none"> • Recurrent binge-eating without compensatory behavior (\geq once per week for ≥ 3 months) • During a binge episode, larger than typical quantity of food intake within 2 h • Sensation of no control over intake during binge-eating • Episode associated with ≥ 3 of: <ol style="list-style-type: none"> 1. Unusually rapid eating; 2. Uncomfortable fullness attained; 3. Lack of physiological hunger; 4. Eating alone; 5. Feeling of guilt, disgust, and/or depression after eating; 6. Sensation of distress with binge-eating
Body image	<ul style="list-style-type: none"> • Disturbance • Dissatisfaction • Distortion 	<ul style="list-style-type: none"> • Disturbance • Dissatisfaction • Distortion 	<ul style="list-style-type: none"> • Disturbance • Dissatisfaction
Type	<ul style="list-style-type: none"> • Restricting • Binge-eating/purging 	<ul style="list-style-type: none"> • Purging as compensatory behavior^a • Nonpurging but with other compensatory behaviors^a 	<ul style="list-style-type: none"> • Not applicable
Menstrual function (not part of diagnostic criteria)	<ul style="list-style-type: none"> • Amenorrhea in $>75\%$ 	<ul style="list-style-type: none"> • Eumenorrhea in 50%; oligomenorrhea or amenorrhea in 50% 	<ul style="list-style-type: none"> • Generally normal

^aIndependent of AN

those who use self-induced vomiting as a purging behavior. Use of enemas, laxatives, and diuretics as well as vomiting can lead to electrolyte imbalances, cardiac dysfunction, and other neurologic disorders. Gastrointestinal symptoms may range from constipation to esophageal or gastric rupture. In those who engage in nonpurging behaviors, electrolyte imbalances, renal and cardiac dysfunction, and gastrointestinal disorders are common. Mortality occurs in less than 10% of individuals with BN [3].

Binge-Eating Disorder

Overweight and obesity are common in individuals with BED, as is normal weight. The prevalence of BED is 0.2–11.2% in individuals [3]. Behavioral signs of BED include excessive eating in the absence of hunger not followed by purging or other compensatory action, loss of control over intake, feelings of guilt, depression, and/or anxiety, along with low self-esteem, and hiding of food, or eating alone. Comorbid conditions may include type 2 diabetes, cardiovascular disease, chronic gastrointestinal and/or renal dysfunction, and musculoskeletal disorders. Biochemical evaluation is generally consistent with indices of obesity-related metabolic abnormalities. Mortality due solely to BED is less than 3% [3].

Etiology

Several models for the etiology of AN, BN, and BED have been developed. Genetic foundations may explain roughly 40–60% of the variance in AN, BN, and BED [5, 6]. Candidate genes include the serotonergic neurotransmitter system (5-HT_{2A}), agouti related melanocortin-4 receptor, uncoupling protein-2/-3, estrogen-beta-receptor, and the *FTO* locus [7, 8]. Alterations in these genes would impact appetite regulation, mood, energy utilization, eating restraint, and body weight, but much more needs to be revealed about the genetic determinants of eating disorders [6, 7]. Other variables included in explanatory models involve biologic, psychologic, sociologic, and behavioral factors [9]. While multifactorial in nature, AN, BN, and BED have relatively clear clinical manifestations and anticipated outcomes. Dire consequences of these eating disorders are expected in untreated and long-term conditions. Because of such complications, pregnancy places the woman with AN, BN, or BED and her fetus at high risk for adverse outcomes.

Eating Disorders During Pregnancy

AN, BN, and BED are typically manifested in the early postpubertal to young adult years [10] and continue throughout the reproductive years [11]. Menstrual dysregulation is commonly present in AN and BN, suggesting that pregnancy may be of

little concern in women with these eating disorders. However, close to 10% of women who sought treatment in an infertility clinic presented with an eating disorder [12]. In another fertility clinic, 60% of women with oligomenorrhea had eating disorders [13], indicating the desire for fertility despite any dysmenorrhea associated with AN or BN. In a separate report, almost 9% of women seeking initial prenatal care presented with BED [14].

Women with eating disorders may become pregnant, particularly those women who are undergoing active treatment or are in remission [15]. While pregnancies in women with active BN and BED are more common than in women with active AN, women with histories of AN, BN, and BED have pregnancy rates similar to the general population of women of childbearing age [16].

Many factors are important to a successful course and outcome of pregnancy. Yet, prepregnancy weight and weight gain by the mother during pregnancy are the two most salient indicators of infant outcome [17, 18]. Common characteristics of AN, BN, and BED are body image dissatisfaction or disturbances and deviations from normal in how food and eating episodes are regarded. Thus, pregnancy presents a pivotal life cycle stage for a woman with an eating disorder, because body weight and shape transform gradually with steady patterns of food intake over the course of pregnancy and change abruptly upon delivery.

Nutritional Concerns

Adequate dietary intake is essential to meet the energy demands of pregnancy as well as to provide micronutrients that are critical to the growth and development of the woman and her fetus. Specific nutrient requirements for pregnancy are presented in Chap. 1 (“Nutrient Recommendations and Dietary Guidelines for Pregnant Women”). Nutrients of special concern in the woman with AN, BN, or BED are discussed here (Table 2).

Energy and Macronutrients

Energy needs increase in the last two trimesters to support the maternal and fetal products of pregnancy as well as spare protein to build these new tissues. Weight gain serves as a proxy indicator that these tissues have developed normally. What is unique in AN is the controlled intake of food energy in those with restricting subtype. Intakes of 200–700 kcal per day, typical of an individual with restricting-type AN, are simply inadequate to supply the energy required for most successful pregnancies. In AN of binge-eating/purging subtype and purging-type BN, adequate and even overly abundant kilocalories may be consumed—but are purged before the body has the opportunity to either fully digest or absorb nutrients. With nonpurging-type BN, adequate energy may be consumed; however, laxative, diuretic, and/or enema use as well as excessive exercise may result in

Table 2 Nutrients of special concern in women with anorexia nervosa (AN), bulimia nervosa (BN), or binge-eating disorder (BED) during pregnancy

Nutrient	Concern in AN, BN or BED	Dietary reference intake during pregnancy	Role during pregnancy
Energy and macronutrients^a			
• Energy	• Energy severely restricted in AN (200–700 kcal per day) or excessive (1500–9000 kcal per binge episode) followed by compensatory behavior in AN or BN with limited energy availability; in BED, inconsistent excessive energy (1500–9000 kcal per binge episode) availability	• +340 kcal per day in second trimester and +452 kcal per day in third trimester	• Energy to supply production and growth of maternal and fetal tissues of pregnancy
• Carbohydrate	• Severely restricted in AN or binged but purged in BN; episodically excessive in BED	• Minimum of 175 g per day	• Glucose availability and non-protein energy needs for mother and fetus
• Protein	• Adequate proportion relative to energy intake, but total intake limited in AN	• 71 g per day	• Amino acid supply for maternal and fetal tissue production, maternal blood volume expansion and fluid balance
• Fat (lipids)	• Intake generally avoided or purposefully restricted in AN	• 13 g per day of linoleic acid and 1.4 g per day of alpha-linolenic acid	• Growth, development, and function of fetal nerve and brain tissue, cell membranes, and organs
Vitamins			
• Folate	• Poor intake and subclinical deficiency in AN and BN	• 600 mcg per day (14–50 years)	• Fetal neural tube formation
• Pyridoxine (B ₆)	• Poor intake and subclinical deficiency in AN and BN	• 1.9 mg per day (14–50 years)	• Coenzyme for maternal energy metabolism
• Cobalamin (B ₁₂)	• Poor intake (especially in vegans) and subclinical deficiency in AN and BN	• 2.6 mcg per day (14–50 years)	• Required for maternal folate metabolism and DNA and RNA synthesis for fetal tissues
• Vitamin A	• Hypercarotenemia in AN due to catabolism	• 770 mcg retinal activity equivalents per day (19–50 years) • 750 mcg retinal activity equivalents per day (14–18 years)	• Cellular differentiation for fetal tissue development

Table 2 (continued)

Nutrient	Concern in AN, BN or BED	Dietary reference intake during pregnancy	Role during pregnancy
Minerals			
• Calcium	• In AN, skeletal calcium stores may be compromised	• 1000 mg per day (19–50 years) • 1300 mg per day (14–18 years)	• Fetal skeletal mineralization
• Iron	• Poor intake (especially in vegans) in AN and BN	• 27 mg per day (14–50 years)	• Hemoglobin synthesis; support of maternal blood volume expansion
• Zinc	• Poor intake (especially in vegans) in AN and BN	• 11 mg per day (19–50 years) • 12 mg per day (14–18 years)	• DNA and RNA synthesis and cofactor for enzymes
• Potassium	• Hypokalemia due to purging and other compensatory behaviors in AN and BN	• 4.7 g per day (14–50 years)	• Transmission of nerve impulses; major intracellular cation
• Sodium	• Hyponatremia due to purging and other compensatory behaviors in AN and BN	• 1.5 g per day (14–50 years)	• Transmission of nerve impulses; major extracellular cation
• Chloride	• Hypochloremia due to purging and other compensatory behaviors in AN and BN	• 2.3 g per day (14–50 years)	• Part of hydrochloric acid in stomach; transmission of nerve impulses; major extracellular anion

Compiled from Food and Nutrition Board, Institute of Medicine (1998) Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B₆, folate, vitamin B₁₂, pantothenic acid, biotin, and choline. National Academies Press, Washington, D.C.; Food and Nutrition Board, Institute of Medicine (2001) Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. National Academies Press, Washington, D.C.; Food and Nutrition Board, Institute of Medicine (1997) Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. National Academies Press, Washington, D.C.; and Food and Nutrition Board, Institute of Medicine (2004) Dietary Reference Intakes for water, potassium, sodium, chloride, and sulfate. National Academies Press, Washington, D.C.

*From [24]

malabsorption, excessive excretion, or altered utilization of nutrients such that the stream of nutrients is inadequate during pregnancy. Recurrent binge-eating of BED may result in excess intake of kilocalories associated with unnecessary maternal and fetal weight gain.

To provide an adequate amount of glucose and nonprotein kilocalories, over 175 g of carbohydrate per day is needed in pregnancy. If composed solely of carbohydrate, 700 kcal would meet this minimum need; however, most intakes of women with active restricting subtype AN do not contain adequate carbohydrate levels. Conversely, foods ingested during binge-eating episodes have been shown to contain high amounts of carbohydrate [19, 20]. Yet, if purged, malabsorbed, or used to sup-

port increased energy expenditure of exercise, this carbohydrate is not readily available to support growth and development of the mother and fetus. Low-carbohydrate diets do not meet the minimum need for carbohydrate during pregnancy. Moreover, these diets result in mild ketosis [21], which may pose harm to the fetus [22]. Excess carbohydrate intake such as in BED may result in dysregulated glucose metabolism with short- and long-term consequences for mother and fetus [23].

Protein intake is crucial to supply the amino acids needed for production of new tissues and to support blood volume expansion and fluid balance. Restricted intake and purging and nonpurging behaviors often do not allow for the provision of adequate protein during pregnancy. Vegetarianism is common in women with eating disorders [25]. Dietary protein and specific amino acid deficiencies may be of concern in women with AN or BN who are also vegetarians.

A small portion of total kilocalories as dietary fat is needed to supply the essential fatty acids—linoleic acid and alpha-linolenic acid. These fatty acids are crucial, however, to the growth, development, and function of nerve and brain tissues, cell membranes, and organs. Docosahexaenoic acid (DHA) plays a role in cognitive development and visual acuity. Avoidance of dietary fat in women with AN or BN, but not BED where dietary fat intake may be increased during binge-eating, has been documented [26, 27]. This has implication for overall energy intake as well as absorption, metabolism, and utilization of fat-soluble vitamins.

Balanced energy intake is critical to adequate weight gain and micronutrient availability during pregnancy. In general, total energy intake should be made up of 45–65% carbohydrate, 10–35% protein, and 20–35% lipids or dietary fat [24].

Micronutrients

Vitamins

The B-complex vitamins—folate, pyridoxine (B_6), and cobalamin (B_{12})—are of special concern in pregnant women with AN or BN. The metabolic needs for these vitamins do not appear to be greater in pregnant women with AN or BN compared with pregnant women without these eating disorders. However, due to past and present eating behaviors, women with AN or BN may have subclinical deficiencies prior to pregnancy and poor dietary intakes of these nutrients during pregnancy.

Folic acid supplementation prior to and in early pregnancy has been shown to reduce the risk and incidence of neural tube defect (NTD) in the infant. The risk for NTD incidence was 1.7 times greater in women with eating disorders compared with controls [28]. Moreover, NTD incidence was 2.7 times higher in women who used diuretics compared with control women [28]. Folate intake is generally suboptimal in women with active AN and BN [29].

Pyridoxine and B₁₂ intakes are of concern in women with AN and BN as eating pattern data show limited intakes of meat and whole-grain foods [25, 29], the primary sources of these two nutrients. Vitamin B₆ is required for serotonin synthesis. Serotonin is a neurotransmitter that controls satiety and mood, and serotonin deficiency has been implicated in AN, BN, BED, and depression. A lack of dietary B₆ limits the conversion of the amino acid tryptophan to serotonin, leading to poor functioning of the serotonergic transmitter system. Moreover, in niacin deficiency, dietary tryptophan is competitively converted to niacin. Thus, in certain phenotypes, inadequate dietary B₆ intake may precipitate or exacerbate AN, BN, BED and associated mood disorders.

Because a vegetarian pattern of eating is relatively common in eating disorders, consumption of meat, chicken, fish, milk products, and eggs varies widely. Cobalamin deficiency may result in pernicious anemia for the mother and may impair deoxyribonucleic acid (DNA) synthesis and nerve function in the offspring. Inadequate B₁₂ intake has been reported in women with AN [29].

Hypercarotenemia is common in AN [30] and results in the yellowish skin tone sometimes observed clinically. Elevated blood carotene is due to catabolism of lipid stores and not excessive intake. During pregnancy, vitamin A needs, inclusive of carotenoids and retinoids, increase slightly to support cellular differentiation and tissue and organ formation. Excessive consumption should be avoided.

Minerals

Notably in the last trimester of pregnancy, maternal skeletal calcium is mobilized and calcium absorption is upregulated to meet the calcium demands of the fetus [31]. An adequate supply of calcium is necessary to support mineralization of the fetal skeleton. Osteoporosis risk is significantly greater in women who have experienced amenorrhea due to low estrogen concentration, often as in AN. Therefore, women with AN may begin their pregnancies with poor skeletal calcium reserves [32]. At least 1000 mg of dietary calcium per day is needed during pregnancy for adult women; however, this requirement may be higher in the woman with AN who also has osteopenia or osteoporosis. Dietary calcium intake in those with BN or BED is generally adequate, with the exception of vegan or fruitarian diets.

The physiologic need for iron decreases in a woman with AN in relation to the duration of amenorrhea and degree of catabolism. However, during pregnancy, the iron requirement increases by 50%. A woman with AN may have difficulty meeting this requirement during pregnancy. Moreover, in those women with AN who also present with iron-deficiency anemia prior to or during pregnancy, supplemental iron may be necessary to meet the increased need.

Zinc intake is poor in women with AN and BN [29, 33], particularly in vegetarians. This mineral is required for DNA and ribonucleic acid (RNA) synthesis, protein production, and as a cofactor for enzymatic activity.

Electrolyte balance may be moderately to severely disturbed in those who engage in purging, laxative and diuretic use, and excessive exercise. Self-induced vomiting can lead to hypokalemia and hypochloremic alkalosis. Laxative and diuretic abuse is associated with hypokalemia. Excessive exercise may result in hyponatremia and hypokalemia. These compensatory behaviors lead to dehydration, elevation in blood urea nitrogen (BUN), and retardation of glomerular filtration rate. Alterations in maternal kidney function due to AN or BN may impair the efficiency with which fetal waste products are excreted during pregnancy.

Maternal and Fetal Risks and Outcomes

Pregnancy represents a life cycle stage during which energy balance is critical to optimal outcomes for both mother and fetus. Body weight and shape changes that occur during pregnancy and serve as indicators of appropriate energy, macronutrient, and micronutrient intakes to support fetal growth and development must be accepted by the woman with an eating disorder. A variety of risks and adverse outcomes have been documented in women with AN, BN, or BED during pregnancy (Table 3), although studies with larger, more representative samples suggest that some of these outcomes are no different between women with and without an eating disorder [34–36].

Table 3 Adverse findings during pregnancy in women with anorexia nervosa, bulimia nervosa, or binge-eating disorder

Maternal outcomes	Fetal outcomes
• Inadequate or excessive body weight gain	• Fetal distress
• Spontaneous abortion	• Intrauterine growth restriction
• Hyperemesis gravidarum	• Perinatal death
• Anemia	• Preterm delivery
• Hypertension	• Low birth weight
• Relapse of AN or BN symptoms	• Small for gestational age
• Worsening of AN or BN symptoms	• High birth weight
• Premature contractions	• Macrosomia
• Prolonged labor	• Microcephaly
• Cesarean section	• Short body length
• Death	• Neural tube defect
• Postpartum depression	• Other birth defects
	• Poor Apgar scores

Findings Related to Anorexia Nervosa

In studies that investigated AN in pregnant women, inadequate weight gain [37, 38], excessive weight gain [34], spontaneous abortion [39], and delivery by cesarean section [38, 39] were common. Other adverse events included anemia, hyperemesis gravidarum, intrauterine growth restriction (IUGR), perinatal death, premature contractions, preterm delivery, fetal distress, small for gestational age (SGA), and low birth weight (LBW) [34, 37, 38, 40–45]. Relapse of AN occurred in one case [46], and unexpected maternal death occurred in another pregnant woman with AN [47]. Pregnancy and poor postpartum coping appeared to have precipitated AN in a separate woman [48].

Findings Related to Bulimia Nervosa

Individual case studies and case series reports show a range of maternal and fetal outcomes, largely due to the inconsistencies in use of diagnostic criteria, length of BN history, treatment interventions during pregnancy, and lack of comparison to appropriate controls [49–54]. One consistent finding in these studies, however, was inadequate [50, 51, 53] or excessive [51, 54] weight gain.

Adverse outcomes in larger studies include inappropriate weight gain [34, 55–57], spontaneous abortion [22, 55, 58, 59], hyperemesis gravidarum, premature contractions, preterm delivery, LBW, SGA, and poor Apgar scores [22, 45, 55, 59, 60], as well as postpartum depression (PPD) [59].

Findings Related to Binge-Eating Disorder

Excessive weight gain during pregnancy is prevalent in BED [36, 57] and may coexist with hypertension [45]. Spontaneous abortion, prolonged labor, and delivery by cesarean section are common [35, 45, 61]. Macrosomia and high birth weight is more frequent in infants of women with BED [36, 45, 61].

Findings Related to Anorexia Nervosa, Bulimia Nervosa, and Binge-Eating Disorder

In those studies in which women with AN, BN, or BED were investigated together, risk and incidence of inappropriate weight gain [61–64], hyperemesis gravidarum [65], cesarean section [66, 67], preterm delivery [67, 68], LBW [65, 67–69], SGA

[65, 68], small head circumference or microcephaly [65, 70], short body length [69], NTD [28], and other birth defects [66] were high. In the first year of life, infants of mothers with eating disorders before and during pregnancy had a reduced weight-for-length growth pattern compared to infants of mothers with eating disorders [71]. In general, women who entered pregnancy in remission from their AN or BN had optimal maternal and fetal outcomes [55, 72], while women with active eating disorders prior to conception and during pregnancy fared less well [22, 68].

Changes in Behaviors

A relapse in eating disorder symptoms in women who were previously in remission may occur during pregnancy [65]. In active AN or BN, body dissatisfaction and low body esteem may worsen during and after pregnancy [46, 73–75] in addition to an increased frequency of restricting, binge-eating/purging, and non-purging behaviors [38, 49, 51, 58, 68, 76]. Conversely, eating disorder symptoms and behaviors improved during pregnancy in general [56, 75, 77–79] and in women receiving treatment [50, 51, 62, 63] and not currently receiving treatment [52, 54, 56, 64, 73, 80, 81]. Yet, postpartum resumption of eating disorder behaviors occurred with some regularity [50, 51, 53, 54, 56, 63, 64, 77, 80–82]. Pregnancy may precipitate new BED behaviors in some women [14, 79, 83, 84]. During pregnancy, BED tends to continue in women with preexisting BED status [79, 83, 85].

PPD requires assessment in women with eating disorders as this mood disorder is tightly linked to eating disorders [86, 87]. While most studies report an increased incidence of PPD in women with AN or BN [22, 66, 86, 87], one study reported fewer symptoms of depression in women with treated BN who delivered infants compared to women with treated BN who had not given birth [88].

Nutrition Care of Women with Anorexia Nervosa, Bulimia Nervosa, or Binge-Eating Disorder During Pregnancy

The first step in the nutrition management of the pregnant woman with AN, BN, or BED is identification of the eating disorder. Assuming that prenatal care is sought, many women with AN, BN, or BED do not disclose their conditions at any of their prenatal visits [47, 51, 54]. In addition, most obstetricians do not inquire about eating disorders in their patients [89]. For example, only 18% of obstetricians in prenatal clinics questioned their pregnant patients about AN and BN [90]. The secrecy of these disorders and lack of inquiry lead to suboptimal care of these pregnant women.

Assessment

Clinicians may pose several questions to their patients to identify preexisting or newly developed eating disorders (Table 4). Once such screening suggests the coexistence of pregnancy and an eating disorder, medical nutrition therapy (MNT) can be applied. As part of MNT, a full nutritional assessment involves systematic collection and evaluation of anthropometric, biochemical, clinical, and dietary intake data. In addition, functional and behavioral status may be evaluated based on responses to screening questions (Table 4) or screening tools such as the “SCOFF” (Sick, Control, One, Fat, Food) questionnaire [91].

Table 4 Screening for an eating disorder during pregnancy

Body weight
1. What is your current weight? Current height?
2. What is your usual weight?
3. What was your highest weight as an adult?
4. What was your lowest weight as an adult?
5. Have you had any changes in weight in the last month?
6. Does your weight fluctuate very often? If yes, by how much and how often?
7. How much weight do you think that you will gain during this pregnancy?
8. How much weight do you want to gain during this pregnancy?
9. Are you concerned about gaining weight during pregnancy?
10. Do you think that your body shape will change during this pregnancy?
11. What do you think about any body shape changes?
Weight control tactics
Have you previously (or are you currently):
1. Gone on (On) a diet to lose weight?
2. Fasted (Fasting) for more than or equal to 8 h (other than during sleep)?
3. Made yourself vomit (Vomiting frequently)?
4. Used (Using) laxatives? If yes, how often?
5. Used (Using) diuretics? If yes, how often?
6. Eaten (Eating) very large amounts of food in a short period of time? If yes, how often? If yes, did you feel in control of this food intake?
7. Restricted (Restricting) the amount of food or beverages that you consume(d)? If yes, how often?
8. Eaten (Eating) in private or in secret?
9. Avoided (Avoiding) certain types of food?
10. Engaged (Engaging) in exercise? If yes, what type, frequency, duration, and intensity?
Dietary intake
1. How frequently do you eat foods and drink beverages?
2. Do you ever skip meals?
3. Do you have any food allergies?

(continued)

Table 4 (continued)

4. Do you have any food cravings?
5. Do you have any food aversions?
6. Have you had morning sickness?
7. Do you drink fluids in place of solid foods or meals?
8. Do you take any vitamin and/or mineral supplements?
9. Do you take any other supplements such as herbal products?
10. Do you use sugar substitutes or fat substitutes?
11. How often do you think about food or eating?
12. Do you purposefully eat until you are uncomfortably full?
13. Have you been hungry during your pregnancy?
14. Are you hungry when you eat?
15. How do you feel when you eat?
General health
1. Were your menstrual cycles regular prior to this pregnancy?
2. Have you experienced constipation or diarrhea?
3. Have you experienced heartburn?
4. Do you feel "stressed" or anxious?
5. Do you think that you are "retaining fluid"?
6. Have you felt weak or light-headed?
7. Are you experiencing frequent urination?
8. Are you taking any over-the-counter or prescription medications?
9. Do you plan to breastfeed your infant?
10. How does this pregnancy compare to your previous pregnancy (pregnancies)?

Anthropometric Data

An easily obtained parameter of adequate dietary intake and fetal growth is maternal body weight. Body weight should be measured at each prenatal visit, recognizing that this assessment may make a woman with AN, BN, or BED uncomfortable. Some women may even refuse to have body weight measured. In those women who may increase eating disorder behaviors with body weight gain [51, 53, 55], nondisclosure of weight changes may be appropriate. Alternatively, in women who relax their eating disorder behaviors during pregnancy [50–52, 54, 64], discussion of weight changes may provide positive reinforcement of healthy behaviors. Inadequate [34, 37, 38, 50, 51, 53–56] and excessive [34, 36, 51, 54, 57] weight gain must be tracked and compared to the recommended weight gain based on prepregnancy body mass index (BMI) and any needed nutritional repletion in AN.

Body weight and weight gain may be affected by the patient's hydration status, glycogen stores (in AN), and changes in lean and fat mass. Body composition testing during pregnancy may be performed by bioelectrical impedance analysis but is significantly affected by hydration status. Skin fold and circumferential measurements

will be affected by differential changes in maternal body fat deposition. Dual-energy X-ray absorptiometry should not be performed during pregnancy. Pitting edema may be a sign of BN.

Biochemical or Laboratory Data

Biochemical or laboratory values are generally normal in women with AN, BN, or BED. During semi-starvation in AN, catabolic and compensatory mechanisms mobilize tissue stores, releasing nutrients to the serum pool. As a result, hypercarotenemia is often found in women with moderate to severe AN. Yet when serum concentrations of nutrients are low, severe AN is likely. At this point, several B vitamins, including B₆ and B₁₂, and minerals, such as zinc, will show signs of depletion. Dehydration in either AN or BN may falsely normalize or elevate several biochemical markers of nutritional status, such as serum albumin and iron. Thus, establishing normal hydration is important for accurate nutrition assessment. Vitamin and mineral supplement use is common in eating disorders and may mask nutrient deficiencies [92]. Elevated blood lipids may be noted in the majority of women, due to liver and hypothalamic dysfunction in AN, inappropriate intake of dietary fats or lipids in AN, BN, or BED during binge-eating, and metabolic abnormalities that are consistent with overweight and obesity status that is more common in BED.

Clinical Data

Upon clinical assessment, signs and symptoms of AN, BN, or BED will be present (see section “Eating Disorders Defined” and Table 1). Bleeding gums or sensitive teeth may present as new symptoms or worsened conditions. Assessment instruments such as the Eating Disorders Examination [93] may also be useful when evaluating the full clinical picture and relate to the functional and behavioral aspects of the specific eating disorder.

Dietary Intake Data

Methods designed to gather dietary intake information include the dietary history, food frequency questionnaire, 24-h recall, and food diary or record. A variety of techniques for data collection, including written, computerized, and Web based have been used with validated instruments. Dietary intake data may be evaluated for energy, macronutrient, and micronutrient intakes; food patterns; food groups; and/or food variety. Comparison to established standards is important, as is comparison to the woman’s previous intake. Such evaluation will identify foods, nutrients, and/or eating behaviors of concern as well as areas where improvements have been made.

Inquiry about eating behaviors may also uncover related issues such as food cravings or aversions, timing and triggers of intake, and fasting and ritualistic behaviors. These may be linked to dental problems, morning sickness, hyperemesis gravidarum, gastrointestinal symptoms, and mood changes during pregnancy.

Nutrition Diagnosis

Based on the nutrition assessment, the registered dietitian can establish a nutrition diagnosis (or diagnoses). Such statements identify nutrition problems (diagnostic labels), related etiology, and distinguishing characteristics (signs and symptoms) and are important to document in the medical record. These nutrition diagnoses serve as the foundation for nutrition interventions, monitoring and evaluation, and anticipated outcomes. Table 5 presents examples of nutrition diagnostic statements for AN, BN, or BED during pregnancy.

Nutrition Intervention

Working from nutrition diagnoses, areas for nutrition intervention that will positively alter behaviors, reduce risks, and improve and/or promote the health of the mother and fetus can be identified. Pregnancy can provide a unique opportunity to improve AN, BN, or BED behaviors if interventions focus on fetal nutritional requirements [50, 52, 56, 64, 75, 78, 79], fetal growth and development [50, 51, 56], and relationships among maternal body weight gain, shape changes, and fetal growth [52, 56, 74]. Planning individualized, patient-focused care,

Table 5 Examples of nutrition diagnostic statements for women with anorexia nervosa, bulimia nervosa, or binge-eating disorder during pregnancy

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- Inadequate energy intake (problem) related to restriction of food intake (etiology) as evidenced by mean daily dietary intake of less than 1000 kcal per day and 7-lb weight loss during the past 6 weeks (signs)

 - Frequent stool output (problem) related to thrice daily use of laxatives and low-dietary fiber intake (etiology) as evidenced by increased diarrhea, dehydration, and estimated average daily dietary intake of fiber of less than 2 g per day (signs and symptoms)

 - Suboptimal folate intake (problem) related to avoidance of leafy green vegetables, orange fruits, and fortified grain products (etiology) as evidenced by red blood cell folate of 2.7 nmol/l (sign)

 - Hypokalemia (problem) related to increased frequency of self-induced vomiting (etiology) as evidenced by change in self-reported behaviors and serum potassium of 2.9 mmol/l (sign)

 - Rapid weight gain (problem) related to increase in binge-eating from once per week to four times per week (etiology) as evidenced by self-reported change in behaviors, weight gain of 16 lb. from the 14th to 18th week of gestation, and average dietary intake of approximately 2000 kcal per day beyond estimated energy needs (signs)

activities, and expected outcomes is essential. The overall goal of nutrition intervention is to “promote the consumption of foods that will best meet the nutritional requirements of pregnancy, essential for fetal growth and development, within the context of the woman’s often uncontrolled [or overly restricted] eating” ([72], p 452).

The primary objective for AN is to gradually increase energy intake to support a positive energy balance to allow repletion of the mother while meeting fetal energy demands. An intake of 130% of estimated energy needs is initially recommended. Reaching this goal should be attained through incremental increases of 100–200 kcal per day approximately twice per week. In the first trimester, additional kilocalories are not needed to support fetal growth and development; however, maternal weight gain of one to two pounds per week may be expected due to repletion of maternal energy stores. During the second and third trimesters, energy intake should increase beyond maternal repletion needs to supply requirements of the fetus (see Table 2). Frequent recalculation of estimated energy needs is necessary to adjust for changes in body composition, basal metabolic rate, and energy expenditure, including physical activity. Any micronutrient deficiencies will need to be corrected, and frequent monitoring of biochemical indicators of nutritional status is critical to prevent refeeding syndrome in the mother and to assure adequate micronutrient supply to the fetus during all trimesters.

The primary objective for BN is to disrupt binge-eating/purging episodes and eating restraint so that intake becomes more consistent and to stop other compensatory behaviors to achieve a stable energy and nutrient supply. In the first trimester, when additional energy is not required, body weight stabilization is critical. Approximately 100–130% of estimated energy needs are recommended, depending on prepregnancy BMI, weight fluctuations, and energy expenditure of physical activity. Through the second and third trimesters, additional energy intake should match recommended increases. In women with AN or BN who abuse laxatives, discussion about anticipated gastrointestinal function throughout pregnancy should be undertaken. Dietary fiber and adequate fluid intake recommendations should be provided to support positive changes in bowel habits and hydration status.

The primary objective for BED is to reduce the frequency of eating binges. Nutrition education regarding consistent eating for a steady, and not overly abundant, macronutrient and micronutrient supply during pregnancy is recommended. In those women with BN or BED who are also overweight or obese, dietary recommendations specific to these conditions should also be considered when setting energy intake levels.

As stated previously, macronutrient distribution of total energy in AN, BN, or BED should be made up of 45–65% carbohydrate, 10–35% protein, and 20–35% dietary fat or lipids. Adjustments may be needed based on food aversions, gastrointestinal complaints, continued binge-eating/purging episodes, or other issues.

Vitamin and mineral supplementation is warranted in pregnant women with an eating disorder. A prenatal supplement that meets but does not exceed 100% of the Dietary Reference Intake for micronutrients for adult women is suggested to allow

Table 6 Nutrition education topics during pregnancy in women with anorexia nervosa, bulimia nervosa, or binge-eating disorder

• Body weight gain: where does this weight go?
• Pregnancy outcomes with maternal malnutrition: what are the risks?
• Pregnancy outcomes with excess weight gain: what are the risks?
• Behavioral strategies to improve eating and intake
• Menu planning, food choices, and portion sizes
• Differences between nutrients from foods and from prenatal supplements
• Folate intake and neural tube defect
• Meeting fetal nutrient needs with a vegetarian diet
• Alcohol intake: what are the effects?
• Caffeine intake: what are the effects?
• Distinguishing morning sickness from self-induced vomiting
• Severe vomiting, prolonged morning sickness, and hyperemesis gravidarum
• Managing constipation, diarrhea, hemorrhoids, and heartburn
• Pica practices
• Exercise recommendations
• Delivery: what can be expected prenatally and postnatally?
• Postpartum body weight loss: what can be expected?
• Planning for lactation
• Energy and nutrient needs of lactation
• Postpartum eating: maintaining healthy habits

for consumption of food-based nutrients and to avoid excessive intakes that may potentially occur from binge-eating.

The registered dietitian should involve the patient in menu planning and food selection. Emphasis on specific micronutrient intake is important to stress the relationship of these nutrients to optimal fetal growth and development [94].

Nutrition education is a vital intervention component. Most women with eating disorders are well versed in nutrition facts and knowledge. However, they may be less aware of nutrition needs for healthy pregnancies. Discussion of micronutrient requirements and roles of these nutrients in fetal growth and development may redirect the mother's preoccupation with body weight and shape to fetal needs for intrauterine health [94]. Other important nutrition education topics are listed in Table 6.

Monitoring and Evaluation

At each prenatal visit, eating disorders screening may be conducted (see Table 4) along with measurement and documentation of parameters or outcomes related to nutrition interventions and diagnoses. Body weight and rate of weight gain should be tracked and evaluated. Adjustments in energy intake should be based on

appropriateness of weight changes. Eating behaviors and dietary intake should be examined at each prenatal visit to assess the adequacy of dietary composition and patterns of intake. Changes in restricting, bingeing, purging, and nonpurging behaviors should be noted and addressed. Fingersticks to check hematocrit and glucose may be useful in the monitoring of iron status and hypoglycemia or hyperglycemia. In women with established eating disorders, urinalysis may detect starvation or dehydration as noted by urinary ketones, elevated specific gravity, and alkaline urine. Vital signs will show any change in general health status, such as hypotension or hypertension. Glucose tolerance testing should be conducted in the 24th to 28th week of pregnancy to screen for gestational diabetes mellitus. Resolution of any nutrition diagnoses should be documented and any new issues addressed.

More aggressive and intensive inpatient care may be warranted if monitoring and evaluation shows a worsening of the eating disorder, IUGR, or other fetal growth and development problems. In AN or BN, a reduction in body weight to less than 75% of expected; hypokalemia, hyponatremia, or hypochloremic alkalosis; dehydration; hyperemesis gravidarum; cardiovascular changes; prolonged fasting; and/or uncontrolled binge-eating/purging cycles; as well as severe depression; suicidal ideation; and any obstetrical complication in AN, BN, or BED are justification for hospitalization.

Planning for Postpartum Care

Relapses in eating disorders often occur in the postpartum period [46, 51–55, 64, 66]. Moreover, the rate of PPD in women with eating disorders is high. Changes in estrogen status and estrogen-beta-receptor function or other gene–nutrient interactions may be responsible for observed relapses. The registered dietitian should work closely with the patient toward the end of pregnancy to set realistic goals for dietary intake, weight loss, eating behaviors, and expectations during lactation.

Interdisciplinary Care

Nutrition care is but one part of treatment for AN, BN, or BED. These complex disorders require multidisciplinary and integrated care, due to the multifactorial etiology and wide scope of signs and symptoms. The obstetrician, nurse practitioner, psychologist or psychiatrist, dietitian, dentist, social worker, family therapist, occupational therapist, pharmacologist, certified exercise physiologist, and other allied health care professionals must openly and cohesively interact with one another and most importantly with the patient to provide effective treatment. Cognitive-behavioral and dialectical-behavioral therapies are used to modify anorexic, bulimic,

and binge-eating behaviors. Medications may be used in treatment, but a risk–benefit assessment for use during pregnancy should be completed by the obstetrician and pharmacologist in consultation with the pregnant (and later lactating) woman. The dietitian may advise on any medication–nutrient interactions that require dietary modifications. An increased frequency of prenatal visits is warranted in these high-risk conditions. Monitoring of fetal heart rate and more frequent ultrasounds may shift the center of attention from the mother’s AN, BN, or BED behaviors to the growing fetus. An informal or formal support network that includes friends, family members, and possibly other patients can provide more constant reassurance, advice, assistance, and positive reinforcement, often valued by women with eating disorders.

Conclusion

Women with active AN, BN, or BED during pregnancy are at high risk for adverse outcomes. Ideally, treatment of the eating disorder should occur prior to conception. If not feasible, screening for and assessment of eating disorders during prenatal visits is critical. If an eating disorder is detected, then interdisciplinary care is vital to address all medical issues of the mother and developing fetus. Nutrition requirements of both the mother and fetus must be considered, and eating patterns and behaviors that optimize a consistent and appropriate stream of nutrients to mother and fetus are key components of care. Treatment of the woman with AN, BN, or BED during pregnancy should not end at delivery, but rather, must continue into the postpartum period and beyond.

Case Study: Bulimia Nervosa During Pregnancy

T.J. is a 32-year-old Caucasian, married woman, gravida 2, para 1, seeking prenatal care in the 11th week of gestation. Medical history reveals current BN, the onset of which occurred in the third month postpartum of her previous pregnancy. Since the onset of BN at age 27, T.J. has engaged in binge-eating/purging cycles at least twice per day, consuming approximately 2200 kcal of high-fat, high-carbohydrate snack-type foods during each binge with subsequent vomiting. She reports “problems with my teeth” and “frequent heartburn.” T.J. denies laxative, diuretic, or enema use, but admits to moderate exercise of “fast-paced walking” of up to 2 h per day. She was dissatisfied with her body shape and inability to quickly lose weight after her first pregnancy and is fearful that she will lose control of her body weight during this pregnancy. She gained 47 lb. during her first pregnancy. T.J. currently weighs 145 lb. and is 5’ 7”. Laboratory values are within normal limits. She reports having the “baby blues” after her first delivery and “frustration” with her husband who “travels too much to be of

any help with our child.” T.J. has not confided in her husband regarding her BN and engages in binge-eating/purging episodes “in secret.”

1. Calculate T.J.’s body mass index and determine an appropriate weight gain for T.J. for her current pregnancy.
2. Estimate T.J.’s energy needs for weight maintenance and weight gain during pregnancy.
3. With T.J., plan a 7-day menu that includes appropriate food choices to meet nutrient needs of pregnancy and strategies to avoid binge-eating.
4. Identify potential adverse outcomes for T.J. and her fetus if BN continues during this pregnancy.
5. Discuss the impact of T.J.’s exercise habits on her energy needs and course of pregnancy.
6. Establish criteria to monitor and evaluate T.J.’s BN during pregnancy on an out-patient basis. Identify key indicators that will be used to determine if inpatient care is needed.
7. List all of the health professionals and others who should be involved in T.J.’s prenatal care and provide reasons for their involvement.

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Diabetes and Pregnancy

Alyce M. Thomas

Keywords Preexisting diabetes · Gestational diabetes mellitus · Congenital anomaly · Insulin resistance · Insulin sensitivity · Normoglycemia

Key Points

- Diabetes is the most common complication affecting pregnancy
- While the macronutrient intake for women with diabetes may be different from the pregnant woman without diabetes, there is no difference in the micronutrient intake
- According to the Dietary Reference Intakes, the minimum carbohydrate intake for pregnant women with diabetes is 175 grams according to the Dietary Reference Intakes (DRI)
- Insulin is the preferred method of pharmacological therapy, if necessary, to promote optimal glucose control in pregnancy
- Either the one-step or two-step method can be used to diagnose diabetes in pregnancy
- Recent research has shown various meal plans, besides restricting the total amount of carbohydrates, may have a positive effect on maternal blood glucose levels

Introduction

Diabetes mellitus affects 29.1 million or 9.3% of the United States population, with 21 million diagnosed cases and 8.1 million undiagnosed (27.8% of people with diabetes are undiagnosed) [1]. It affects approximately 240,000 pregnancies a year, making diabetes the most common complication affecting pregnancy [2].

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The prevalence of gestational diabetes is 9.2%, which accounts for almost 90% of the cases of diabetes in pregnancy [3]. Although perinatal morbidity and mortality have decreased in the last 80 years, the prevalence of fetal complications associated with diabetes continues to be higher than in normal pregnancies. With intensive management and optimal glycemic control, prior to and throughout pregnancy, women with diabetes can reduce their risk of perinatal complications.

Historical Background

Before 1921, women with diabetes were advised to avoid pregnancy or, if conception occurred, to abort because of adverse perinatal outcomes. If the pregnancies advanced to the stage of fetal viability, the infants were often stillborn or were born with major malformations. Before the discovery of insulin in 1921, medical nutrition therapy was the primary method of management for pregnant women with diabetes, however diets were often severely restricted or nutritionally unbalanced. These dietary approaches varied from high carbohydrate-low protein, high protein-high fat, or restricted calories to brief periods of starvation [4, 5]. Alcohol was often included because of its calming effect on the mother [6].

Although insulin revolutionized diabetes management, medical nutrition therapy remained virtually unchanged in the early years after its discovery. In 1937, Priscilla White, a physician at the Joslin Diabetes Center in Boston, MA, developed a new meal plan which consisted of 30 kcal/kg body weight, 1 g protein/kg actual body weight, and 180–250 g carbohydrate with the remainder as fat [7]. Other researchers used similar meal plans to achieve maternal blood glucose control [8, 9].

During the 1950s to 1960s, health care providers were concerned with the risk of macrosomia and hypertension in pregnancy. Weight gain and sodium were restricted to less than 15 lb. (6.8 kg) and 2000 mg, respectively, in all pregnant women. After the publication of *Maternal Nutrition and the Course of Pregnancy* in 1970 [10], weight gain recommendations were increased to 22–30 lbs. (10–13.6 kg) and sodium restriction was eliminated. A comprehensive literature review found no evidence to support the restriction of weight or sodium in pregnancy. However, weight gain and sodium restrictions for pregnant women with diabetes continued until 1970, when the American Diabetes Association recommended the same regimen for pregnant women with diabetes as the non-diabetes pregnant population [11]. Today, pregnant women with and without diabetes follow the same weight gain guidelines.

Preexisting Diabetes

Pathophysiology of Normal Pregnancy

During pregnancy, the fetus receives nutrients across the placenta, including glucose, amino acids, and fatty acids, either via active transport or facilitated diffusion. Maternal glycogen storage and endogenous glucose production increase in the first

trimester. Pregnancy hormones (human placental lactogen and cortisol), estrogen, progesterone, and the constant fetal demand for glucose lower fasting maternal blood glucose levels [12, 13]. This will result in the need for additional calories. In the second trimester, fasting and postprandial glucose levels rise in response to the extra glucose required for fetal growth. Elevated hormonal levels increase insulin resistance, resulting in the production and secretion of additional insulin by the beta cells as glucose is transported across the placenta. Insulin resistance peaks by the latter part of the third trimester, characterized by a three-fold increase in insulin production and secretion. After delivery, insulin production returns to pre-pregnancy levels.

Other hormones thought to affect insulin resistance include leptin, insulin-like growth factors, relaxin, and adiponectin [14, 15]. Maternal insulin does not cross the placental barrier unless bound to insulin immunoglobulins. Fat is deposited and stored primarily in early pregnancy, then mobilized in the third trimester as fetal energy demands increase. Free fatty acids have been shown to contribute to insulin resistance in late pregnancy [16].

Type 1 Diabetes

Women with type 1 diabetes will experience elevated blood glucose levels as the lack of insulin and the rise in free fatty acids lead to the formation of ketones and beta-hydroxybutyrate. There is a risk of diabetic ketoacidosis in the absence or lack of insulin. However, women with type 1 diabetes in optimal glycemic control may experience increased insulin sensitivity and decreased insulin requirements in the first trimester. During the second and third trimesters, elevated hormonal levels increase insulin resistance and extra insulin is necessary to maintain normal maternal glycemic levels and decrease fetal complications.

Type 2 Diabetes

Type 2 diabetes is associated with impaired insulin secretion, insulin resistance, and pancreatic beta cell dysfunction. If the fetus is exposed to excessive maternal glucose, the fetal pancreas is stimulated to secrete additional insulin, which may result in macrosomic growth. Elevated maternal glycemic levels during organogenesis may increase the risk of fetal complications, including congenital anomalies. Exogenous insulin may be necessary to maintain normoglycemia with increasing insulin deficiency and insulin resistance.

Complications Associated with Preexisting Diabetes

Complications associated with diabetes can adversely affect both the woman and fetus. The rate of complications in the fetus is correlated with maternal glycemic control and the trimester of pregnancy.

Fetal

Congenital malformations and spontaneous abortions are associated with maternal hyperglycemia in the first 12 weeks of gestation. The central nervous system, heart, lungs, gastrointestinal tract, kidneys, urinary tract, skeleton, and placenta are all vulnerable to adverse effects (Table 1) [17–19]. The frequency and severity of complications decrease if maternal normoglycemia is maintained throughout pregnancy.

Second and third trimester fetal complications include macrosomia, neonatal hypoglycemia, neonatal hypocalcemia, hyperbilirubinemia, polycythemia, respiratory distress syndrome, preterm delivery, and fetal demise. With the exception of fetal demise, other complications are more closely associated with infant morbidity than mortality.

Table 1 Congenital anomalies associated with preexisting diabetes and pregnancy

Central nervous system
• Neural tube defects (e.g., anencephaly, spina bifida, hydrocephalus)
• Microcephaly
• Dandy-Walker complex
Cardiovascular
• Coarctation
• Transportation of great vessels
• Truncus arteriosus
• Aortic stenosis
• Situs inversus
Gastrointestinal
• Duodenal atresia
• Anorectal atresia
• Gastroschisis
• Anal agenesis
Genitourinary
• Renal agenesis
• Hydronephrosis
• Cystic kidneys
• Anal/rectal atresia
• Ureter duplex
Skeletal
• Caudal regression syndrome

Adapted from Gabrielli S, Pilu G, Reese EA. Prenatal diagnosis and management of congenital malformations in pregnancies complicated by diabetes. In: Reece EA, Coustan DR, Gabbe SG, eds. *Diabetes in Women: Adolescence, Pregnancy and Menopause*. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2004:299–319; and Coustan DR. Prepregnancy counseling and management of women with preexisting diabetes or previous gestational diabetes. In: Coustan DR, ed. *Medical Management of Pregnancy Complicated by Diabetes*. 5th ed. Alexandria, VA: American Diabetes Association; 2013

Macrosomia, which is fetal growth greater than 4000 g regardless of gestational age, is the most common complication associated with diabetes and pregnancy [20]. Macrosomia is thought to occur if maternal glycemic levels are elevated in the third trimester. Pedersen hypothesized that maternal hyperglycemia leads to fetal hyperglycemia, which stimulates the fetal pancreas to produce excessive insulin and results in excess growth [21]. Macrosomic infants have disproportionately large fetal trunks in relation to their head size, thereby increasing the risk of difficult delivery, shoulder dystocia, brachial plexus palsy, or facial nerve injury.

Neonatal hypoglycemia is another complication associated with diabetes and pregnancy. The American Academy of Pediatrics has developed a guide to screen and manage neonatal hypoglycemia [22]. There is currently no evidence-based guideline to define the exact level of hypoglycemia that could result in brain injury to the neonate. The protocol depends on the age of the infant and whether the infant is asymptomatic or symptomatic for hypoglycemia. If the infant is asymptomatic, the initial feeding is within 1 h of birth and the glucose level is screened after 30 min. If the initial screen is <25 mg/dL (1.39 mmol/L), the infant is re-fed and checked in 1 h. If the result is <25 mg/dL (1.39 mmol/L) after the second feeding, intravenous glucose is given. The target glucose screen is ≥ 45 mg/dL (2.5 mmol/L) prior to routine feeds. Respiratory distress syndrome is caused by a deficiency of surfactant, necessary for fetal lung maturity. Neonatal hypocalcemia is serum calcium <7 mg/dL (0.38 mmol/L) in the premature infant with a birth weight <1500 g, and <8 mg/dL (0.4 mmol/L) in the term infant, or the premature infant whose birth weight is >1500 g. The definition of hypocalcemia depends upon gestational age and birth weight.

Hyperbilirubinemia occurs when the serum bilirubin level of the neonate >13 mg/dL (0.72 mmol/L). Polycythemia, which is a hematocrit $>65\%$ at delivery, could lead to perinatal asphyxia. The risk of these conditions decreases if optimal glycaemic control is maintained throughout the pregnancy.

Advances in diabetes research and management have led to decreased risks of fetal demise in infants born to women with preexisting diabetes, though it remains higher than in the non-diabetes pregnant population. Maternal vascular complications, poor blood glucose control, and inadequate or no prenatal care are associated with higher rates of fetal demise than in women with diabetes prior to pregnancy.

Maternal

Preexisting conditions that can complicate the pregnancy in women with type 1 or type 2 diabetes include nephropathy, neuropathy, retinopathy, hypertension, and diabetic ketoacidosis. Diabetic nephropathy is associated with other complications, including preeclampsia, anemia, intrauterine growth restriction, fetal demise, and preterm delivery [23, 24]. If maternal glycemic levels are in optimal control before conception, the severity of complications and further renal deterioration during and after the pregnancy are reduced. Pregnancy itself is not a risk factor for the development or progression of diabetic neuropathy. Gastroparesis, a condition in which the stomach's ability to empty its contents is delayed or impaired, occurs more often in

type 1 diabetes. Women with gastroparesis may experience nausea, vomiting, abdominal discomfort, and difficulty in controlling their glycemic levels. Few studies have been published on gastroparesis and pregnancy. One case report noted severe and intractable vomiting in two women with gastroparesis, resulting in fetal demise in one of the pregnancies [25]. In another case report, one woman with an implantable gastric neurostimulator and on continuous subcutaneous infusion delivered vaginally at 38 weeks gestation with no complications [26].

The effect of pregnancy on diabetic retinopathy depends on the severity of the condition, or whether proteinuria or hypertension is present. In most cases, background retinopathy regresses after delivery. Proliferative retinopathy may progress if the condition was untreated prior to pregnancy [27]. Laser photocoagulation is indicated in the pregnant woman with high-risk proliferative diabetic neuropathy [23]. Obesity is a risk factor for hypertension, and is primarily associated with type 2 diabetes [28]. Diabetic ketoacidosis occurs more rapidly in pregnancy than in the non-pregnant state because of increased insulin resistance and accelerated starvation ketosis. Factors that precipitate diabetic ketoacidosis include hyperemesis, gastroparesis, insulin pump failure, and certain medications, such as steroids [23, 29].

Complications that may develop during pregnancy include hypertensive disorders, polyhydramnios, preterm delivery, and cesarean section. Poor blood glucose control in early pregnancy is associated with the development of preeclampsia and pregnancy-induced hypertension [29]. Although the etiology of polyhydramnios (excessive amniotic fluid) is not well understood, it is associated with suboptimal blood glucose control. Macrosomia may warrant preterm or cesarean delivery.

Medical Nutrition Therapy

There are no specific dietary guidelines for pregnant women with preexisting diabetes [30]. Current guidelines for nutrition recommendations in pregnant women without diabetes may be used for pregnant women with preexisting type 1 diabetes and type 2 diabetes [23]. Individualizing the meal plan is key to providing adequate calories and nutrients in pregnancy. The meal plan works concurrently with insulin therapy to achieve target blood glucose levels. The goals of medical nutrition therapy for pregnancy and diabetes are: (1) to provide adequate nutrients for maternal-fetal nutrition, (2) to provide sufficient calories for appropriate weight gain, and (3) to achieve and maintain optimal glycemic control.

Weight Gain

Weight gain guidelines are based on the 2009 Institute of Medicine's publication, *Weight Gain During Pregnancy: Reexamining the Guidelines*, according to the women's pre-pregnancy body mass index (Table 2) [31]. The pre-pregnancy body mass index and the amount of weight gained during pregnancy are two factors that

Table 2 Institute of medicine weight gain in pregnancy guidelines

Pre-pregnancy BMI	Recommended weight gain	Rate of gain/week (2nd and 3rd trimesters)	Recommended total weight gain (twin gestation)
Underweight (<18.6)	28–40 lb. (12.7–18.2 kg)	1 ½ lb. (0.7 kg)	
Normal weight (18.6–24.9)	25–35 lb. (11.2–15.9 kg)	1 lb. (0.5 kg)	37–54 lb. (16.8–24.4 kg)
Overweight (25.0–29.9)	15–25 lb. (6.8–11.3 kg)	2/3 lb. (0.3 kg)	31–50 lb. (14.1–22.7 kg)
Obese (>30.0)	11–20 lb. (4.5–9.0 kg)	1/2 lb. (0.25 kg)	25–42 lb. (11.3–19.1 kg)

Adapted from National Academy of Sciences. *Weight Gain During Pregnancy: Reexamining the Guidelines*. Washington, DC: National Academy Press; 2009

affect perinatal outcome. Weight gain below the Institute of Medicine's guidelines is associated with low birth weight and small-for-gestational age infants. Excessive weight gain may lead to macrosomia, cesarean section, and postpartum weight retention. Overweight women with diabetes may need to gain minimum weight to decrease the risk of macrosomia.

Energy Requirements

The estimated energy requirements (EER) during pregnancy are based on the 2002 Dietary Reference Intakes [32]. The estimated energy requirements for pregnancy is:

- First trimester: adult EER for women (no calorie increase)
- Second trimester: adult EER for women +160 kcal (8 kcal/weeks × 20 weeks) +180 kcal
- Third trimester: adult EER for women +272 kcal (8 kcal/weeks × 34 weeks) +180 kcal

The estimated energy requirement for adult women is based on age, height, weight, and physical activity level. The 8 kcal per week is the estimated change in the total energy expenditure in pregnancy; while the 180 kcal is the mean energy deposition during pregnancy. A comprehensive nutrition history/questionnaire, food and blood glucose records, and regular monitoring of weight are used to develop individualized meal plans. Fluctuating blood glucose levels may necessitate frequent adjustments in the meal plan.

Macronutrients

The requirement for protein is 71 g/day or 1.1 g/kg/day for women over 18 years of age [32]. High-fat diets are not recommended, and saturated fats are limited to less than 10% of total calories from fat.

The Dietary Reference Intake for carbohydrates in pregnancy is a minimum of 175 g/day to ensure sufficient glucose for fetal brain growth and development, which is estimated to be 33 g/day [32]. While there is no carbohydrate restriction for women with preexisting diabetes, adjustments may be necessary to maintain normoglycemia.

Micronutrients

There is no difference in the Dietary Reference Intakes for micronutrients for pregnant women with and without diabetes (Table 3) [33–36].

High-Intensity Sweeteners

Six high-intensity sweeteners are approved for use in pregnancy when used within the Acceptable Daily Intakes: saccharin, aspartame, acesulfame potassium, sucralose, neotame, and advantame [37, 38].

Meal Planning Approaches

Various meal planning approaches are used in diabetes management. A woman who follows a meal plan prior to conception may need only minor adjustments to account for fetal growth. Women with no previous medical nutrition therapy will need more intensive self-management education. The appropriate meal planning tool selected depends on the woman's ability and motivation to follow the meal plan [39]. Meal planning tools include menus, My Plate, or Choose Your Food [40]. Carbohydrate counting is used more often today as clients learn the importance of amounts and food sources of carbohydrates, label reading, and food records. Pattern management, calculating insulin-to-carbohydrate ratios, and correction factors are advanced self-management skills used with meal planning [39].

Medications

Exogenous insulin therapy is used for women with preexisting diabetes, however a few recent studies have used metformin in the management of pregnant women with type 2 diabetes [40–42].

Rapid-acting insulin analogs (lispro and aspart) are frequently used in pregnancy [43, 44]. Glargine, detemir, and degludec are long-acting peakless insulin analogs. No clinical studies have been conducted on the use of degludec in pregnancy. Injectable therapies that have not been safely demonstrated in pregnancy include amylin analogs (pramlintide), incretin mimetics (GLP-1, DPP-4), and

Table 3 Dietary reference intakes (DRIs) (over non-pregnant requirements) for protein in pregnant and lactation

Nutrient	Pregnant woman	Lactating woman
Protein (g)	+25	+25
Vitamin A (mcg)		
14–18 years	750	1200
19–50 years	770	770
Vitamin D (mcg)	5	5
Vitamin K (mcg)		
14–18 years	75	75
19–50 years	90	90
Vitamin C (mg)		
14–18 years	80	115
19–50 years	85	120
Thiamin (mg)	1.4	1.4
Riboflavin (mg)	1.4	1.6
Niacin (mg NE)	18	17
Vitamin B ₆ (mg)	1.9	2.0
Folate (mcg FE)	600	500
Vitamin B ₁₂ (mcg)	2.6	2.8
Calcium (mg)		
14–18 years	1300	1300
19–50 years	1000	1000
Phosphorus (mg)		
14–18 years	1250	1250
19–50 years	700	700
Magnesium (mg)		
14–18 years	400	360
19–50 years	360	320
Iron (mg)		
14–18 years	27	10
19–50 years	27	9
Zinc (mg)		
14–18 years	12	13
19–50 years	11	12
Iodine (mcg)	220	290
Selenium (mcg)	60	70

Adapted from Institute of Medicine. Dietary Reference Intakes: Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press; 2002; and Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: The National Academies Press; 2001; and Food and Nutrition Board, Institute of Medicine. DRI Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B₆, Folate, Vitamin B₁₂, Pantothenic Acid, Biotin, and Choline. Washington, DC: The National Academies Press; 1998; and Food and Nutrition Board. Institute of Medicine. DRI Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: The National Academies Press; 2001

sodium-glucose cotransporters 2 inhibitors (SGLTZ). Since 2015, the FDA no longer uses a lettering system to categorize drugs used in pregnancy. Medications used in pregnancy and lactation are now grouped into three categories: pregnancy, lactation, and males and females of reproductive potential.

Multiple daily injections of rapid-acting insulin or short-acting insulin with an intermediate-acting are the most frequently used insulin regimens in pregnancy. Women on a fixed dose of insulin before conception are often switched to multiple daily injections because of frequent insulin adjustments.

A common insulin regimen is rapid-acting or short-acting insulin before breakfast and dinner or before each meal, and intermediate-acting before breakfast and at bedtime. Intermediate-acting insulin is not injected before dinner because of possible nocturnal hypoglycemia.

Insulin requirements change during pregnancy as fetal growth continues and insulin resistance increases. First trimester insulin regimen varies, but is usually 0.7–0.8 units/kg actual body weight/day; second trimester: 0.8–1 unit/kg actual body weight/day. This dose of insulin is increased to 0.9–1.2 units/kg actual body weight/day in the third trimester [25, 30]. The requirements for obese women may be higher (e.g., 1.5–2 units/kg actual body weight/day).

Insulin injection devices include syringes, pens, and continuous subcutaneous insulin infusion (insulin pump therapy). Pump therapy requires rapid-acting insulin, with 50–60% of the dose as basal for continuous insulin, and 40–50% as boluses before meals and snacks. Advantages to the insulin pump are flexibility with lifestyle and meal times, and improved glucose control. The disadvantages include cost, risk of interruption in insulin delivery, and infection at the infusion site [45–48].

Self-Management Tools

Medical nutrition therapy and insulin therapy are only two of the components for successful self-management. Food records will assist the registered dietitian to adjust the meal plan, when necessary. Other self-management tools include sick day rules, self-monitoring of blood glucose and ketones, and physical activity.

Sick Day Rules

Hypoglycemia is a concern if a pregnant woman with diabetes is ill and unable to consume adequate calories. All pregnant women with preexisting diabetes must become aware of hypoglycemia symptoms, which include sweating, blurred vision, nervousness, anxiety, headache, weakness, or in severe cases, seizures or unconsciousness. The treatment for hypoglycemia depends on the severity of the symptoms. Mild to moderate symptoms are treated with 15 g of carbohydrate if the blood glucose level is <70 mg/dL (3.9 mmol/L). This is repeated 15 min later if the blood

glucose level remains <70 mg/dL (3.9 mmol/L). If severe hypoglycemia occurs, either glucagon or intravenous glucose is used [49].

Self-Monitoring

Monitoring provides a necessary tool for adjusting food, medication, and physical activity in diabetes management. Women with preexisting diabetes should monitor their blood glucose levels before and after meals using a glucose meter. Blood glucose goals for diabetes and pregnancy are [50]:

- Fasting: ≤ 95 mg/dL (5.3 mmol/L)
- 1-h postprandial: ≤ 140 mg/dL (7.8 mmol/L)
- 2-h postprandial: ≤ 120 mg/dL 6.7 mmol/L)

Urine ketone monitoring is recommended in pregnant women with type 1 diabetes who are at risk for diabetic ketoacidosis at lower blood glucose levels than when not pregnant [50]. Glycosylated hemoglobin (A1C), while not a self-monitoring tool, is useful in measuring blood glucose levels to determine metabolic control and treatment. A1C levels are monitored more frequently in pregnancy because of the more rapid turnover of red blood cells [50].

Physical Activity

There is no empirical evidence demonstrating a beneficial effect of physical activity on glycemic control in women with preexisting diabetes. Unless contraindicated, women who were physically active before pregnancy are encouraged to continue; however, high-intensity or prolonged exercise longer than 45 min could lead to hypoglycemia. Contraindications to exercising with diabetes in pregnancy include poorly controlled type 1 diabetes, and glycemic levels <100 mg/dL (5.6 mmol/L) or >250 mg/dL (13.9 mmol/L) [51].

Postpartum

Insulin requirements usually decrease after delivery. It is not uncommon for the woman with type 1 diabetes to forego insulin for the first 1–2 days after delivery. Insulin adjustments are necessary to prevent hypoglycemia.

There are no contraindications to lactation and diabetes; women should be encouraged to breastfeed. The meal plan is adjusted to include additional snacks and to avoid hypoglycemia, which may be more frequent during lactation. Women with type 2 diabetes who choose to breastfeed may be switched from insulin therapy to an oral antidiabetes agent. Glipizide, glyburide, metformin, and acarbose are considered compatible with breastfeeding [24].

Family planning is an important topic to be discussed with the woman with preexisting diabetes. The use of contraceptive agents will depend on whether cardiovascular diseases are present [52]. Contraceptive agents that contain estrogen should not be prescribed to women with diabetes-related complications, such as retinopathy, nephropathy, or neuropathy, or who are hypertensive. Women with hyperlipidemia or hypertension are recommended to use progestin-only oral contraceptive agents because of their non-effect on liver globulins and possible clotting factors. Intrauterine devices and barrier methods were not found to affect blood glucose levels.

Preconceptional Counseling

Preconception counseling is essential for all women with diabetes in their child-bearing years. Women with preexisting diabetes should delay pregnancy until their glycosylated hemoglobin (A1C) levels are $<6.5\%$ to decrease the risk of fetal congenital anomalies [50]. Preconceptional care includes a complete physical examination to identify and treat any preexisting diabetes-related or other medical condition, an assessment of her nutritional status, and self-management education, including psychosocial assessment. A discussion of finances is also important because of the additional expense of more frequent testing or diabetes supplies.

Although all women with preexisting diabetes should receive preconceptional counseling, such is not often the case [53, 54]. An observational study from France found that women with type 2 diabetes had a three-fold higher rate of infants born with malformations than women in the general population. Only four of the 87 women in the study received preconception care [55]. Another study conducted in Northern Ireland found a lack of awareness of the risks associated with diabetes in pregnancy and the role of preconception care. One reason for this higher prevalence of complications could be misconception that type 2 diabetes is not as severe as type 1 diabetes [56].

Gestational Diabetes Mellitus

It is estimated that 90% of cases of diabetes in pregnancy are gestational diabetes [3]. Women who are diagnosed with diabetes in their first trimester are classified as having type 2 diabetes. Gestational diabetes is diabetes diagnosed in the second and third trimester of pregnancy, that is clearly not preexisting type 1 or type 2 diabetes [57].

Pathophysiology

The exact mechanism of gestational diabetes is not fully understood, however, it is associated with insulin resistance and decreased insulin secretion. Fasting blood glucose levels are elevated as insulin deficiency and resistance increase. Delayed

insulin response, insulin resistance, and placental hormonal antagonism are responsible for postprandial glucose excursions. Human placental lactogen and cortisol block insulin receptors. This creates a deficiency in circulating insulin production, and glucose intolerance [58].

Complications

Maternal risks associated with gestational diabetes include hypertension, higher rates of cesarean sections, and preterm deliveries [50]. Macrosomia is the most common complication in gestational diabetes. Other complications include neonatal hypoglycemia, neonatal hypocalcemia, neonatal hyperbilirubinemia, and polycythemia. The risk for respiratory distress syndrome decreases if delivery occurs at term.

Risk Factors for Gestational Diabetes

Considerable controversy exists in the screening and diagnosis of gestational diabetes. The American Diabetes Association (ADA) recommends testing for undiagnosed type 2 diabetes at the first prenatal visit if a woman has risk factors associated with type 2 diabetes. The risk factors are found in the American Diabetes Association's 2017 Standards of Medical Care in Diabetes [57]. All pregnant women not previously diagnosed with diabetes should be tested for gestational diabetes at 24–28 weeks' gestation.

The American College of Obstetricians and Gynecologists (ACOG) recommends all pregnant patients be screened for GDM, whether by the patient's medical history, clinical risk factors, or laboratory screening test results, to determine their blood glucose levels. However, this recommendation was given a Level B grade because it is based on limited or inconclusive scientific evidence [59].

Screening and Diagnosis of Gestational Diabetes

In the United States, two methods are used to diagnose gestational diabetes: the one-step and the two-step method [57]. The one-step approach uses a 75 g glucose solution as the oral glucose tolerance test and the blood is drawn at fasting, 1 and 2 h. This method is based on the recommendations from the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [60]. The IADPSG derived their recommendations from the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large multinational cohort study of 25,000 pregnant women, which demonstrated the risk of adverse outcomes in the fetus, neonate, and mother were at lower glycemic levels than what were considered normal for pregnancy [61]. In 2011, ADA adopted the IADPSG's recommendations.

The two-step method is based on the Carpenter-Coustan criteria for screening and diagnosing GDM. In the first step, a Glucose Challenge Test (GCT) is administered using a 50 g glucose solution and the plasma glucose level is checked in 1 h. The second step, the Oral Glucose Tolerance Test (OGTT), is performed if the result of the 1-h test is ≥ 130 mg/dL to 140 mg/dL (7.2 to 8.1 mmol/L), depending on the threshold used. The OGTT follows 3 days of unrestricted carbohydrate intake (at least 150 g/day) and unlimited physical activity. The woman fasts for at least 8 h the night before the test. Blood is drawn for a fasting glucose level, followed by 100 g of glucose solution given orally and again at 1, 2, and 3 h. The oral glucose tolerance test is discontinued if the fasting glucose is ≥ 126 mg/dL (7.0 mmol/L) or a random glucose is ≥ 200 mg/dL (11.1 mmol/L). Gestational diabetes is diagnosed if at least two of the values exceed the Carpenter and Coustan criteria of:

- Fasting: ≤ 95 mg/dL (5.3 mmol/L)
- 1-h: ≤ 180 mg/dL (10.0 mmol/L)
- 2-h: ≤ 155 mg/dL (8.6 mmol/L)
- 3-h: ≤ 140 mg/dL (7.8 mmol/L)

In 2013, the National Institutes of Health convened a consensus development panel on diagnosing criteria for GDM. The panel examined the research related to the current diagnostic criteria and recommended the two-step approach because of the lack of intervention studies on the one-step approach to diagnosing GDM [62]. As a result, ACOG has continued to use the two-step strategy.

Management of Gestational Diabetes

The treatment for GDM begins with medical nutrition therapy, physical activity, weight management depending on the pregestational weight, and self-monitoring of blood glucose. The goal of management is to optimize blood glucose levels, thereby decreasing the risk of perinatal complications. A 2005 study showed a reduction in perinatal complications in women with GDM who received medical nutrition therapy, self-monitored their blood glucose levels, and used insulin therapy when necessary, compared to women who received routine care [63].

Medical Nutrition Therapy

The primary goals of medical nutrition therapy in GDM is to achieve and maintain normal blood glucose levels as safely as possible, while at the same time providing adequate calories and nutrients for maternal and fetal health [64]. Carbohydrates are the main contributors of postprandial glucose excursions in gestational diabetes, and for many years were restricted to approximately 40–45% of total calories [64–66]. However, newer research has indicated that the type and amount of carbohydrate may impact maternal blood glucose levels without negatively affecting

perinatal outcomes. This includes higher carbohydrate [67], low glycemic index [68, 69, 70], and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern [71]. Iranian women with GDM who followed the DASH dietary pattern, in which the carbohydrate amount exceeded 65% of the total calories, had infants with lower birth weight, head circumference, and ponderal index compared to those born to women on a control diet [71].

The Institute of Medicine's guidelines are used to determine the appropriate weight gain for women with gestational diabetes [32]. The estimated energy requirements are the same for pregnant women without diabetes. Monitoring weight gain and reviewing blood glucose, food, and if necessary, ketone records, are other useful tools to determine diet adequacy.

There is insufficient evidence to increase the protein requirement for women with gestational diabetes, although the intake may be higher than the Dietary Reference Intake in pregnancy if the carbohydrate intake is decreased. The amount of fat has not been shown to affect pregnancy outcome, however, there is limited evidence to suggest that monounsaturated fats may lower diastolic blood pressure and improve insulin sensitivity [72].

Self-Management Tools

Self-management is important for improving perinatal outcome in gestational diabetes. Self-management tools include self-monitoring of blood glucose, physical activity, and pharmacological therapy, when necessary.

Self-Monitoring of Blood Glucose

While limited research has indicated that post-meal blood glucose monitoring yields better outcomes (decreased fetal macrosomia and large-for-gestational age infants), there are no established optimal testing times in gestational diabetes [73]. The general consensus is to self-monitor blood glucose levels four times a day [50, 59].

Ketone Monitoring

Neither the American Diabetes Association's Standards of Medical Care nor the American College of Obstetricians and Gynecologists' Practice Bulletin has recommended ketone testing in women with gestational diabetes. One study is frequently cited as a rationale for recommending ketone testing in gestational diabetes because of the correlation between ketonemia and decreased intelligence scores in the offspring of women with diabetes [74]. It may be advantageous for women with gestational diabetes to monitor for urinary ketones if there is weight loss or inadequate weight gain or energy intake.

Physical Activity

Physical activity may have a positive effect in gestational diabetes by lowering blood glucose levels [75]. Low-impact aerobics such as walking, stair climbing, or swimming are acceptable. The activity should be performed after meals to improve glycemic levels. Pregnant women with any medical or obstetric complications should be evaluated by an obstetrical care provider before recommending any physical activity during pregnancy [75].

Pharmacological Therapy

If normoglycemia cannot be maintained with medical nutrition therapy alone, pharmacological therapy is added. However, there is no consensus among clinicians when pharmacologic therapy should be instituted. The Academy of Nutrition and Dietetics nutrition practice guideline recommends initiating pharmacological therapy if targeted blood glucose levels are not reached after 2 weeks of medical nutrition therapy [65]. Ultrasound measurement of the fetal abdominal circumference to determine macrosomic growth is also used to determine if and when to initiate insulin therapy [76].

Insulin is the first-line therapy used in the management of gestational diabetes, when indicated, because it does not cross the placenta. The types of insulin recommended in gestational diabetes are the same as for pregnant women with preexisting diabetes.

The use of oral antidiabetes agents in the management of gestational diabetes has increased in recent years. A randomized trial in 2000 which compared glyburide to insulin reported no difference in the incidence of maternal or fetal complications [77]. In this study, glyburide was not detected in the cord serum. However, a more recent study has shown glyburide crosses the placenta in varying amounts [78]. A retrospective cohort study showed that infants born to women with gestational diabetes and treated with glyburide were at increased risk for neonatal intensive care admission, respiratory distress, hypoglycemia, birth injury, and large-for-gestational age than those treated with insulin [79]. Metformin is another oral agent used in the management of gestational diabetes [80]. In a systematic review and meta-analysis that compared glibenclamide, metformin, and insulin in the treatment of gestational diabetes, glibenclamide was found to be inferior to insulin and metformin. The authors recommended that glibenclamide not be used if insulin or metformin is available [81].

Postpartum

Women with gestational diabetes are at increased risk for developing type 2 diabetes after pregnancy, and should be screened 6–12 weeks postpartum [50, 59]. The American Diabetes Association recommends a 75 g, 2-h oral glucose tolerance test to identify women with possible undiagnosed diabetes before conception, impaired glucose tolerance, or risk for future diabetes [50]. If the oral glucose tolerance test

is normal, the woman should be reassessed every 1–3 years depending on her other risk factors, which include family history, pre-pregnancy BMI, and the necessity of pharmacologic therapy during pregnancy [50].

Breastfeeding, unless contraindicated, is recommended for women with gestational diabetes [50]. Lactation may improve glucose control, mobilize fat stores, promote weight loss, and protect against future risk of developing type 2 diabetes and metabolic syndrome [82, 83]. A gradual weight loss of 1–2 kg per month is encouraged.

Women with previous histories of gestational diabetes are also at risk of developing gestational diabetes in recurring pregnancies. The Diabetes Prevention Program has shown that women with a history of gestational diabetes or prediabetes prevented or delayed the progression to diabetes with metformin or intensive lifestyle intervention [84]. In a 10-year follow-up study, women in the lifestyle intervention and metformin groups reduced the progression to type 2 diabetes by 35% and 40%, respectively [85]. Women should be encouraged to adopt healthy lifestyles to lessen their risk of developing type 2 diabetes or gestational diabetes in subsequent pregnancies. Lifestyle modifications include achieving and maintaining normal body weight, healthy eating habits, and consistent physical activity [65].

Conclusion

Advances in diabetes management have greatly improved pregnancy outcomes. For the woman with preexisting diabetes, optimal maternal blood glucose control must begin prior to conception and continue throughout the pregnancy. All women with type 1 diabetes and type 2 diabetes of childbearing age should be referred for preconceptional care to incorporate self-management strategies that can decrease perinatal morbidity and mortality. Self-management care includes medical nutrition therapy, self-monitoring of blood glucose, and if necessary, ketone testing, insulin therapy, and physical activity.

Medical nutrition therapy is a key component in the management of gestational diabetes. An individualized meal plan should be designed to provide adequate energy and nutrients for maternal and fetal health and promote appropriate weight gain based on pre-pregnancy body mass index. Food, blood glucose and, if necessary, ketone records, are used to adjust the meal plan. After delivery, lifestyle modifications are necessary to reduce the long-term risk of developing type 2 diabetes. These modifications should focus on diet, physical activity, and achieving and maintaining a healthy weight.

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Pregnant Behind Bars: Meeting the Nutrition Needs of Incarcerated Pregnant Women

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Keywords Incarceration · Nutrition knowledge · Breastfeeding · High-risk pregnancy · Jail · Prison

Key Points

- Due to their marginalized background, incarcerated pregnant women have a complex set of health-related needs.
- Medical guidelines recommend screening for pregnancy upon entry, routine prenatal care, provision of dietary supplements, and regular nutritious meals during incarceration.
- Jail protocols often fail to address these recommendations and as a result pregnant women's health-related needs are often underserved.
- Evidence from the William & Mary Healthy Beginnings Program suggests that incarceration could be an ideal opportunity to provide pregnant women with health-related skills to better care for themselves and their newborns.

Introduction

Over the past 20 years, the population of female inmates has almost doubled in the United States, rising from 51,300 in 1996 to 93,300 in 2011 [1]. Despite this large increase, incarcerated women make up less than 10% of the overall imprisoned population [2]. As a result, jail policies, health-care protocols, and interventions, which continue to focus primarily on men [3], fail to consider the gender-specific needs of the growing female population [4]. This lack of attention to the complex health-related needs of women often results in the neglect of their human rights and in social injustices [5, 6].

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Women in the correctional system are typically of childbearing age (between 18 and 44 years old), [7] and approximately 6–10% of incarcerated women are pregnant [8]. This represents a significant challenge for the criminal justice system because the pre- and postnatal needs of this high-risk group of women and their babies are extensive. In the current chapter we will first describe the characteristics of incarcerated women and consider how involvement with the criminal justice system impacts their nutritional status during pregnancy. Next, we will discuss postpartum needs of incarcerated women and their newborn babies, with a special focus on breastfeeding in the context of incarceration. Finally, we will describe the William & Mary Healthy Beginnings Project; a nutrition intervention implemented with pregnant incarcerated women throughout Southeastern Virginia, and report on how this program affects women's nutritional knowledge and their birth outcomes. Our discussion of correctional facilities will include jails, which typically incarcerate people for relatively short periods of time; often as little as a couple of hours and generally not longer than 1 year, as well as prisons, which incarcerate people for longer periods of time for more serious offenses [9].

A Profile of Women in the Criminal Justice System

Incarcerated women represent a population marginalized by race, class, and gender [10]. These women are disproportionately from ethnic or racial minorities, and many lack educational and vocational training [11]. They tend to struggle with poverty, trauma, such as physical and sexual abuse, mental illness, such as depression and post-traumatic stress disorder, and drug addiction [12, 13]. Research indicates that for many women, these psychological and social issues motivate their criminal behavior [14, 15]. This is demonstrated by the types of crimes they commit, which commonly involve drug or property offenses rather than violent crimes [11].

Their extensive history of substance abuse is often linked with commercial sex work and other risky sexual behaviors [16], yet, in a recent study, close to 75% of sexually active incarcerated women reported inconsistent or no birth control use [17]. As a result, these women are at an elevated risk for reproductive health problems, such as HIV and other sexually transmitted diseases, in addition to unintended pregnancies. Because incarcerated women are more likely than those from the general population to experience high-risk pregnancies [18] they require considerable support. Despite this need, they are unlikely to seek prenatal care while in the community. Given that pregnancy is a significant life-changing event for many women, correctional facilities have the unique opportunity to provide services and support to a group of high-risk women at an important turning point in their lives [17]. Yet, according to a 2006 report by the Department of Justice, less than half of pregnant women in the United States receive a medical examination upon intake at a correctional facility or appropriate care during incarceration [19].

Indeed, some research has shown that women who are incarcerated in jails for longer periods of time appear to benefit from better prenatal care, improved nutrition, and a structured environment with more favorable perinatal outcomes [20, 21]. However, these findings have not been consistently supported [18]. It is likely that the association between length of jail stays and birth outcomes is moderated by other variables. Bell et al. [18] found that the length of incarceration was positively associated with birth weight only in white women incarcerated during their first trimester. Because women in jails, as opposed to prisons, are more likely to be incarcerated for relatively short periods of time, they are more reliant on services and resources that can be utilized in their communities.

The Nutritional Needs of Incarcerated Pregnant Women

Although some may think that incarcerated pregnant women should receive care comparable to women in the community, there are additional institutional considerations that make caring for this group of women more complicated. Specific conditions posed by the jail environment as well as personal health issues such as drug addiction, increased risk of infectious diseases, and mental health problems must also be considered with this high-risk population. With these considerations in mind, various medical groups, including the National Commission on Correctional Health Care (NCCHC) and the American College of Obstetricians and Gynecologists (ACOG), have developed guidelines for providing care to pregnant incarcerated women. These guidelines include a range of recommendations, such as screening for substance abuse, mental health, and pregnancy upon entry to the facility; routine prenatal care from qualified health professionals; appropriate treatment for substance abuse; and provision of dietary supplements and regular nutritious meals [8, 22].

Meeting the dietary needs of pregnant women is particularly important in corrections facilities because many come from food-insecure environments and will likely be returning to these environments after their release. Although the NCCHC recommends dietary supplements of folate (600 mcg), their dietary guidelines are otherwise vague [22]. While adequate folic acid intake protects the fetus from neural tube defects, low birth weight, and prematurity [23], iron is also recommended (27 mg/day) to protect against a range of negative birth outcomes, such as risk of preterm delivery and low birthweight [24]. Yet, despite their importance, the recommended levels of folic acid and iron are often not met in meals served in correctional settings [25], and many facilities fail to provide prenatal vitamins [26], which serve as an important dietary supplement of folic acid and iron.

In addition to folic acid and iron, other nutrients are needed to promote positive pregnancy outcomes that are not addressed in the NCCHC guidelines. For example, the degree to which our bodies absorb iron is dependent on vitamin C intake; as a result, adequate consumption of fruits and vegetables, which are high in vitamin C, is vital. Moreover, adequate levels of omega3 fatty acids are especially important for this high-risk population because they are associated with longer pregnancies,

increased weight gain, and brain development in the fetus [27, 28], as well as decreased postpartum depression for the mother [29]. Because our bodies cannot produce these fatty acids, we get them from dietary sources such as fatty fish like salmon and omega-3 fortified milk and yogurt. These foods additionally provide vitamin D, which aids in the absorption of calcium, an important nutrient for the development of bones and teeth and proper functioning of the circulatory, muscular, and nervous systems. More recent research suggests that vitamin D may affect susceptibility to chronic diseases soon after birth as well as later in life [30].

Because vitamin D is primarily produced endogenously in the skin with exposure to sunlight, incarcerated women are at high risk for deficiency given their limited sun exposure. According to the Food and Nutrition Board at the Institute of Medicine of the National Academies of Science, adequate intake of vitamin D during pregnancy and lactation is 600 international units (IU) per day [31]. However, it has recently been suggested that higher daily intake—up to 4000 IU per day [32]—may be optimal for maintaining maternal vitamin D sufficiency during pregnancy.

From a cultural perspective, food has important symbolic power for pregnant women because it provides the nourishment needed not only for their own bodies, but it also serves as a lifeline for the developing fetus. For most pregnant women, food choices are driven not only by internal factors such as cravings and aversions, but they are also influenced by the cultural food practices and beliefs that have been created through past experiences and are grounded in their race, class, and culture (see [33] for a review). While incarcerated, inmates lack the freedom to make food choices that reflect their preferences and cultural backgrounds. This can serve as a source of anxiety and frustration [34]. For some, a creative and social outlet that counters the constraints of jail food involves the invention of alternative meals called “spreads” or “swoles.” These concoctions are most often built around a single ingredient, such as instant ramen noodles that can be purchased through the jail commissary (see [35] for an overview of this practice). Beginning with this noodle base, inmates create variations from foods provided in their meals and the commissary to approximate their favorite foods, which often have distinctive flavorings and textures. In this manner, pregnant women may assume some responsibility for their own intake, however the addition of swoles to the diet, though they may add calories, does not necessarily improve nutrition [5].

While overweight and obesity during pregnancy heightens the risk of conditions like pre-eclampsia, gestational diabetes, and postpartum hemorrhage, undernutrition negatively impacts embryonic and fetal growth and development. Moreover, recent research shows that the mother’s eating behavior during the 3 months prior to conception and during prenatal development can have long-lasting effects on her children, increasing the incidence of disease states, such as obesity and diabetes, over the course of their lives. Epigenetic changes that occur as a function of a poor diet serve to “tune” the phenotype, causing the child to become predisposed to metabolic disorders later in life, such as obesity or cardiovascular disease [36]. Perhaps even more concerning, these predispositions can be passed down to subsequent generations through the process of transgenerational inheritance [37]. In this manner,

certain biological predispositions are passed from generation to generation not through the promotion of genetic mutations in DNA sequence, but rather through altered gene expression. Thus, a woman's diet, whether it lacks essential nutrients that ultimately produce malnourishment or it provides excessive calories through the overconsumption of energy-dense foods, not only negatively impacts her own health, but also that of her children and potentially her grandchildren. Given the far-reaching effects of poor nutrition during prenatal development, it is important to develop effective interventions that help to mitigate such risk in pregnant incarcerated women.

The Challenges of Meeting Nutritional Needs of Incarcerated Pregnant Women

Though the health, nutrition, and well-being of pregnant inmates should be a priority for correctional facilities, it is costly. Many state corrections departments have a registered dietitian nutritionist on staff who oversees the nutritional value of meals served to inmates, however currently, there are no federal regulations that mandate nutritional standards of correctional facilities [25]. Moreover, because financing of correctional facilities depends on legislative appropriations that compete with other important issues, provision of sufficient nutrition for inmates, and especially pregnant women, is often not a fiscal priority. As a result of poor funding and oversight, incarcerated pregnant women's dietary needs are often underserved, with many jails failing to provide healthier food options to these women [38].

Correctional facilities often attempt to offset the cost of meals by providing foods that are heavily processed, high in sodium, and contain high levels of texturized vegetable protein and soy, which can be unpalatable and difficult to digest. In many facilities deli meats, such as bologna and hot dogs, are a staple, which carry the risk of contamination by *Listeria*, a bacteria that can cause fetal complications [39]. On average, the cost of each meal at correctional facilities ranges from \$3 to \$4 per inmate [25]. Some facilities provide pregnant inmates with an additional daily snack, however access to fresh fruits and vegetables, unprocessed meat and fish, whole grains, and milk can be limited, and the food provided does not necessarily meet the nutritional or caloric requirements for pregnant women [25, 40].

In addition to the lack of quality of meals, their timing, presentation, preparation, and the size of portions are usually tightly controlled by the facility. For women who are pregnant, this aspect of institutional control has a range of health-related consequences. Because many women suffer from nausea or acid reflux during pregnancy, they may prefer to eat multiple small meals a day to aid in digestion and reduce nausea. This is difficult to achieve in most jail settings, where the timing and portion size of meals is inflexible. In most cases, if a pregnant woman chooses not to eat during a scheduled meal, she will likely not have the opportunity to eat until the next meal is served.

In view of the challenges that pregnant women face in correctional settings, Schlafer et al. [41] have suggested best practices for addressing the dietary needs of incarcerated pregnant women. In addition to suggesting approaches to increase incarcerated pregnant women's access to nutrients, calories, and water, they advocate for providing inmates with education on proper nutrition. Because many pregnant women who are involved in the criminal justice system have relatively low levels of health literacy, they are often unaware of how their dietary habits impact their developing fetus, and they engage in poor nutritional habits that can lead to serious complications before and after their pregnancies [42]. Incarceration could be an ideal opportunity to provide educational programming that focuses on a variety of health-related topics, including nutrition. Previous research has shown that nutrition education programs not only improve women's nutritional knowledge [43], but they can also improve birth outcomes in low-income women [44]. Although educational programs could be an effective means for improving birth outcomes in incarcerated women, they are limited in most jail facilities.

Breastfeeding in the Context of Incarceration

The World Health Organization (WHO) and American Academy of Pediatrics (AAP) recommend that infants should be exclusively breastfed from birth to six months of age, barring contraindications [45, 46]. It is well documented that breastfeeding has a direct beneficial effect on infants by promoting growth and normal development, and providing immunological protection against various infantile diseases and infections. Because the flavor of the mother's milk reflects the flavors of the foods she eats, breastfeeding also provides one of the earliest opportunities for children to learn to appreciate the flavors of their culture [47]. In support of this early learning, research shows that infants who are breastfed are less likely to become picky eaters [48, 49]. But lactation is far more than merely a biological process that helps to prevent disease and to develop a healthful diet; it represents an important aspect of mothering that involves the formation of an emotional connection or bond between a mother and her child. That this bond benefits both mother and child is supported by research that demonstrates that mothers who breastfeed are more sensitive in responding to the cues of their infants [50, 51]. Of special note for incarcerated women, who tend to experience profound sadness and clinical depression [52, 53], breastfeeding has been shown to decrease mothers' negative affectivity [50, 54, 55].

Recent research from our laboratory suggests that women who are incarcerated for longer periods of time and those with poorer diets are less likely to initiate breastfeeding [56]. These findings may be connected to a number of factors, such as the lack of prenatal education that women receive while they are incarcerated. The

longer women are incarcerated during pregnancy, the less accessibility they have to early prenatal breastfeeding programs. Studies show that early breastfeeding support [57, 58] that addresses a range of topics including the benefits of breastfeeding, principles of lactation, common problems and their solutions, and skills training increase breastfeeding initiation [59].

To be sure, the practice of breastfeeding is surrounded by a great deal of folklore, especially regarding the dietary practices of the mother. For example, in a qualitative study conducted by Hannon et al. [60] adolescent minority mothers reported beliefs that certain foods, such as chocolate, orange juice, and corn, should be avoided while breastfeeding. Although few of these traditional beliefs are supported by scientific evidence, they continue to be communicated to new mothers. In order to counteract these breastfeeding myths, additional information about how maternal dietary habits affect the quantity and quality of milk may also be helpful, especially for those with poor diets. While it is possible that women with poor dietary behaviors may be less likely to initiate breastfeeding because they are less interested in engaging in healthful behaviors, they may also mistakenly believe their poor diet prevents them from producing nutritious breastmilk for their babies [58, 61]. Mothers may be more inclined to breastfeed if they believe that the quality of their breastmilk does not depend on eating a highly nutritious diet. Rather, the importance of a healthy diet for the mothers' own benefit should be emphasized through educational programs [62].

In order to increase breastfeeding initiation among incarcerated mothers, changes in protocols are necessary in most US jails. Currently, many states do not have laws or statutes that prevent jails from denying inmates lactation accommodations. Women who return to jail after the birth of their child are generally not permitted to pump their breastmilk for their newborn, and they are unable to have contact visitations that would make breastfeeding possible. Despite this inability, there is evidence to suggest that breastfeeding is valued by some incarcerated pregnant women [61]. Given the important benefits that breastfeeding confers to both the mother and child, both federal and state legislatures should consider enacting laws that promote breastfeeding in correctional facilities. Not only should jail protocols facilitate breastfeeding for incarcerated women with infants, but they should also provide comprehensive prenatal education to increase breastfeeding initiation amongst these women.

In many other countries, such as Canada, the United Kingdom, Germany, Bolivia, and Kenya, incarcerated women are able to keep their infants through weaning and, in some cases, longer [63]. Although several states, such as New York, Nebraska, South Dakota, Washington, and California [63] have prison nurseries, similar facilities are not available in most jails. This need is addressed through residential mother-child programs for women who have shorter sentences in other countries. In the USA, these community-based programs are not widespread, and those that do exist are often limited to women who suffer from drug addictions.

The William & Mary Healthy Beginnings Project

In an attempt to address the needs of pregnant incarcerated women in Southeastern Virginia, our group developed the William & Mary Healthy Beginnings Project. The goal of this program is to provide resources and nutrition information in a manner that is not intimidating and is personalized for the needs of the participants. In addition to providing jails with pregnancy tests to identify pregnant women upon entering each facility, and prenatal vitamins for all women for the duration of their pregnancy, nutritional counseling is delivered. Our primary participants include women who range in age from 19 to 41 years of age. Almost all (90%) of these women are single, approximately half (55%) are African American, half (49%) have not completed high school, and about a quarter (24%) are first-time mothers. Prior to pregnancy, 83% reported smoking cigarettes regularly, 50% reported using illegal drugs, and 23% report being homeless. Amongst women who have previous children, 17% report having had a premature baby and 14% reported having a low-birth-weight baby. To put this into context, approximately 11% of babies are born preterm in Virginia and there is a state-wide goal to reduce this rate to 8%.

Nutrition counseling sessions begin with motivational interviewing techniques to discuss participants' pregnancy-related goals. This is followed by an activity in which each participant fills an empty plate with images of various foods that they would be most likely to eat if the foods were available. Participants select a main course, a starch, a vegetable, a dessert, and a drink from a variety of pictures of foods that range in caloric content and healthfulness. This activity provides an opportunity for the team member to discuss the nutritional benefits of the participants' selections and acts as a segue for discussing guidelines for healthy eating using the USDA ChooseMyPlate.gov handout. Because the recommendations on this handout are for adults who are not pregnant, team members also discuss pregnancy-related issues such as the dangers associated with consuming deli meats and frequent consumption of certain types of fish during pregnancy. The team member also reviews nutritional content of various foods such as whole versus skim milk, how to read food nutrition fact labels, and the contents and benefits of vitamins and minerals in foods and prenatal vitamins. Throughout the session, the team member endeavors to provide information that is relevant and personalized for the participant. For example, if a pregnant woman is in a jail that provides her with a "snack bag," the team member will discuss the contents of the snack and the added nutrition provided. In cases where these snacks consist of a cold bologna sandwich (or similar deli meat), we inform the women that they can request a snack that has a peanut butter sandwich to decrease the chance of contracting Listeriosis. There is also an opportunity for the participant to report and discuss any pregnancy-related ailments she may be experiencing (e.g., nausea, heart burn). In addition, participants' pre-pregnancy body mass index (BMI) is calculated, and based on this, the research team member discusses participants' suggested weight gains following the recommendations [64]. On average, nutritional counseling sessions last between 45 and 75 min. In subsequent visits, team members follow up with participants to

provide them with additional support, information, or referrals for other services, if requested. For example, the team member will discuss issues that are personally relevant to the women, such as breastfeeding or addiction, assist women with completing paperwork required to receive resources, such as Medicaid, WIC, or a free car seat, or provide referrals to programs, such as those that offer residential drug rehabilitation.

Close to one-third of the participants in this program discovered they were pregnant upon entering the jail facility. This was a direct result of the pregnancy tests provided by the William & Mary Healthy Beginnings Project. Because these women were identified early, they were able to receive prenatal vitamins and timely prenatal care, as well as nutrition counseling and additional support to help them plan for their pregnancy. Moreover, our results show participants' nutrition and pregnancy-related knowledge increased from pre- to post-counseling, and this increase in knowledge was associated with positive birth outcomes [65].

Our hope is that incarcerated pregnant women will start to feel empowered to make better choices about the foods they consume. Although, as discussed above, the correctional environment poses certain immediate challenges to accomplishing this goal, there are some opportunities to help pregnant women make healthier nutrition decisions while incarcerated. For example, discussing the value of food choices that they make when purchasing commissary items and encouraging them to eat the vegetables provided to them in their meals may help to improve their diet while in jail. There are also straightforward changes that jails could make to aid women's food choices. For example, providing a list of commissary items that may be healthy options for pregnant women or labeling such foods would help increase self-efficacy and promote adherence to nutrition recommendations. In addition, correctional facilities should include a list of items that may be unsafe for pregnant women (e.g., uncooked deli meat) and foods that should be consumed in moderation [41]. Once women are released, their improved nutrition knowledge may enhance the nutritional quality of the foods they purchase for themselves and for their families with the resources they have available. It is also our hope that through discussions about the advantages of breastfeeding during program meetings, women who deliver after their release will be more likely to initiate this important feeding regimen with their newborn infant.

Conclusion

The needs of pregnant incarcerated women involve a complex interconnected web of social, cultural, economic, and political issues. From an ecological systems perspective, changes are needed not only within our communities and the criminal justice system, but also in our belief systems and societal values regarding the treatment of incarcerated women who are carrying an innocent child. Most individuals in the general population have never been incarcerated themselves, let alone incarcerated while pregnant. Therefore, many have never considered the issues and

challenges that these pregnant women and their children face. For this reason, awareness of these issues needs to increase amongst the general population.

Even with increased awareness, not everyone will support these women, especially given the fact that they are serving a sentence for crimes they have committed. However, it is important to remember that these women are largely victims of poverty and abuse and have learned to cope with these challenges, not through engaging in violent crimes, but through other maladaptive behaviors. Although beyond the scope of this chapter, these women contend with a host of health and social issues that include the use of illicit drugs, psychological problems, and homelessness, all of which also need to be addressed through effective rehabilitation programs.

Mass incarceration of women, rather than rehabilitation, places an undue burden on families, the often-forgotten victims of the correctional system. Emotionally and physically supporting pregnant incarcerated women begins specifically with pregnancy testing and screening procedures at intake. Early pregnancy identification may be key to improving perinatal health outcomes if facilities subsequently provide proper prenatal and postnatal care. When healthcare services include the provision of proper nutrition, nutrition counseling, opportunities for bonding after birth, and other services to address issues such as drug addiction, jails can play a pivotal role in helping incarcerated women begin to build a better life for themselves and their babies.

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Depression in Pregnancy: A Role for Yoga, a Lifestyle Practice to Complement Nutrition

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Keywords Pregnancy · Depression · Yoga · Prenatal yoga · Complementary and alternative medicine · Perinatal depression

Key Points

- Depression is common during the perinatal period, with approximately 13% of women experiencing a major depressive episode and even more experiencing sub-clinical depressive symptoms.
- Adverse outcomes associated with perinatal depression include pre-term birth, low birth weight, and difficulties with mother–infant bonding.
- Multiple barriers limit access to traditional mental health care during the perinatal period, so new non-pharmacologic treatment alternatives are being examined, such as yoga.
- Clinical trials with non-pregnant adults suggest that yoga may be effective in lowering depression; however, not enough research has examined the impact of yoga on perinatal depression.
- Recent studies provide encouraging preliminary support for the usage of yoga as a means of improving mood and reducing stress during pregnancy.

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Introduction

Pregnancy can prompt wide-ranging emotional experiences for women, including strong feelings of joy and excitement, as well as intense worry and sadness. Although cultural beliefs have promoted the idea that pregnancy is primarily a time of happiness, a large literature now documents that pregnant women frequently experience anxiety or stress, and symptoms of antenatal depression are common. Though some pregnant women have more mild and transitory periods of sadness, estimates suggest that a substantial proportion of US women, approximately 13%, experience a major depressive disorder during pregnancy [1], making it one of the most common complications of the perinatal period. A larger proportion of women suffer from elevated sub-clinical depression that often serves as a precursor to a more severe clinical episode. Women from some communities, such as lower-income populations and urban settings, experience even higher rates of antenatal depressive symptoms [2, 3].

The high prevalence of antenatal depression is of concern, not only because of the suffering experienced by women and significant disruptions in their day-to-day functioning during pregnancy, but additionally due to numerous adverse outcomes associated with maternal depression for the infants, including pre-term birth and low birth weight [4–6]. Further, symptoms of depression, or a clinical diagnosis of depression during pregnancy, substantially raise a mother's risk for postpartum depression after the baby is born [7]. Postpartum depression can disrupt a mother's functioning and, in some cases, create significant difficulties with mother–infant bonding and interactions which may prompt long-term cognitive and developmental problems for the offspring [8, 9].

In light of data documenting the high prevalence and risks of antenatal and postpartum depression, nationwide initiatives have promoted screening for depression during routine prenatal care visits [10], and innovative programs have been evaluated to find strategies to identify and refer women in need of services [11]. In addition, experts have developed new therapeutic approaches to target the unique symptoms and difficulties commonly experienced by pregnant women with depression [12], as well as preventative interventions to target women at risk [13]. However, even with these new approaches, significant challenges remain in engaging women into depression treatment [14], and empirical support for antenatal depression treatments remains somewhat limited [15, 16].

Multiple barriers can prevent pregnant women from engaging in treatment for depression during pregnancy. Some women do not recognize symptoms as related to depression because they may be similar to, or viewed as, pregnancy symptoms (e.g., appetite and sleep disturbances). Other women may recognize symptoms but be reluctant to disclose them to healthcare providers and others. Logistical and financial barriers in accessing care can be particularly salient during pregnancy, as women are managing additional medical appointments and financial pressures related to planning for a new baby [17, 18]. Another important factor that impacts engagement in depression treatment is reticence to take antidepressant medication,

the most commonly utilized form of depression treatment, due to concerns about negative effects on the fetus [19].

Challenges in engaging in standard depression treatments, as well as a desire to pursue a form of care regarded as healthy and holistic, have prompted exploration of whether perinatal depression symptoms can potentially be improved via non-pharmacologic strategies such as yoga, exercise, and other modalities (acupressure, massage) [20]. Because it is useful for women to have a wider range of acceptable and effective alternatives available to them, the field is beginning to explore the efficacy and safety of some of these non-traditional means of improving mood. One such approach that has gained increased attention as a promising non-pharmacologic strategy to improve mood is yoga [21].

A Role for Yoga

Yoga is an ancient practice dating back 5000 years that has long been used as a means of promoting overall health, well-being, and spiritual attunement [22]. Although there are many types of yoga, the most common forms of yoga practiced in the United States are variants of *hatha* yoga. Hatha yoga includes three core components: breath control (*pranayama*), physical postures (*asanas*), and meditation (*dhyana*). A growing percentage of the US population regularly practices yoga, with most recent estimates suggesting that over 36 million US citizens aged 18 or older practice yoga regularly either at a studio, gym, or at home, a number that has increased dramatically in the past 10 years [23]. The majority of regular yoga practitioners, approximately 72%, are women. While some practitioners develop a yoga practice for general wellness, improved flexibility, or relaxation, it has been increasingly suggested that yoga can also be utilized to address a range of medical and psychiatric conditions [24, 25]. As such, yoga is starting to be utilized more readily as a complementary or alternative form of treatment, either used in conjunction with, or instead of, traditional Western medicine. To date, the clinical application of yoga has been evaluated in individuals with a wide variety of conditions, including back pain, asthma, cardiovascular disease, cancer, arthritis, and various orthopedic conditions, such as carpal tunnel syndrome [26, 27]. Many initial empirical studies examining the potential benefit of yoga have documented measurable gains following yoga practice, including increased flexibility and strength, reduced lower back pain, improved balance, better concentration, and an increased sense of well-being [27]. In addition, yoga has been associated with improvements in functioning in patients with chronic conditions that impair functioning and mobility [28, 29]. In spite of the growth of research in this area, this field of inquiry regarding the efficacy of yoga is still relatively new, and definitive findings are still forthcoming regarding efficacy and safety for treating medical symptoms and conditions.

In terms of mental health, various types of yoga interventions have been evaluated as treatments for mental health conditions among non-pregnant adults, including post-traumatic stress disorder, depression, obsessive-compulsive disorder, attention

deficit hyperactivity disorder, and generalized anxiety [25], with a large number of studies to date focusing on depression [30]. Though studies vary in methodological rigor, sample characteristics, outcomes assessed, and the specific type of yoga intervention, the current body of literature suggests that yoga may possibly be effective in improving mood among depressed individuals [30, 31]. For example, in a study of 34 depressed adults, Streeter and colleagues [32] found that participants randomized to a weekly 60 min *Iyengar* yoga session for 12 weeks had greater gains in mood and reductions in anxiety in comparison to participants randomized to a 12-week walking program. In addition to a growing number of studies examining the efficacy of yoga as a treatment, some have also begun to examine potential mechanisms of action that may account for the positive effects associated with yoga. Some proposed mechanisms include biological and physiological processes such as decreased inflammation and reduced hypothalamic-pituitary-adrenal activity, and psychological processes, such as increased skills in mindfulness, and reduction of contemplation. Due to the special needs of various patient groups, there has also been an increase in the number of studies examining the safety and efficacy of yoga among specific depressed populations. In light of the physical changes inherent with pregnancy and childbearing, it is important to develop and evaluate yoga interventions among pregnant women, in order to examine the potential risks and benefits of prenatal yoga practice [33].

Prenatal Yoga

Prenatal yoga differs from yoga for the general population in a number of ways [34]. First, prenatal yoga is designed to be gentle in nature, and is safely modified in light of women's changing physiology during pregnancy. Certain postures (*asanas*) are generally avoided (e.g., full inversions, twists, backbends), and other postures are modified in order to ensure safety. For example, because of higher levels of the hormone relaxin during pregnancy, extra care is taken during certain postures in order to avoid over-stretching and over-extending joints, as ligaments are often more flexible than usual. Also, in later stages of pregnancy, certain postures are not possible as they may put too much pressure on the woman's abdomen and developing baby. Second, in prenatal yoga classes, it is common for instructors to encourage use of certain props (e.g., blocks, chairs, straps) in a more routine way in order to modify postures for safety and to ensure balance for pregnant participants. Often, postures will also be modified by trimester of pregnancy, so that women at different stages of pregnancy can tailor their practice safely to their current point in the pregnancy. Third, some approaches to prenatal yoga include breathing practices, postures, and meditations that focus specifically on preparation for labor and birth of the baby, or meditations intended to help women develop a stronger connection to the baby. Last, prenatal yoga classes may specifically address common aches and pains experienced by women during pregnancy, or may address swelling and water retention that can often occur in legs and feet, particularly as women progress to later stages in the pregnancy.

Recent data suggest that many expectant mothers and their providers generally view prenatal yoga to be acceptable and safe during pregnancy. For example, a survey of 950 US pregnant women regarding use of complementary and alternative medicine (CAM) therapies suggests that nearly one-fifth (18.3%) of the sample practiced yoga at some point in their pregnancy [35]. Similarly, surveys of maternity care professionals suggest a growing acceptability of CAM therapies among midwives and obstetricians [36], with prenatal yoga identified as one of the most commonly utilized complementary treatments among pregnant women [37].

In concert with the growing popularity of prenatal yoga practice, an emerging empirical literature has examined clinical and medical benefits to prenatal yoga practice. To date, research has documented that pregnant women who practice yoga report fewer aches and pains during pregnancy, shorter duration of labor, decreased labor pain, higher birthweight babies, and lower rates of intra-uterine growth retardation in comparison to pregnant women who did not practice yoga [38–40]. A large-scale study in India randomized healthy pregnant women into a yoga group vs. a control condition and found that women who practiced yoga were less likely to deliver their infants pre-term [41]. The majority of prenatal yoga studies to date have investigated the physical health benefits of yoga practice and potential impact on labor and delivery. More recently, attention has focused on the emotional and mental health benefits of prenatal yoga [38].

Can Prenatal Yoga Improve Mood During Pregnancy?

There are a number of mechanisms by which prenatal yoga could potentially reduce symptoms of depression during pregnancy, and therefore reasons to believe it might be a helpful approach. First, the practice of mindfulness, as an inherent part of yoga, may help train women to focus their attention on the present moment, rather than focus on worries about the future or dwell upon past or current problems. Mindfulness-based behavioral health treatments have been shown to be effective for other populations, [42] and have recently shown promise as a depression prevention strategy for perinatal women [13]. Second, the physical movement, stretching, and relaxation components of yoga could lower inflammation and have other physical health benefits that result in reductions in depression. Given that increased inflammation is increasingly recognized as a critical correlate of stress and depression in the perinatal period [43], attempts to promote behavioral interventions that lower inflammation are worth pursuing. Prenatal yoga could also bring about positive changes via reduction in the aches and pains associated with pregnancy, improvements in sleep, or a feeling of greater overall comfort in one's changing pregnant body. Further, because some approaches to prenatal yoga involve explicit attention to developing a stronger attachment between the mother and developing baby [44], it is possible that some women may experience a benefit to yoga practice by increasing their sense of connection to the baby, which may bring about a greater overall feeling of comfort and acceptance with the pregnancy and accompanying life changes. Finally, yoga that is practiced in a group setting may have the added benefit of reducing social isolation and increasing connection to other expectant mothers.

Findings from a recent qualitative investigation of women's experiences in prenatal yoga classes also provide insights into why yoga practice during pregnancy may be helpful or appealing to pregnant women [45]. Kinser and Masho interviewed 14 pregnant or postpartum women who had practiced prenatal yoga at some point in the past 6 months regarding motivations that prompted them to engage in prenatal yoga and how they benefited from yoga practice during pregnancy. Three themes emerged from the focus group discussions. First, women noted that feelings of stress and depression were often the prompting reasons for seeking out yoga, and they felt that yoga was a non-stigmatizing way to seek out help and connection with others. Second, women who had participated in prenatal yoga felt that it was helpful to them for a variety of reasons: it was an effective "mind-body" approach to self-care that represented a highly valued block of protected time focused on their own well-being; and it provided a means of community building, as well as physical health benefits that impacted emotional well-being. A third theme that arose was the sense that prenatal yoga classes were perceived by women as being more beneficial than other prenatal classes they had taken during the pregnancy (such as childbirth education classes), in that prenatal yoga involved a higher level of engagement.

Acceptability of Prenatal Yoga Among Pregnant Women Seeking Depression Care

Although prenatal yoga has grown in popularity among pregnant women in general, it is important to consider whether pregnant women experiencing clinical levels of depression would be amenable to engaging in yoga. It is not uncommon for depressed individuals to experience difficulty engaging in self-care activities due to low levels of energy and motivation, symptoms that come hand-in-hand with depression. Such symptoms could potentially also make it challenging for depressed women to engage in yoga classes in the community. Also, because prenatal yoga is not currently considered a standard form of care for antenatal depression, some women may have questions about whether it could help, or concerns about the safety of yoga practice during pregnancy.

To examine the question of whether women with depression and related concerns were open to pursuing prenatal yoga, Battle et al. [46] conducted an investigation into the acceptability of yoga among perinatal behavioral health patients. In this survey study, 250 pregnant and postpartum women who were seeking psychiatric care completed an anonymous questionnaire regarding the likelihood that they would be willing to try prenatal yoga as a treatment strategy. The majority of respondents (62%) were yoga-naïve in that they had never taken a yoga class during the perinatal period, or practiced yoga prior to the pregnancy. Among women seeking care for antenatal depression specifically, a large majority of respondents (88%) expressed interest in trying yoga to improve their emotional well-being, suggesting that women with clinical levels of antenatal depression view yoga to be a valid and potentially helpful intervention. Women were also asked to endorse one or more perceived benefits of prenatal yoga practice; the most common benefits noted by

pregnant women were reducing stress, lowering symptoms of depression, and reducing anxiety [46]. These findings provide encouraging support for the likelihood that women with antenatal depression view prenatal yoga as potentially helpful in lowering their distress, and also as an activity that they are willing to try—even if they have no prior yoga experience.

Efficacy of Prenatal Yoga in Reducing Depression

The question of whether prenatal yoga could help women reduce symptoms of depression has been explored in a few clinical trials to date (for reviews, see Babbar and Shyken [33] and Sheffield and Woods-Giscombe [47]). Many studies have utilized an open trial design [21, 44], yet some have involved randomizing participants to yoga classes or one or more comparison conditions [48–50]. Patient samples have been varied, with some studies enrolling women with a range of clinical diagnoses and symptoms [44, 51], and others focusing specifically on samples of women with elevated depression [21, 48]. The style and amount of yoga (i.e., number of classes, length of each class) has also varied considerably across trials. Approaches to prenatal yoga have ranged from using a relatively brief, 20-minute yoga routine [48] to full-length classes more consistent with prenatal yoga offered in the community [21, 44]. Among randomized trials, comparison conditions frequently consist of non-active conditions such as wait list control groups or standard prenatal care (“treatment as usual”) [51]; however, some trials have utilized more active conditions, such as massage [48] or perinatal health education classes [50]. In light of the variability in styles of yoga, sample selection, methodology and design, and the lack of randomized trials, there is not yet definitive information regarding the efficacy of prenatal yoga in lowering depression during pregnancy. However, preliminary findings at this stage of the research have been promising [47], with a number of trials [21, 44, 48–50] reporting positive results in terms of reduction of depression symptoms following yoga practice.

As one example, Battle and colleagues [21] developed a prenatal yoga intervention and evaluated the feasibility, acceptability, and preliminary efficacy of the intervention in a sample of 34 pregnant women with clinically elevated depression. On average, participants experienced significant reductions in depression severity over the course of the nine-week yoga intervention. In addition, ratings of participant satisfaction and attendance indicated that the yoga classes were feasible to administer and acceptable to the pregnant women enrolled. A small pilot randomized trial [50] provided an additional opportunity to test the prenatal yoga intervention in comparison to a nine-week perinatal education program (the Mom & Baby Wellness Workshop) geared toward expectant mothers. No serious adverse events related to prenatal yoga practice were observed in either trial. In our current randomized trial (R01 HD081868), we are examining whether the prenatal yoga intervention is more effective in lowering prenatal depressive symptoms than the wellness workshop. We are also evaluating differences in other related maternal symptoms (anxiety, sleep) and in important infant outcomes, such as rates of pre-term delivery.

Safety of Prenatal Yoga

An important consideration for pregnant women when engaging in any form of physical activity is safety. As noted earlier, prenatal yoga is, by design, structured to be gentle and safe for pregnant women. The pace of prenatal yoga tends to be slower, and postures and breathing practices that could potentially be harmful for women or the developing fetus are intentionally avoided. Moreover, prenatal yoga classes are typically geared toward beginning-level yoga practitioners, and for women at all levels of physical fitness. However, as with any form of physical activity, the American College of Obstetricians and Gynecologists (ACOG) recommends that pregnant women speak with their own prenatal health care provider prior to engaging in a physical activity program to discuss whether it is safe for them. In some cases, such as women who are carrying multiple gestation pregnancies or those experiencing certain medical conditions (e.g., placenta previa, severe anemia) even gentle prenatal yoga may not be recommended. Consulting with one's individual provider about safety is important—not only prior to starting a yoga practice, but also throughout the pregnancy, in case new symptoms arise, or one's medical status changes.

Current ACOG recommendations note that, with only some exceptions (i.e., “hot yoga”), prenatal yoga is safe for the majority of pregnant women. Yoga practice that is modified for pregnancy is in fact listed as a recommended form of physical activity for pregnant women [52]. Community yoga instructors generally promote safety by asking new pregnant participants to consult with their prenatal care providers before starting yoga class; once enrolled, pregnant women are typically encouraged to not exert themselves, take breaks as necessary, and stay well-hydrated.

Encouragingly, the findings of a recent meta-analysis of yoga interventions geared for non-pregnant populations suggested that there were no greater risk of injury or adverse events for those who engaged in yoga practice, compared to those who participated in exercise or usual care [53]. Though not all studies have systematically assessed or reported rates of adverse outcomes, the relatively small body of research on prenatal yoga to date has not documented any clear risks or adverse outcomes related to prenatal yoga practice [33]. Though the gentle nature of prenatal yoga would suggest that the practice is likely to be safe for most women without serious medical conditions, it is important that future studies carefully document safety outcomes.

For pregnant women seeking a prenatal yoga class in their community, assessing prior training and experience of the instructor is critical. Although licensing requirements differ by geographic location, at present the majority of yoga instructors are not required to undergo licensing procedures in the same manner as other health professionals (e.g. nurses, physical therapists). Some national organizations, such as the Yoga Alliance, are, however, starting to put forth standards to identify minimum qualifications for prenatal yoga instructors.

Conclusions and Future Directions

Prenatal yoga is already a popular activity among pregnant women, and recent data suggest that it is regarded as safe and helpful by many prenatal health care

providers. Research on prenatal yoga has increased substantially in the past decade, with specific attention on the role of yoga in improving mood and emotional well-being. Initial findings from yoga trials with pregnant women suggest that prenatal yoga practice may be associated with clear benefits to both women and offspring, in terms of pain management and birth outcomes. In addition, trials examining the impact of prenatal yoga on improving maternal mood are highly encouraging, however more research is needed, both with clinically depressed samples and using methodologically rigorous randomized controlled trial study designs, to clarify not only the efficacy of yoga in improving women's mood, but also to explore the reasons why it may be helpful, and to further assess the safety of yoga for both mother and baby. Given the widespread prevalence of perinatal depression and potentially lasting adverse effects of untreated depression on mother and baby, finding effective and acceptable treatment strategies and adjunctive therapies is critical.

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Part IV
The Postpartum Period

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Nutrition Issues During Lactation

Deborah L. O'Connor, Susan Trang, and Yen-Ming Chan

Keywords Breastfeeding · Lactation · Postpartum · Nursing · LC-PUFAs

Key Points

- Breastfeeding is the normal and best way of feeding infants. Exclusive breastfeeding is encouraged for the first 6 months, and sustained for 2 years or longer, with appropriate complementary feeding.
- Energy and nutrient requirements of lactating women are elevated during lactation but can be met by 2 or 3 extra servings each day of nutrient dense foods from any of the following groups: fruits, vegetables, grains, protein, and dairy. Gradual weight loss postpartum to achieve prepregnancy weight and a healthy body weight is encouraged and will not negatively affect breastmilk volume or quality.
- Due to low levels of vitamin D in breastmilk at usual maternal dietary and supplemental intakes, women should be advised to provide their infants with 400 IU vitamin D each day.
- Breastmilk composition will be affected by maternal intake for some nutrients including vitamin B₁₂ and the long-chain fatty acids; both important in neural development. Hence a well-balanced diet during lactation not only ensures optimal health of women but also that of their offspring.

Introduction

Breastfeeding is the normal and unequalled method of feeding infants. The World Health Organization, the American Academy of Pediatrics, and Health Canada all recommend human milk as the exclusive nutrient source for the first six months of

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life. These organizations also indicate that breastfeeding should be continued at least through the first 12 months of life, and thereafter as long as mother and baby mutually desire [1–3]. The scientific rationale for recommending breastfeeding as the preferred feeding choice for infants stems from its acknowledged benefits to infant nutrition; infection rates, gastrointestinal function; host defense; neurodevelopment; and psychological, economic, and environmental well-being [1, 4, 5]. The American Academy of Pediatrics Policy Statement entitled, “Breastfeeding and the Use of Human Milk” is an excellent resource, which includes a succinct discussion of the specific benefits of breastfeeding [1]. Briefly, the policy acknowledges that research provides good evidence that breastfeeding decreases the rate of postneonatal infant mortality and reduces the incidence of a wide range of infectious diseases, including non-specific gastrointestinal tract infections, respiratory tract infection, otitis media, urinary tract infection, and late-onset sepsis and necrotizing enterocolitis rates in preterm infants. Breastfeeding is also associated with improvements in cognitive development in both term-born and prematurely born infants, although the benefits, at least in part, may be related to sociodemographic differences between families providing breastmilk compared to formula feeding [6]. Other long-term benefits include protection from diabetes, and reduction in overweight and obesity.

Documented benefits to the mother include protection against breast cancer and possibly protection from ovarian cancer and type 2 diabetes. Many of the associations between incidence and duration of breastfeeding and positive maternal and infant health outcomes were recently reaffirmed by Victora et al. [5] in their comprehensive review of 28 systematic reviews and meta-analyses.

The energy and nutrient needs of lactating women who exclusively breastfeed their infant for the first 6 months postnatally exceed those of pregnancy. These additional nutrient requirements can be met by a very modest increase in the number servings of nutrient-dense foods consumed each day (two to three servings) [7]. For the most part, nutrient requirements for the lactating woman are based on those of nonpregnant, nonlactating women, with an incremental amount added to account for the amount of the nutrient secreted into breast milk. Lactation success has traditionally been defined by infant outcomes, such as infant growth and volume and nutrient content of milk consumed, and nutritional status [8]. Few studies to date have directly examined the nutritional status of lactating women or the short- or long-term consequences of suboptimal maternal nutrition on maternal health. It is noteworthy that maternal deficiency of some nutrients can adversely affect the concentration of these nutrients in breast milk. These nutrients include thiamin, riboflavin, vitamin B₆, vitamin B₁₂, choline, retinol, vitamin A, vitamin D, selenium, and iodine. In contrast, the content of folate, calcium, iron, copper and zinc in breast milk is unrelated to maternal status or intake [9].

The purpose of this chapter is to examine the energy demands of lactation as well as a select list of nutrients known to be sometimes provided in short supply for reproductive-age women in developed countries. These nutrients include calcium,

vitamin D, folate, vitamin B₁₂, and iron. As energy balance is currently an area of concern for many lactating women and their health care providers, we also review the literature in relation to dieting and exercise during lactation. Finally, we will close by discussing long-chain polyunsaturated fatty acids (LC-PUFAs), variability in breast milk content, and the implications of maternal LC-PUFA supplementation on maternal and infant outcomes.

Energy

Estimated Energy Requirements

The incremental energy cost of lactation is determined by the amount of milk produced (exclusivity and duration), the energy density of the milk secreted, and the energy cost of milk synthesis [10]. The Estimated Energy Requirements (EERs) for lactation, or the average daily energy intake predicted to maintain energy balance in a healthy lactating woman, of a given age, weight, height, and level of physical activity can be estimated by a factorial approach from the sum of the (1) EER of a nonpregnant, nonlactating woman (of a given age, weight and activity level), plus (2) estimated milk energy output, plus (3) energy mobilization from tissue stores (i.e., weight loss) [11]:

The EER of a nonpregnant, nonlactating woman can be calculated using information provided in Table 1. The current age, weight, and relative physical activity level must be known.

Milk energy output is tabulated by multiplying the volume of milk produced by its energy density (Table 2). The figure used by the US Institute of Medicine to estimate the daily volume of milk produced from birth to 6 months is 0.78l/day [11]. From 7 to 12 months, mean milk production is estimated to be 0.61l/day, reduced with the introduction of solid foods. While the daily volume of breast milk produced among exclusively breastfeeding mothers is remarkably consistent from woman to woman and country to country, it varies considerably, of course, if a woman is partially or totally breastfeeding [10]. The US Institute of Medicine reviewed studies where human milk energy density was measured by bomb calorimetry and found an average value of 0.67 kcal/g.

Energy mobilization from tissue stores is the energy derived from the weight lost in the first 6 months postpartum (Table 2). For the purposes of calculating the EERs for lactation, this value was set at 0.8 kg/month [11]. Women meet most of the incremental energy requirements of lactation by eating more calories, decreasing physical activity early postpartum, and mobilizing fat stores laid down during pregnancy [10]. Mobilization of fat stores laid down during pregnancy is not obligatory, and the extent to which they are used to support lactation depends on the nutritional status of the lactating mother and the amount of weight gained during pregnancy. A

Table 1 Calculating the estimated energy requirement (EER) for a nonpregnant, nonlactating woman 30 years of age^a [11]

Height m (in.)	PAL ^b	Weight for BMI of 18.5 kg/m ² kg (lb)	Weight for BMI of 24.99 kg/m ² kg (lb)	EER, women (kcal/day) ^c	
				BMI of 18.5 kg/m ²	BMI of 24.99 kg/m ²
1.45 (57)	Sedentary	38.9 (86)	52.5 (116)	1563	1691
	Low active			1733	1877
	Active			1946	2108
	Very active			2201	2386
1.50 (59)	Sedentary	41.6 (92)	56.2 (124)	1625	1762
	Low active			1803	1956
	Active			2025	2198
	Very active			2291	2489
1.55 (61)	Sedentary	44.4 (98)	60.0 (132)	1688	1834
	Low active			1873	2036
	Active			2104	2290
	Very active			2382	2593
1.60 (63)	Sedentary	47.4 (104)	64.0 (141)	1752	1907
	Low active			1944	2118
	Active			2185	2383
	Very active			2474	2699
1.65 (65)	Sedentary	50.4 (111)	68.0 (150)	1816	1981
	Low active			2016	2202
	Active			2267	2477
	Very active			2567	2807
1.70 (67)	Sedentary	53.5 (118)	72.2 (159)	1881	2057
	Low active			2090	2286
	Active			2350	2573
	Very active			2662	2916
1.75 (69)	Sedentary	56.7 (125)	76.5 (168)	1948	2134
	Low active			2164	2372
	Active			2434	2670

Table 1 (continued)

Height m (in.)	PAL ^b	Weight for BMI of 18.5 kg/m ² kg (lb)	Weight for BMI of 24.99 kg/m ² kg (lb)	EER, women (kcal/day) ^c	
				BMI of 18.5 kg/m ²	BMI of 24.99 kg/m ²
	Very active			2758	3028
1.80 (71)	Sedentary	59.9 (132)	81.0 (178)	2015	2211
	Low active			2239	2459
	Active			2519	2769
1.85 (73)	Very active			2855	3140
	Sedentary	63.3 (139)	85.5 (188)	2082	2290
	Low active			2315	2548
	Active			2605	2869
1.90 (75)	Very active			2954	3255
	Sedentary	66.8 (147)	90.2 (198)	2151	2371
	Low active			2392	2637
	Active			2692	2971
1.95 (77)	Very active			3053	3371
	Sedentary	70.3 (155)	95.0 (209)	2221	2452
	Low active			2470	2728
	Active			2781	3074
	Very active			3154	3489

^aFor each year below 30, add 7 kcal/day, for each year above 30, subtract 7 kcal/day

^bPAL physical activity level

^cEER for women can be calculated as follows: $EER = 354 - (6.91 \times \text{age [years]}) + PA \times (9.36 \times \text{weight [kg]} + 726 \times \text{height [m]})$, where PA is the physical activity coefficient of 1 for sedentary PAL, 1.12 for low active PAL, 1.27 for active PAL, and 1.45 for very active PAL

well-nourished woman will mobilize approximately 0.72 MJ/day (~170 kcal/day) of fat stores to help support breastfeeding in the first 6 months postpartum. Physical activity tends to be lower in the early postpartum period among women in the developed world, as daily activities change in response to caring for a newborn. While the expectation of many women is that they will lose weight rapidly by breastfeeding, weight changes postpartum are highly variable. Some women may actually gain weight postpartum. Generally, well-nourished women will lose on average 0.8 kg/month (1.8 pounds/month) for the first 6 months postpartum; undernourished women can expect to lose 0.1 kg/month. Postpartum weight change varies consider-

Table 2 Calculating the estimated energy requirement (EER) for a lactating woman [11]

Equals adult EER	Plus milk energy output	Minus weight loss
See Table 1	500 kcal the first 6 months	170 kcal the first 6 months
	400 kcal the second 6 months	0 kcal the second 6 months
	Why?	Why?
Calculate based on a nonpregnant woman's weight, age, and physical activity level	This equals milk production \times energy density the first 6 months: 0.78 l/day \times 0.67 kcal/g rounded to 500 kcal/day second 6 months: 0.6 l/day \times 0.67 kcal/g rounded, to 400 kcal/day	Weight loss seen in first 6 months with an average loss of 0.8 kg/month equivalent to 170-kcal/day deficit

ably from country to country; this variation is not explained by lactation intensity or duration [12–14].

The reported energy intakes of lactating women in the literature are generally lower than that recommended by the Institute of Medicine [11]. Under-reporting may be a reason for these low energy intakes or the EER may be set too high. Alternatively, mobilization of fat stores may play a greater role in energy balance or energy expenditure is lower than expected. There is little evidence to suggest energy conservation in the lactating woman, e.g., more efficient metabolism due to a change in the hormonal milieu. Most research data do not suggest that an individual's basal metabolic rate is lower during lactation than prepregnancy or that more energy is used to complete a physical task. Basal metabolic rate is the rate of energy expenditure in an individual resting comfortably, awake, and motionless, 12–14 h after last consuming food.

A Sample Calculation of the Estimated Energy Requirement for Lactation

Using Tables 1 and 2, the EER for lactating women may be calculated. Using the example of a “low active,” exclusively, breastfeeding woman 4 months' postpartum who is 35 years of age, and weighs 60 kg and is 1.6 m tall, first refer to Table 1, and calculate her EER as if she were neither pregnant nor lactating. Alternatively, calculate her estimated energy requirement as if she was nonpregnant, nonlactating using the footnote of Table 1. Using the table itself, our sample lactating woman would have a nonpregnant, nonlactating estimated energy requirement of 2083 kcal. To this value add 500 kcal to account for the amount of energy required to produce breast milk, and subtract 170 kcal for the contribution from fat stores laid down in pregnancy (information found in Table 2). Hence, our sample lactating woman's EER would be approximately 2413 kcal (2083 + 330). It is important to stress this is an *estimate* of the energy requirements of an *average* woman only, and follow-up is required to ascertain its appropriateness at an individual level, i.e., some women can gain or lose weight using this recommendation for energy intake.

Postpartum Weight Retention

More than a third of pregnant women gain more weight during pregnancy than is recommended, and this is particularly a problem among women who are already overweight or obese [15]. The increasing prevalence of obesity among women in both developed and developing nations raises concerns about the retention of excess weight gain postpartum and lifestyle changes in the postpartum period as likely contributors to obesity among women [16]. In the Danish National Birth Cohort ($n = 23,701$), postpartum weight retention at 6 months and weight gain from six to 18 months postpartum were associated with an increase in body weight and BMI-adjusted waist circumference after 7 years [17]. Higher weight increases the likelihood of poor health outcomes (e.g., gestational diabetes, delivery intervention, macrosomia) in subsequent pregnancies and lower rates of breastfeeding initiation and duration [18]. While many women express a desire to lose weight postpartum and return to their prepregnancy weight, weight loss among women postpartum is highly variable. Nutrition advice for lactating women has historically been to avoid dieting while breastfeeding to ensure appropriate nutritional status for both infant and mother. Given the global epidemic of obesity and associated health consequences, this advice needs to be reevaluated.

A woman who is lactating has the same physiologic requirements for regulating body weight as one that is not, except that she is producing a continuous supply of milk creating a much higher energy output. As noted above, the total energy cost to a woman who is exclusively breastfeeding an infant 0–6 months is estimated to be 500 kcal/day; theoretically, this output of energy could result in 0.5 kg/week (1.1 pound/week) of weight loss, provided energy intake and physical activity remain unchanged. While the woman-to-woman variability is tremendous, this rate of postpartum weight loss is seldom achieved as energy intake and/or a decrease in physical activity in the early postpartum period compensates, at least in part, for the energy costs of lactation. Higher energy intakes in lactating women versus nonlactating women may be attributed to enhanced appetite due to increased prolactin levels and higher energy demands. Prolactin is a hormone released by the anterior pituitary gland, which stimulates breast development and milk production in women.

The most consistent and strongest determinant of weight loss during lactation is pregnancy weight gain [19–21]. Excessive weight gain during pregnancy predisposes women to higher short- and long-term postpartum weight retention. Women with a pregnancy weight gain consistent with the Institute of Medicine recommendations [22] experienced reduced postpartum weight retention compared to those who gained weight above the recommendations (−6.6 and −10.4 lb after 3 and ≥ 15 years). Other factors that have been shown to influence postpartum weight loss, albeit inconsistently, include prepregnancy weight, age, parity, ethnicity, smoking, exercise, and return to work outside the home. Baker et al. [23] showed that women who exclusively breastfed for 6 months would retain about 4.4 lb less weight at 6 months postpartum compared to women who did not breastfeed. However, two

meta-analyses suggest that lactating women are not more likely to lose weight postpartum than women who feed their infants formula [12, 13].

Body composition also changes throughout pregnancy and lactation. Due to high levels of estrogen in pregnancy, a pregnant body favors the gynoid shape. Specifically, body fat distributes to the thigh area and to a lesser extent the suprailiac, subscapular, costal, biceps, and triceps areas [19]. Changes in body composition with breastfeeding are then reversed and fat is mobilized from the trunk and thigh areas.

Exercise and Lactation

Physical activity at any stage of the life cycle is associated with improved cardiorespiratory fitness and a reduction in the risk of obesity and associated morbidities [24]. Specifically in lactation, regular activity improves cardiovascular fitness, plasma lipid levels, and insulin response [25]. Regular activity also has the potential to benefit psychosocial well-being in lactation, such as improving self-esteem and reducing depression and anxiety. Engagement in regular activity by the mother may also encourage the same in her offspring, promoting a healthy lifestyle and body weight management for the entire family.

Women can actively engage in moderate exercise during lactation without affecting milk production, milk composition, or infant growth [26, 27]. Lovelady et al. demonstrated that overweight sedentary lactating women randomized to a regimen of reduced energy intake (-500 kcal/day) and aerobic exercise (45 min/4 days each week) had babies who grew similarly to those of women who both were not on an energy-restricted diet and exercised once or never per week [26]. Aerobic exercise in that study consisted of walking, jogging, and dancing at 65–80% of maximum heart rate. The duration of exercise was initially 15 min, increased by at least 2 min each day until the women were exercising for 45 min at the target heart rate. There is evidence that exercise in the absence of energy restriction will not promote weight loss postpartum, [28] and diet restriction alone results in a greater percentage of lean body mass loss compared to exercise in combination with energy restriction [27, 29]. However, a combined diet restriction (-500 kcal/day) and moderate exercise program (45 min, 4 days each week, 60–70% of maximum heart rate) was no better at preserving lean body mass compared with diet restriction alone in overweight and obese lactating women [30]. Exercise during lactation has also been shown to slow bone mineral density loss [31]. Further studies are needed to confirm the role of diet and exercise on weight loss and changes in body composition.

The American College of Obstetricians and Gynecologists has developed guidelines for exercising in pregnancy and the postpartum period [24]. The Society of Obstetricians and Gynaecologists of Canada and the Canadian Society for Exercise Physiology have also published a joint guideline for exercise in pregnancy and during the postpartum period [32]. For the postpartum period, these guidelines include resuming physical activity gradually, and only when a woman's body has healed substantially from pregnancy and delivery. Women are encouraged to discuss with their primary care physician a timeline to resume physical activity and, once com-

menced, they should avoid becoming excessively fatigued, remain well hydrated, and watch for abnormal bleeding or pain [25]. Some women may find it more comfortable to exercise after breastfeeding.

Achieving a Balance of Diet and Exercise for Mom and Baby

Some basic guidelines regarding energy control for lactating women are summarized in Table 3. Maintaining a healthy diet during lactation is not only essential as a weight loss strategy, but it also ensures that macro- and micronutrient intake is adequate to support optimal maternal health and breastfeeding success.

Calcium

Background

Calcium is important for the normal development and maintenance of the skeleton, with over 99% of total body calcium found in bones and teeth [36]. The remainder of total body calcium is tightly regulated in blood, extracellular fluid, and muscle,

Table 3 Guidelines for energy control during lactation

<i>Diet</i>
<ul style="list-style-type: none"> Eat a well-balanced diet consisting of nutrient-dense foods. Compare your typical daily food choices against the 2015–2020 US Department of Agriculture Dietary Guidelines and MyPlate, or dietary guidance from your country of origin, and make appropriate modifications [33–35]. In the event that you need help making modifications, see your primary care physician or a dietitian
<ul style="list-style-type: none"> Restricting dietary intake by 500 kcal/day is safe as is moderate weight loss. Neither affects breast milk composition
<ul style="list-style-type: none"> Reduce consumption of foods high in fat, sodium, and added simple sugars (e.g., sucrose, fructose)
<ul style="list-style-type: none"> Emphasize whole fruit and vegetable consumption
<ul style="list-style-type: none"> Emphasize foods high in calcium and vitamin D
<ul style="list-style-type: none"> If capable of becoming pregnant, then consume 400 mcg/day of folic acid for neural tube defect prevention
<i>Exercise</i>
<ul style="list-style-type: none"> Prepregnancy activities may be resumed gradually after receiving medical clearance from your doctor. This usually occurs around 4–6 weeks postpartum
<ul style="list-style-type: none"> Gradually work up to 30 min of moderate exercise each day for most days of the week
<ul style="list-style-type: none"> An exercise regimen consisting of 45 min of moderate aerobic exercise 4 days/week (60–80% maximum heart rate) in combination with a 500 kcal/day diet restriction has been shown to promote postpartum weight loss and does not negatively affect breastfeeding [32]
<ul style="list-style-type: none"> Avoid excessive fatigue and keep hydrated
<ul style="list-style-type: none"> Wear a bra that is supportive to your activity

where it plays a role in blood pressure regulation, muscle contraction, nerve transmission, and hormone secretion. Calcium homeostasis is maintained by parathyroid hormone, which increases blood calcium, and calcitonin, thus lowering blood calcium. If blood calcium levels fall, parathyroid hormone is secreted, stimulating the release of calcium from bone. Chronic calcium deficiency, due to inadequate intake, will result in progressive loss of skeletal mass and increase the risk of osteoporosis.

During lactation, secretion of calcium into breast milk averages about 200 mg/day to accommodate the whole-body mineral accretion rate of the infant [37]. Although renal calcium excretion rates are lowered and intestinal absorption rates increase to meet the elevated calcium demands of lactation, the primary source of calcium secreted in breast milk appears to be from increased maternal bone resorption. The concentration of calcium in breast milk decreases after 3–6 months and thus, the greatest loss of bone mineral content occurs within the first few months postpartum [37]. Serial measurements of bone density after 2–6 months of lactation have shown a decrease of 5–10% in bone mineral content of trabecular bone (sponge-like interior) in the lumbar spine, hip, femur, and distal radius, with smaller losses occurring with cortical bone (exterior shell) [37–40]. Loss of calcium from the maternal skeleton is not prevented by increased dietary calcium, even among women with low baseline calcium intakes [41–43]. Upon return of menses, and restoration of estrogen, maternal bone lost during lactation is restored within 3–12 months of cessation of breastfeeding [38–40, 42, 44, 45]. Based on the majority of epidemiological studies, there is no adverse effect of lactation history on peak bone mass, bone density, or hip fracture risk [46]. One study demonstrated an improvement in hip and tibia bone-strength indices in women who breastfed for at least 33 total months compared to those who breastfed for <12 months [47]; however, long duration of lactation has been shown to increase risk of vertebral fracture later in life (>18 months duration, OR = 2.12 compared to never breastfeeding) [48]. Duration of lactation has also been associated with lower lumbar spine bone mineral density, but not fracture risk [49]. Thus, the majority of the evidence suggests that the bone mineral changes that occur during and following lactation are a normal physiological response and do not reflect an increased requirement for calcium.

Recommended Dietary Intake for Calcium

The Recommended Dietary Allowance (RDA) for calcium during lactation is set at 1000 mg/day for women who are 19–50 years of age [36]. It is recommended that breastfeeding women younger than 19 years of age consume 1300 mg calcium/day due to the increased need to support ongoing bone growth of the teen herself [36]. As defined by the US Institute of Medicine, an RDA is the average daily nutrient intake level that meets the nutrient requirement of almost all

healthy individuals. The tolerable upper intake level (UL) is 2500 mg for women 19–50 years of age [36].

Calcium Intakes of Women

The lack of effect of calcium supplementation on maternal bone metabolism during lactation does not lessen the importance of consuming foods rich in calcium. Available data from both the US National Health and Nutrition Examination Survey (NHANES) and Canadian Community Health Survey (CCHS) 2.2 suggest that women, regardless of reproductive stage, are not meeting recommended intakes for calcium [50, 51]. Daily mean calcium intakes from diet alone by American adult women aged 19–30 and 31–50 years are reported to be about 838 mg/day and 864 mg/day, respectively [52]. In African-American and other ethnic minority groups, calcium intake is particularly low [53, 54]. While the calcium intakes of lactating women, specifically, have not been extensively studied in North America, Mackey et al. reported that lactating American women from the midwest ($n = 52$), had average calcium intakes of approximately 1218 mg and 1128 mg/day at 3 and 6 months postpartum, respectively [55]. A study of overweight fully breastfeeding American women ($n = 160$) estimated an average calcium intake of 1029 mg/day and consumption of an average of 2.3 servings of dairy at 6 weeks' postpartum [56].

Sources of Calcium in the Diet

Approximately one-third of dietary calcium intake in the United States is from fluid milk and other dairy products [57]. Nondairy sources include calcium-fortified orange juice, and rice or soy beverages. Salmon with bones and some green leafy vegetables such as broccoli may also contribute to the intake of calcium (Table 4). The calcium bioavailability of nondairy foods is variable [58, 59]. For most solid foods, the bioavailability of calcium is inversely associated with its oxalate content. For example, the calcium bioavailability from foods high in oxalates such as spinach and rhubarb is low, whereas it is high in foods with low concentrations of oxalates such as kale, broccoli, and bok choy [60]. Supplemental sources of calcium come in a variety of preparations, both liquid and solid. Calcium from carbonate and citrate are the most common forms of calcium supplements [61]. Ingestion of a meal with dietary and supplemental calcium results in a 20–25% improvement in absorption relative to absorption obtained when a source is ingested on an empty stomach [61, 62]. The absorption of supplemental calcium is greatest when calcium is taken in doses of 500–600 mg or less [36]. It is important to counsel women to look for the amount of “elemental calcium” on the label of supplements to ensure an adequate dose is consumed.

Table 4 Dietary sources of calcium

Food	Portion size	Calcium content per serving (mg)
Milk, whole, 2%, 1%, skim	1 cup	291–316
Yogurt, low fat, plain	3/4 cup	270–320
Calcium-enriched orange juice	1 cup	320
Fortified rice or soy beverage	1 cup	320
Yogurt, fruit bottom	3/4 cup	214
Cheese, hard	1.5 oz.	370
Salmon, canned with bones	2.5 oz.	208
Tofu, firm, made with calcium sulfate	5 oz.	525
Cottage cheese 1% milk fat	1 cup	146
White beans, cooked	3/4 cup	119
Almonds, dry roast	1/4 cup	93
Turnip greens, boiled, drained	1/2 cup	104
Ice cream, vanilla	1/2 cup	76
Navy beans, cooked	3/4 cup	93
Orange	1 medium	52
Kale, boiled, drained	1/2 cup	49
Chickpeas, cooked	3/4 cup	58
Broccoli, boiled, drained	1/2 cup	33
Regular unfortified soy beverage	1 cup	65

Adapted from British Columbia Ministry of Health (2014) HealthLinkBC no. 68e, Nutrition Series. Available at: <http://www.healthlinkbc.ca/healthfiles/hfile68e.stm>

Vitamin D

Background

The most well-appreciated function of vitamin D is to maintain normal blood calcium and phosphorus concentrations, thereby promoting bone health. Vitamin D can be obtained from food, or synthesized in the skin by exposure to ultraviolet light. Solar ultraviolet-B (UVB) photons are absorbed by 7-dehydrocholesterol in the skin, transformed to previtamin D, and then rapidly converted to vitamin D. Total body exposure to 10–15 min of peak sunlight during the summer months in a Caucasian is equivalent to approximately 20,000 IU of vitamin D [63, 64]. Seasonal changes, time of day, latitude, aging, sunscreen use, and skin pigmentation can influence the cutaneous production of vitamin D. Above 37°N latitude during the months of November to February, there is marked reduction in the UVB radiation reaching the earth's surface [65]. To give the reader an approximate idea of the location of the 37°N latitude, Richmond, Virginia, and Oakland, California, are located here. Likewise, most of Europe lies above 37°N. Therefore, very little, if any, vitamin D is produced in the skin in the winter north of Richmond or Oakland or in Europe. Once produced in the

skin, or absorbed, vitamin D is metabolized in the liver to the major circulating form, 25-hydroxyvitamin D. The circulating concentration of 25-hydroxyvitamin D is a good indicator of the cumulative effects of sunlight exposure and dietary vitamin D intake. Following production, 25-hydroxyvitamin D is converted in the kidney to its biologically active form, 1,25-dihydroxyvitamin D, and transported to major target tissues. 1,25-Dihydroxyvitamin D is responsible for an increase in intestinal calcium absorption and mobilization of calcium from the bone.

Results from the NHANES 2001–2006 showed that approximately one-third of the American population, including pregnant and lactating women, had circulating 25-hydroxyvitamin D concentrations <50 nmol/l [66]. Similarly, data from the national Canadian Health Measures Survey suggest 40% of Canadians 6 years of age and older have 25-hydroxyvitamin D levels <50 nmol/l [67]. The US Institute of Medicine states that serum 25-hydroxyvitamin D levels ≥ 50 nmol/l (≥ 20 ng/ml) are adequate for bone and overall health in most people [36].

Human milk contains low amounts of vitamin D, estimated to be approximately 29 IU/l [36] while infant formula is routinely fortified with vitamin D. Unlike the formula-fed infant, the breastfed infant is primarily dependent upon stores and supplemental sources of vitamin D. Currently the American Academy of Pediatrics recommends that infants <6 months of age not be exposed to direct sunlight [68]; hence, the opportunity for cutaneous exposure is limited. Thus, breastfed infants are recommended to be given a 400 IU vitamin D supplement each day [2, 69]. High-dose maternal vitamin D supplementation (5000–6400 IU/day) has been shown to improve both the vitamin D status of lactating women and their infants [70–72]. A maternal intake of 4000 and 6400 IU/day increased the vitamin D activity of milk by 100 IU/l and 873 IU/l, respectively. While these data are promising, these doses of supplemental vitamin D are above the UL of 4000 IU/day for pregnant and lactating women [36]. Either a formal risk assessment, additional studies, or both are needed before routine high-dose supplementation to the mother over prolonged periods can be recommended.

Recommended Dietary Intake for Vitamin D

The current RDA for vitamin D is the same for both nonlactating and lactating adults (600 IU/day) [36]. In setting this RDA, the Institute of Medicine assumed minimum sun exposure. As discussed earlier a significant proportion of North Americans do not have blood values consistent with optimal health set by the Institute of Medicine (≥ 50 nmol/l) and some experts believe that a desirable 25-hydroxyvitamin D concentration is ≥ 75 nmol/l (30 ng/ml) to benefit other non-bone related functions in the body, including modulation of cell proliferation, differentiation, apoptosis, and neuromuscular and immune function [73–75].

Currently, the US Institute of Medicine considers an intake of 4000 IU/day for lactating women to be the UL. The UL, as defined by the US Institute of Medicine, is the highest level of continuing daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals. Hathcock and colleagues [76]

focused on the risk of hypercalcemia and demonstrated that the margin of safety for vitamin D consumption for adults is likely greater than ten times any current recommended level. These authors conclude that the UL for vitamin D consumption by adults should be set at 10,000 IU/day [76].

Furthermore, vitamin D is a fat-soluble vitamin and is stored in body fat. As a result, several studies have linked obesity with poorer vitamin D status, as demonstrated by lower circulating 25-hydroxyvitamin D concentrations [77–80]. A study conducted by Wortsman et al. [80] confirmed that obese patients had lower basal 25-hydroxyvitamin D and higher serum parathyroid hormone concentrations than nonobese patients. Following exposure to an identical amount of UVB radiation, the blood concentration of vitamin D was 57% less in obese than in nonobese subjects. It was proposed that the lower serum 25-hydroxyvitamin D levels seen among obese subjects were the result of increased sequestering of vitamin D in fat tissue. Likewise, body mass index (BMI) was inversely correlated with peak blood vitamin D concentrations after oral dosing. In conclusion, obese subjects may have a greater requirement for vitamin D than their nonobese counterparts.

Dietary Intake of Vitamin D

While data on the dietary intakes of lactating women are sparse, data from the CCHS 2.2 in Canada suggest that more than 90% of women of reproductive age have intakes from diet alone of vitamin D below their estimated average requirement [51]. As the widespread use of sunscreens and public health recommendations to avoid sun exposure limit this endogenous source of vitamin D, most people necessarily rely on vitamin D from either dietary or supplemental sources. Although dietary sources may provide an amount to meet the currently published 2010 recommendations for vitamin D, they fall short of meeting the suggested requirement proposed in other studies [52, 81, 82]. A supplemental source of vitamin D is likely required to meet these latter proposed recommendations, at least in the winter months when sun exposure is limited.

Sources of Vitamin D in the Diet

Only a few foods are natural sources of vitamin D. These include liver, fatty fish such as salmon, and egg yolks. Cod liver oil is an excellent source of vitamin D, containing approximately 1360 IU/tablespoon. The major dietary sources of vitamin D, however, are vitamin D-fortified foods including milk (104 IU per 8-oz. serving), some orange juices (100 IU per 8-oz. serving), plant-based beverages such as soy milk, and some margarines (76 IU/tablespoon). Fortification of fluid milk is required in both Canada and the United States. Careful label reading is required to ensure other food sources contain vitamin D as a fortificant.

Folate

Background

Folate is a generic term used to describe a number of related compounds that are involved in the metabolism of nucleic and amino acids, and therefore the synthesis of DNA, RNA, and proteins. Folate plays a role in the conversion of homocysteine to methionine. Folic acid is a synthetic form of the vitamin, used in vitamin supplements and food fortification. It exhibits a high degree of stability, and is more bioavailable than naturally occurring folate from food. With the exception of severe maternal folate deficiency (i.e., megaloblastic anemia), the content of folate in human milk remains stable and appears to be conserved at the expense of the mother's folate stores [83].

Recommended Dietary Intake for Folate

The bioavailability of naturally occurring folates in food and synthetic forms of the vitamin is thought to differ considerably. A folic acid supplement taken on an empty stomach is thought to be 100% bioavailable compared to about 50% for naturally occurring food folate (Table 5) [84]. In an effort to take into account the different bioavailability of folate from natural versus synthetic sources, folate requirements are now expressed as dietary folate equivalents (micrograms of DFE): micrograms of food folate + $(1.7 \times \text{mcg of folic acid})$.

The RDA for folate, published by the US Institute of Medicine for breastfeeding women aged 14–50 years, is 500 mcg DFEs per day. The RDA of 500 mcg DFEs per day is the amount of folate estimated to replace the folate secreted daily in human milk plus the amount of folate required by the nonlactating woman to maintain healthy folate status, but it does not factor in the metabolic cost of milk synthesis [84]. Lactating women who are planning a subsequent pregnancy, or who are not taking effective precautions to prevent one, should be encouraged to consume 400 mcg folic acid supplement daily for at least four weeks before and 12 weeks after conception to reduce the risk of having a subsequent child with a neural tube defect. The reader is referred to updated guidelines for use of folic acid supplements for the prevention of folate-related birth defects [85, 86]. These guidelines provide information on folic acid supplementation for women who are at elevated risk of having an infant with a neural tube defect. It is estimated that appropriate intake of folic acid during the peri-conceptual period reduces the risk of neural tube defects by about 50%.

Table 5 Relative bioavailability of naturally occurring and synthetic folate

-
- 1 mcg of folate from food provides 1 mcg of dietary folate equivalent (DFE)
 - 1 mcg of folic acid supplement taken on an empty stomach provides 2.0 mcg of DFE
 - 1 mcg of folic acid supplement taken with meals or from fortified food provides 1.7 mcg of DFE
-

The UL for folate for lactating women aged 14–18 years and aged 19 years and older is set at 800 mcg and 1000 mcg of folic acid from fortified foods or supplements [84]. It should be noted that the UL for folate does not include naturally occurring food folate, as no adverse effects have been linked with the consumption of excess food folate. The UL is based on preventing the masking of vitamin B₁₂ deficiency by correcting its characteristic symptom, megaloblastic anemia. Delayed diagnosis of vitamin B₁₂ deficiency can result in increased risk of irreversible neurological damage. It is also postulated that supraphysiologic intakes of folate may be related to the progression of precancer cell to cancers [87]. Several systematic reviews and meta-analyses have summarized results from human clinical trials or observational studies investigating the association between high folate intake and cancer incidence [88–92]. Findings remain inconclusive; however, the results from an expert panel convened by the US National Institutes of Health (NIH) suggest “there is a consistent enough suggestion in human studies of an adverse effect on cancer growth from supplemental folic acid to justify further research” [93]. Again the literature remains inconsistent; however, higher maternal blood folate concentrations have been associated with a higher prevalence of insulin resistance [94] and atopic dermatitis in offspring [95]. In addition, comprised respiratory health [96, 97], higher prevalence of childhood retinoblastoma [98], and lower psychomotor scale score in offspring [99] have been linked to higher maternal folic acid intake during pregnancy.

Dietary Intake of Folate

Prior to folic acid fortification of the food supply in North America in 1998, a reduction in maternal folate stores during lactation was usually observed, and was likely due to low dietary folate intakes [100–103]. Since implementation of the fortification program, dietary folate intakes and blood folate concentrations of reproductive-age women, including pregnant and lactating women, have risen considerably [104–107]. At a national level, Canadian Health Measures Survey conducted in 2007–2009 demonstrated <1% Canadians were folate deficient (red blood cell folate <305 nmol/l) whereas 22% of Canadian females of childbearing age had red blood cell folate level below the cut-off for optimal neural tube defects risk reduction (906 nmol/l) [108].

Sources of Folate in the Diet

Natural rich sources of folate are green leafy vegetables, citrus fruit juices, liver, and legumes. After folic acid fortification of the food supply, the category “bread, rolls, and crackers” became the single largest contributor of total folate in the American diet, contributing 16% of total intake, surpassing natural vegetable folate sources

Table 6 Major folate contributors to the daily diet of lactating women post-folic acid fortification [110]

Food	Serving size	Folate (mcg DFE)	Contribution to total folate intake (%)
Orange juice	1 cup	72	11
Pasta, dry	1 cup	391	8.8
Green salad	1½ cup	77	5.2
Bagels	1 medium	226	5
Whole wheat, rye, and other dark breads	1 slice	14	4.8
Cold cereals	1 cup	166	4.5
White bread	1 slice	171	4.2
Cream, milk, eggnog	1 cup	12	3.9
Rice, cooked	1 cup	215	3.8
Cake, cookies, donuts, pies	1 medium ^a	115	3.3

^aExample: donut

[109]. Table 6 presents data on the major dietary contributors of folate in the diets of a sample of pregnant and lactating Canadian women [110]. Orange juice was the largest source of total dietary folate (11.1%), while enriched pasta products were the second largest contributor (8.8%). Based on the US Department of Agriculture's (USDA's) Dietary Guidelines and MyPlate, or Canada's Food Guide for Healthy Eating, the grains food group provided 41% of total dietary folate [34, 35]. Thus, women avoiding white wheat bread and enriched pasta to avoid gluten or lose weight may be at risk of low folate intake if they do not consume a supplement.

The principal form of supplemental folate used in the world today is folic acid; however, supplemental 5-methyltetrahydrofolate is now available in some vitamin and mineral supplements, including prenatal supplements.

Vitamin B₁₂

Background

Vitamin B₁₂, often referred to as cobalamin, is required for the formation of red blood cells and normal neurological function [84]. Similar to folate, vitamin B₁₂ is involved in DNA synthesis. If vitamin B₁₂ deficiency occurs, then DNA production is disrupted, producing megaloblastic changes in blood cells (macrocytosis). Neurological complications occur in 75–90% of individuals with clinically defined vitamin B₁₂ deficiency [84]. Suboptimal vitamin B₁₂ status can occur as a result of low intake of foods of animal origin or inadequate absorption. Inadequate absorption could be caused by chronic antacid use, atrophic gastritis, hypochlorhydria, or pernicious anemia—most frequently found in individuals >50 years of age.

High doses of synthetic folic acid (greater than 1000 mcg) can mask vitamin B₁₂ deficiency by reversing megaloblastic anemia [83, 111]. Megaloblastic anemia is the clinical indicator that often leads a clinician to suspect that vitamin B₁₂ deficiency may be an issue. Vitamin B₁₂ is excreted in the bile and effectively reabsorbed such that it can take up to 20 years for a vitamin B₁₂ deficiency to develop due to low vitamin B₁₂ intake. In contrast, a deficiency due to poor absorption can take only a few years to develop.

During lactation, the concentration of vitamin B₁₂ in human milk varies widely and reflects maternal vitamin B₁₂ intake and status [9, 84]. Low maternal intake or poor absorption of vitamin B₁₂ rapidly leads to a low level of vitamin B₁₂ in human milk [112]. Severe deficiency can occur after approximately 4 months of age in exclusively breastfed infants of mothers with inadequate intake [113]. It is postulated the rapid postnatal development of vitamin B₁₂ deficiency in the infant is due, in part, to poor in utero transfer of vitamin B₁₂ from mother to child. Simply put, if a mother's vitamin B₁₂ status is suboptimal in lactation, it could have been low in pregnancy as well. Symptoms of infantile vitamin B₁₂ deficiency include irritability, abnormal reflexes, feeding difficulties, and developmental delay [114, 115].

Despite woman-to-woman variation in milk vitamin B₁₂ content, the concentration of vitamin B₁₂ in human milk changes very little after the first month postpartum [116]. The average reported concentration of vitamin B₁₂ secreted in the milk of well-nourished mothers is approximately 0.33 mcg/day during the first 6 months of lactation, and 0.25 mcg/day during the second 6 months [116]. In a group of women receiving vitamin B₁₂ containing supplements, the average B₁₂ content of milk was 0.91 mcg/l [117], while the B₁₂ content of milk from unsupplemented vegetarian mothers was lower, averaging 0.31 mcg/l [112]. In 2009, a new method was published which improved the precision human milk vitamin B₁₂ analysis by pre-treating milk samples with cobinamide-sepharose to remove apo-haptocorrin [118]. The median concentration of vitamin B₁₂ in milk from healthy, omnivorous Danish mothers ($n = 25$) taking vitamin B₁₂ supplements utilizing this new pretreatment of samples was reported to be 1.6, 0.6, and 0.9 mcg/l at 2 weeks, 4 months, and 9 months postpartum, respectively [119]. More studies are required to establish the values from unsupplemented mothers using this new method.

Recommended Dietary Intake for Vitamin B₁₂

The RDA for lactating women age 14–50 years is 2.8 mcg/day. This value is higher than the RDA for nonpregnant, nonlactating women (2.4 mcg/day) to account for the amount of vitamin B₁₂ secreted into breast milk. No adverse effects have been linked with excess vitamin B₁₂ from supplements and/or food, and thus no UL has been set by the US Institute of Medicine.

Dietary Intake of Vitamin B₁₂

Based on dietary data from NHANES (1999–2004), it is estimated approximately 7.5% of American women adhere to a vegetarian diet [120]. Though women who follow a strict vegan diet devoid of any animal products are at the highest risk of vitamin B₁₂ deficiency, women who follow other types of vegetarian diets are at risk compared to non-vegetarians [121]. Since the frequent consumption of animal foods is common in North America, median vitamin B₁₂ intake from food in the general adult population in the United States of 4–7 mcg/day [122] and Canada of 4–5 mcg/day [123] are well above recommended levels. Nonetheless, there are data to suggest the prevalence of suboptimal vitamin B₁₂ deficiency may be higher than previously appreciated in some particular groups of reproductive age females. Using national data from NHANES 1999–2004, Bailey et al. reported 3.3% of US adult women below the serum B₁₂ deficiency cut-off of 148 pmol/l [124] whereas the Canadian Health Measure Survey (2009–2011) revealed around 3–4% of adult women in Canada were below such a cut-off [125]. In both surveys, when the cut-off was expanded to include the cut-off thought to maximally protect women against neural tube defects (220 pmol/l), an additional 20% of women were at risk of suboptimal vitamin B₁₂ status [126].

Sources of Vitamin B₁₂ in the Diet

Vitamin B₁₂ is synthesized by bacteria and found primarily in meat, eggs, fish (including shellfish), and to a lesser extent, dairy products. Fortified breakfast cereals provide a significant source of vitamin B₁₂ (6.0 mcg/3/4 cup), particularly for vegetarians. Plant sources, such as spirulina (algae) and nori (seaweed), contain vitamin B₁₂ analogues, which can compete with vitamin B₁₂ and inhibit metabolism. Lactating vegetarians may need to also be advised that milk and milk products are a good source of vitamin B₁₂ (0.9 mcg/250 ml), while vegans are recommended to consume a supplement (~2.8 mcg/day) and/or ensure their diet includes foods fortified with vitamin B₁₂ such as textured vegetable protein and plant-based beverages such as soy milk. Fortification policies differ from country to country and by food category and brand, so women are advised to carefully read food labels to ensure the fortified foods they are relying on for vitamin B₁₂ do contain it and in the amounts required.

The form of vitamin B₁₂ most frequently used in supplements and/or fortified foods is cyanocobalamin, which is readily converted in the body to its utilizable forms of methylcobalamin and 5-deoxyadenosylcobalamin [127]. Other supplemental forms include methylcobalamin and adenosylcobalamin.

Iron

Background

Iron is an essential component of numerous proteins and enzymes in the human body. Over 60% of iron in the body is found in hemoglobin, the oxygen-carrying pigment of the red blood cell that transports oxygen from the lungs to tissues for use in metabolism. About 4% of iron is found in myoglobin, the oxygen binding storage protein of muscle, and trace amounts are associated with electron transport and iron-dependent enzymes. A large portion of the remaining iron in the body is found stored in the form of ferritin, primarily in the liver, but also in bone marrow and the spleen. With the exception of pregnancy and menstruation, where there is a net outward flux of iron, the iron content of the body is highly conserved. The secretion of iron into breast milk is low, with the average milk iron being in the order of 0.35 mg/l [128]. Maternal dietary iron intake appears to have very little effect on milk iron levels.

Recommended Dietary Intake for Iron

Until menstruation resumes, the iron requirements during lactation are considerably lower than those for nonpregnant, nonlactating women. The RDA for iron for nonpregnant, nonlactating women is 18 mg/day, and for lactating women aged 19–50 years it is 9 mg/day [128]. The RDA for iron for lactating adolescents is slightly higher at 10 mg/day to provide additional iron to support the young mother's ongoing growth and development. The UL for all breastfeeding women is 45 mg of iron per day [128].

Iron-deficiency anemia during pregnancy, particularly in the third trimester, is common in both developed and developing countries, and is well described in the literature [8, 128–135]. While less well characterized, due to the net maternal iron deficit accrued during pregnancy (RDA = 27 mg/day), available evidence suggests a high prevalence of maternal iron deficiency early postpartum, despite women meeting dietary recommendations for lactation. The recovery of iron stores and alleviation of iron deficiency during this period is important, as low maternal iron status is related to fatigue, depression, decreased work capacity, and decreased ability of the mother to care for her newborn infant [136–139].

Dietary Intake of Iron

Data from nationally representative surveys in the United States suggest that the median iron intake of nonpregnant, nonlactating women is ~12 mg/day, and that of pregnant women is 15 mg/day [128]. Inclusion of iron supplement use did not

significantly influence these national estimates, and underscores why many women will complete their pregnancy at a net iron deficit. CCHS 2.2 revealed that the usual intake of Canadian females aged 19–50 years is ~11 mg/day from food; ~20% women in this age group consumed iron below the EAR [123]. While the samples of lactating women in these national surveys are small, the iron intake of lactating women is generally higher than those reported for other premenopausal women, including pregnant women. This may reflect a combination of factors, including the small sample size, the health consciousness and socioeconomic status of lactating versus nonlactating women, and treatment for early postpartum iron deficiency anemia. Bodnar et al. [140] reported, using NHANES III national data from the United States, that approximately 10% of postpartum women have iron deficiency anemia. Among postpartum women of low household income, >20% were iron deficient (with or without anemia) compared with 7.5% of postpartum women not defined as low income.

Sources of Iron in the Diet

Two types of iron are present in the diet: heme and non-heme iron. Heme iron is obtained from animal sources such as meat, poultry, and fish, and is about 20–30% absorbed. Non-heme iron, present in plant foods, iron fortificants, and iron supplements, is less bioavailable with absorption of 5–10% [128]. Dietary factors such as vitamin C and the presence of meat, fish, or poultry can enhance the absorption of non-heme iron, while phytates found in legumes, grains and rice, polyphenols (in tea, coffee, and red wine), can inhibit non-heme iron absorption. Iron sources obtained from a typical Western diet consisting of abundant animal foods and sufficient sources of vitamin C were estimated to be approximately 18% bioavailable; the bioavailability of iron from a vegetarian diet is approximately 10% [128]. As a result, the requirement for iron is 1.8 times greater for vegetarians. The average iron content of fruit, vegetables, breads, and pasta ranges from 0.1 to 1.4 mg per serving. Some iron-fortified cereals contain up to 24 mg of iron per 1-cup serving.

Long-Chain Polyunsaturated Fatty Acids

Background

Long-chain polyunsaturated fatty acids (LC-PUFAs) are fatty acids with a backbone of greater than 20 carbons, and are derived from either the omega-3 (e.g., docosahexaenoic acid or DHA, 22:6n-3 and eicosapentaenoic acid or EPA, 20:5n-3) or omega-6 series (e.g., arachidonic acid or ARA, 20:4n-6). Humans are able to synthesize these LC-PUFAs from fatty acid precursors via a series of elongation and desaturation steps at all stages of the life cycle. DHA and EPA, for example,

are synthesized from the shorter, less unsaturated omega-3 fatty acid, alpha-linolenic acid (ALA, 18:3n-3), and ARA is synthesized from linoleic acid. LC-PUFAs are essential for the development and maturation of the fetal and neonatal brain, as well as eicosanoid metabolism, fluidity in membranes, and gene expression. Whether pregnant and lactating women and infants can convert enough ALA to DHA and EPA to meet physiological requirements is uncertain. Further, the 18-carbon fatty acids, linoleic acid (omega-6 series), and ALA (omega-3 series) compete for the same enzymatic machinery to synthesize ARA and DHA. The trend toward higher dietary intakes of the 18-carbon omega-6 versus the omega-3 series of fatty acids may likewise contribute to suboptimal levels of LC-PUFAs of the omega-3 series.

As it has been shown in studies using stable isotopes, even infants have the enzymatic machinery to convert ALA acid to DHA and linoleic acid to ARA [141–145]. These studies alone, however, provide insufficient data to assess whether sufficient quantities of DHA are synthesized to meet the infant's requirements. Infants fed formulas without DHA, but containing adequate levels of alpha-linolenic acid, have lower levels of DHA and ARA in their blood compared with either breastfed infants or infants fed formulas supplemented with DHA [144]. Results from clinical trials with term-born infants designed to evaluate whether preformed DHA needs to be added to infant formula in addition to ALA are mixed, with some showing at least a short-term benefit [146–152] on either visual or cognitive development and others showing no benefit at all [153–158]. Systematic reviews and meta-analyses addressing the effect of adding LC-PUFAs to infant formula on infant health outcomes are available [159–162]. To date, results remain controversial.

The US Institute of Medicine assumes that the fatty acid composition of breast milk meets the requirements of most infants. However, the concentration of DHA in breast milk globally ranges widely from 0.1 to 1.4% of total fatty acids due to the fatty acid composition of the mother's diet [163]. For example, milk from lactating women who consuming vegan or vegetarian diets low in DHA is low in DHA (<0.1% DHA) and milk from women from Japan and Northern Canada whose diets are rich in DHA from fish contains >0.8% DHA [163]. As anticipated, then, maternal supplementation with DHA increases breast milk DHA content in a dose-dependent manner [163–165]. At present, there is insufficient evidence to determine whether the variation in DHA content of human milk has clinical implications for the breastfed infant, including visual function or neurodevelopment. In a meta-analysis of randomized control trials ($n = 8$), Delgado-Noguera et al. found no differences in the neurodevelopment or visual acuity of children who were fed breast milk from mothers who were randomized to receive a DHA supplement [166]. One study included in this review found evidence that maternal DHA supplementation improved child attention at 5 years. A potential role for omega-3 fatty acids in the prevention of depression during the postpartum period has been proposed; however, a recent Cochrane [167] and systematic review [168] suggested current evidence is not yet sufficient to confirm this relationship. Please see Chap. 19 "Postpartum Depression and the Role of Nutritional Factors."

Recommended Dietary Intake for LC-PUFAs

Currently, there are no specific recommendations for DHA, EPA, or ARA intake in North America [11]. There are, however, recommendations for ALA and linoleic acid intake. For nonpregnant, nonlactating women, the US Institute of Medicine recommends an adequate intake level of 1.1 g/day ALA or an acceptable macronutrient distribution range of 0.6–1.2% energy. For pregnant and lactating women, they recommend 1.4 g/day. They do make the recommendation that up to 10% of this range can be consumed as DHA and/or EPA. At a workshop on the “Essentiality of and Recommended Dietary Intakes (RDIs) for Omega-6 and Omega-3 Fatty Acids” held by the NIH in 1999, attendees recommended that pregnant and lactating women consume 300 mg/day of DHA [169].

For nonpregnant, nonlactating women, the US Institute of Medicine recommends an adequate intake level of 12 g/day linoleic acid or an acceptable macronutrient distribution range of 5–10% energy. For pregnant and lactating women, they recommend 13 g/day. In 2010, the European Food Safety Authority recommend 250 mg of EPA and DHA with additional 100–200 mg of DHA/day for pregnant and lactating women [170].

Dietary Intake of LC-PUFAs

The current Western diet is low in omega-3 fatty acids (e.g., ALA, EPA, DHA) and high in the omega-6 series, particularly linoleic acid. The 1994–1996 USDA Continuing Survey of Food Intakes by Individuals, a nationally representative analysis of consumption, provided data on the major polyunsaturated fatty acids in the food supply in a subset of 112 pregnant or lactating women. Median daily intakes of this sample of women in this report indicated DHA intakes of ~44 mg/day, well below the 300 mg/day recommended by expert consensus at the NIH workshop [169]. Pratt et al. reported the mean DHA intake for a group of lactating women ($n = 83$, data collected during 2013–2014) in the USA was ~60 mg/day which was in agreement with the DHA intake data of the entire US female population in the 2009–2010 NHANES [171].

Sources of LC-PUFAs

Meat and eggs are rich sources of ARA, while EPA and DHA are derived mainly from fatty fish such as mackerel, salmon, herring, trout, and sardines. Health Canada advises women of childbearing age to consume at least 150 g (5 oz.) of cooked fish each week [34]. Based on the USDA’s Dietary Guideline (2015–2020) and MyPlate, pregnant and breastfeeding women are to consume at least 8–12 oz. of cooked

Table 7 Guidance for fish consumption during pregnancy and lactation

Females who are or may become pregnant or who are breastfeeding:
<ul style="list-style-type: none"> • May benefit from consuming seafood, especially those with relatively higher concentrations of EPA and DHA—i.e., hake, herring, pollock, salmon, fresh water trout, king or snow crab, shrimp, clams
<ul style="list-style-type: none"> • Can reasonably consume two to three -oz. (cooked) servings of the above varieties of fish. Other “best choices” can be found at: https://www.fda.gov/downloads/Food/FoodborneIllnessContaminants/Metals/UCM537120.pdf
<ul style="list-style-type: none"> • Canned “white” tuna (albacore) is higher in mercury than the “light” variety; limit canned white tuna to less than 6 ounces per week
<ul style="list-style-type: none"> • Should avoid large predatory fish such as shark, swordfish, king mackerel, or tilefish from the Gulf of Mexico
<ul style="list-style-type: none"> • When eating fish others have caught from streams, rivers, and lakes, check for fish advisories on those bodies of water

seafood each week [35]. Several foods that have added omega-3 fats including eggs, milk, yogurt, cheese, pasta, and bread are now available. There is considerable concern about increasing the omega-3 series LC-PUFAs via fish consumption during pregnancy and lactation because of the possible risk of contaminants. This issue, for the most part, centers on the methylmercury and PCB (polychlorinated biphenyls) contamination of fish. (Refer to Table 7 for guidance surrounding fish consumption in pregnancy and lactation.) Recommendations do differ from country to country and are frequently updated as new information becomes available. For specific details regarding the species-to-species methylmercury and PCB content of different fish and current advisories, refer to the following US Environmental Protection Agency website: <http://water.epa.gov/scitech/swguidance/fishshellfish/fishadvisories/index.cfm>. The “Prenatal Nutrition Guidelines for Health Professional—Fish and Omega-3” prepared by Health Canada also provide some strategies to reduce risks from fish contaminants [172]. Recommendations and tips to avoid consumption of seafood that is high in mercury or other contaminants can also be found in the USDA’s MyPlate website [35].

Conclusion

Breastfeeding is the gold standard and strongly recommended method of feeding infants. The World Health Organization recommends human milk as the exclusive nutrient source for the first 6 months of life, with introduction of solids at this time, and continued breastfeeding up to 2 years and beyond. Early postpartum weight is an issue for many women, as they are anxious to return to their prepregnancy body size. Indeed, postpartum weight retention is a significant contributor to the risk of obesity and associated adverse health outcomes. For many women, weight management will be difficult in the face of personal circumstances and multiple demands on their time. Given the elevated nutrient requirements of lactation, women will need to plan meals with care to maximize

nutrient intake while limiting energy-dense foods. Women are encouraged to use the USDA's Dietary Guidelines for Americans 2015–2020 and MyPlate, or Canada's Food Guide or guides from their country of origin, to select foods—including number and portion size. Following this dietary guidance should facilitate adequate intakes of key nutrients including calcium, vitamin D, folate, vitamin B₁₂, and iron.

In the event that a woman is unable to select food choices in the amounts and portions described in the food guides, a referral to a dietitian will be worthwhile, as well as prescribing an appropriate vitamin or mineral supplement. Exercise postpartum is strongly encouraged after medical clearance, usually after 4–6 weeks' postpartum. Women are encouraged to gradually work up to 30 min of moderate exercise each day for most days of the week. Women who wish to tackle their weight more aggressively should be reassured that an exercise regimen consisting of 45 min of moderate aerobic exercise 4 days/week (60–80% maximum heart rate) in combination with a 500 kcal/day diet restriction has been shown to promote postpartum weight loss and does not negatively affect breastfeeding.

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Postpartum Depression and the Role of Nutritional Factors

Michelle Price Judge and Cheryl Tatano Beck

Keywords Postpartum depression · Screening scale · Macronutrients
Breastfeeding

Key Points

- Postpartum depression is the most common complication of childbirth and it is a major public health problem.
- Postpartum depression is a treatable mood disorder that often goes undetected.
- Postpartum depression generally occurs during the first 12 months; however, it has been identified as late as 18 months after the birth of an infant.
- Research is confirming that postpartum depression negatively affects mother–infant interactions during the first year of life.
- Breastfeeding is known to be very beneficial to both mother and infant, and recent reports suggest that it may reduce risk for postpartum depression in women by reducing stress.
- A well-balanced diet comprised of adequate carbohydrates, protein, and fat will help ensure a steady source of fuel to the brain. Key nutrients including omega-3 fatty acids, iron, folate, riboflavin, and vitamin B₆ have been implicated in depression and/or postpartum depression, and care should be taken to ensure adequate intakes of these nutrients for women during pregnancy and the postpartum period.

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Introduction

Postpartum depression is the most common complication of childbirth and it is a major public health problem [1]. Up to as many as 50% of all cases of this mood disorder go undetected [2]. One of the major challenges for clinicians in dealing with postpartum depression is early recognition. A striking characteristic of this devastating mood disorder is how covertly it is suffered by mothers. Another obstacle to recognizing postpartum depression is the failure of clinicians to question women about related symptoms after delivery [3]. Postpartum depression has been a term applied to a wide range of postpartum emotional disorders. As such, this catch-all phrase has resulted in women often being misdiagnosed.

Postpartum depression is a major depressive episode which has a duration of at least 2 weeks. Women experience either depressed mood or a loss of interest or pleasure in activities. For diagnosis, women must experience at least four other symptoms from the following list: “changes in appetite or weight, sleep and psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating, or making decisions; or recurrent thoughts of death or suicidal ideation, plans, or attempts” [4]. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) includes a postpartum onset specifier, which states that the onset of this disorder must occur within the first 4 weeks after delivery. Clinicians and researchers both attest to this time criterion as being much too limited. Postpartum depression generally occurs during the first 12 months; however, it has been identified as late as 18 months after the birth of an infant [5].

Prevalence/Incidence of Postpartum Depression

The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review of studies on the prevalence and incidence of postpartum depression during the first 12 months after delivery [6]. During the postpartum period, the point prevalence of major and minor depressive episodes starts rising and is at its highest in the third month at 12.9%. During the fourth month through the seventh month postpartum, the prevalence decreases slightly to between 9.9 and 10.6% [6]. When looking at the point prevalence for major depression alone, major depressive episodes peak at 2 months (5.7%) and 6 months (5.6%) after delivery.

Regarding period prevalence, the AHRQ report revealed that after delivery, up to 19.2% of mothers have either major or minor depressive episodes during the first 3 months, with 7.1% having a major depressive episode. Incidence of a new episode of major or minor depression during the period of the first 3 months postpartum can be up to 14.5% of mothers, with 6.5% of these women experiencing major depressive episodes.

In a large population-based study in Denmark, Munk-Olsen et al. [7] investigated first lifetime onset of psychiatric illness in 1171 mothers over the first 12 months after their baby's birth. Prevalence of severe mental disorders through the first

3 months after delivery was reported to be 1.03 per 1000 births. Primiparous mothers had an elevated risk of hospital admission with any mental disorder through the first 3 months after birth, with the highest risk 10–19 days after delivery.

In *Listening to Mothers II*, a report of the second national US survey of women's childbearing experiences [8], up to 63% of new mothers reported experiencing some depressive symptomatology on the Postpartum Depression Screening Scale [9].

Onset

Based on the classic research of Kendall et al. [10], for the majority of women the onset of postpartum depression starts within the first 3 months after birth. In this epidemiological study, there was a definite peak in psychiatric admission rate in the first months after delivery.

Stowe et al. [11] reviewed 209 consecutive referrals to a mental health program for mothers with major postpartum depression. Sixty-six percent of the sample reported an early onset for this mood disorder (mean = 2.2 weeks) and 22% reported late onset (mean = 13.3 weeks after delivery). Although postpartum depression has classically associated with the first year following birth, 6.0% of women have reported elevated symptomatology at 18 months following delivery [5].

Causes

Postpartum depression is a complex phenomenon that includes interaction between biochemical, genetic, psychosocial, and situational life-stress factors. No clear consensus on the cause of postpartum depression currently exists. For example, conflicting reports have not supported any one hormonal etiology. A disruption of neurotransmitters in the brain has also been proposed as one biochemical cause of postpartum depression [12]. Currently, two meta-analyses have reported significant associations between markers of inflammation and major depression [13, 14] however, to our knowledge, no investigations have evaluated this link specifically with postpartum depression.

Cultural Perspectives of Postpartum Depression

Evidence is mounting that postpartum depression is a universal phenomenon. Oates et al. [15], for example, investigated women's experiences of postpartum depression in the following 11 countries: United States, United Kingdom, France, Italy, Sweden, Ireland, Japan, Australia, Switzerland, Portugal, and Uganda. This postpartum mood disorder, called "morbid unhappiness" in some countries, was reported to be a common experience after delivery. In some countries, it was not recognized as a mental illness with the specific label of postpartum depression. The symptoms of

postpartum depression in all countries closely approximated the Western concept of the signs and symptoms of this mental illness.

Current international studies that included a formal diagnosis of postpartum depression have reported prevalence rates of 18.7% in Morocco [16], 34.7% in South Africa [17], 27.6% in Japan [18], and 40% in Costa Rica [19].

Examples of reported international rates of postpartum depressive symptomatology include 17.3% in China [20], 17.6% in Portugal [21], 20.7% in Malaysia [22], 22% in the United Arab Emirates [23], and 25.6% in Turkey [24]. Horowitz et al. [25] conducted focus groups with mothers between 2 and 4 months after delivery in nine different countries: the United States, Australia, Finland, Guyana, India, Italy, Korea, Sweden, and Taiwan. How mothers described their postpartum depressive symptoms was remarkably similar across these countries. Common cognitive symptoms reported included poor concentration, worry, and indecisiveness. The most frequently cited emotional symptoms were anger, irritability, depression, sadness, guilt, anxiety, loneliness, fear, inadequacy, and tearfulness.

Postpartum Depression Risk Factors

Results of individual studies in which predictors of this crippling mood disorder were investigated have been summarized in four meta-analyses [26–28]. In Beck's [26] meta-analyses the following risk factors for postpartum depression were significant: prenatal depression, self-esteem, child care stress, life stress, social support, prenatal anxiety, maternity blues, marital satisfaction, history of previous depression, infant temperament, marital status, socioeconomic status, and unplanned/unwanted pregnancy. Prenatal depression was one of the strongest risk factors. O'Hara and Swain's [27] and Robertson's et al. [28] meta-analyses corroborated the predictors identified by Beck [26]. The strongest predictors of postpartum depression reported by O'Hara and Swain [27] were psychopathology history and psychologic disturbance during the prenatal period, poor marital relationship, low social support, and life stressors. In the most recent meta-analysis, Robertson et al. [28] also reported that the strongest risk factors for developing postpartum depression were prenatal depression, prenatal anxiety, stressful life events, low levels of social support, and a previous history of depression. In a recent study of 4332 postpartum women, income level, occupational prestige, marital status, and number of children were significant risk factors for postpartum depression [29]. The strongest of these risk factors was income level. Financially poor women were at higher risk for postpartum depression than were financially affluent women. Research is also revealing that other women at risk for postpartum depression are mothers who have preterm infants, multiple infants, or infants in the neonatal intensive care units [30, 31].

Phenomenology of Postpartum Depression

Loss of control is the basic problem women grapple with when suffering from postpartum depression [32]. Mothers try to resolve this loss of control in a four-stage process as outlined in Fig. 1 [32, 33]. In the first stage, mothers are bombarded with horrifying anxiety, relentless obsessive thoughts, and difficulty concentrating. In the second stage, women feel that their normal selves are “gone.” The women describe feeling “unreal,” like they were just robots going through the motions caring for their infants. In this stage, women often isolate themselves and may begin to contemplate harming themselves. The third stage involves women strategizing ways to survive postpartum depression, including battling the health care system to get appropriate mental health treatment, prayer, and seeking solace in postpartum depression support groups. In the final stage, women finally regain control of their thoughts and emotions as their depression lifts. During this transition period, mothers describe having “good days” and “bad days”; however, when they wake up in the morning they never know what kind of a day it will be. As the postpartum depression lifts, mothers go through a mourning period where they grieve over their lost time with their infants, which had been stolen from them by their depression. When mothers finally recover, they feel fragile and vulnerable and so they call their recovery a “guarded recovery.”

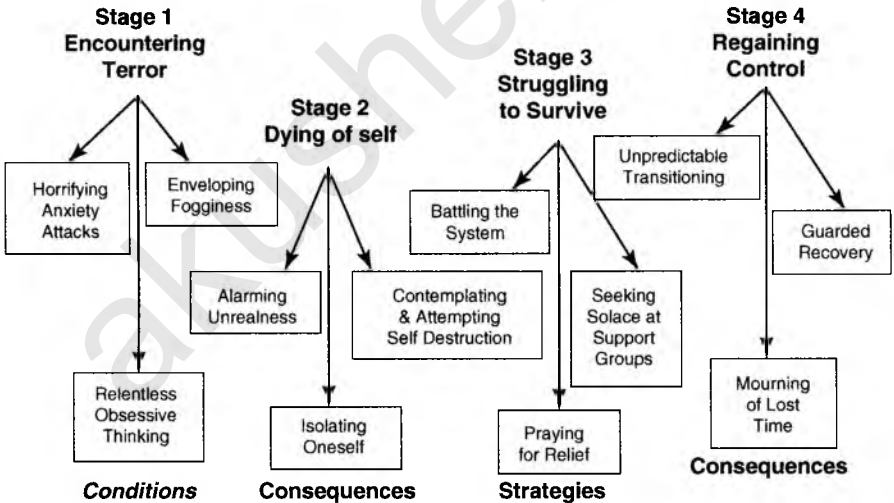


Fig. 1 The four-stage process of “teetering on the edge.” Reprinted with permission from Beck CT. Teetering on the edge: a substantive theory of postpartum depression. *Nurs Res.* 1993;42:42–8

Effects of Postpartum Depression on Mother–Infant Interaction

Research is confirming that postpartum depression negatively affects mother–infant interactions during the first year of life. Field's program of research has repeatedly reported that postpartum depression negatively affects maternal–infant interaction. Field [34], for example, reported a dysregulation profile for infants of mothers suffering from postpartum depression. Infants of postpartum depressed mothers have lower responsivity on the Brazelton scale, higher levels of indeterminate sleep, and elevated levels of norepinephrine and cortisol, activation of right frontal electroencephalogram, decreased responsivity to facial expressions, lower vagal tone, neurological delays, decreased play, decreased Bayley mental and motor scale scores, and lower weight percentiles [35]. Field [34] reported that postpartum depressed mothers displayed two predominant styles of interaction, withdrawn or intrusive. Mother–infant dyads matched negative behavior states more often and positive states less frequently than non-depressed mother–infant dyads [36].

Postpartum depressed mothers displayed significantly lower contingent responsiveness and higher negative contingent responsiveness to their infants [37]. Recently Paulson et al. [38] found that mothers depressed at 9 months after birth were 1.5 times more likely to engage in less positive enrichment activity with their child such as reading, singing songs, and telling stories. Forman et al. [39] reported that at 6 months postpartum depressed mothers were less responsive to the infants, experienced higher levels of parenting stress, and perceived their infants more negatively than non-depressed mothers. Since a mother constitutes the infant's primary social environment during the first months of life, the effects of postpartum depression on the rapidly developing baby is of great concern and merits closer scrutiny and study.

Effects of Postpartum Depression on Child Development

Longitudinal research is revealing that there are long-term sequelae for children whose mothers suffered from postpartum depression. Toddlers of postpartum depressed mothers displayed more insecure attachment to their mothers than toddlers of non-depressed mothers [40]. Eighteen-month-olds whose mothers suffered from postpartum depression performed significantly poorer on Bayley scales for object concepts tasks as compared with children the same age of non-depressed mothers [40]. In a different study of 10-month-old boys, children of postpartum depressed mothers performed significantly poorer on Bayley Scales of Infant Development than did boys of non-depressed mothers [41].

Teachers rated kindergarteners of postpartum depressed mothers as displaying more internalizing problems, i.e., overanxious and depressed, plus more externalizing problems, i.e., more defiant and aggressive, than children of non-depressed

mothers [42]. In a longitudinal study, Hay et al. [43] found that 11-year-old children of postpartum depressed mothers displayed more violent behaviors than did children whose mothers had not experienced postpartum depression. Halligan et al. [44] reported findings from their longitudinal study. Thirteen-year-olds whose mothers had suffered from postpartum depression were at an increased risk for depression if their mothers had later episodes of depression following the postpartum period. Anxiety disorders in these adolescents were increased in the group whose mothers had been depressed in the postpartum period regardless of whether their mothers had suffered from subsequent depressive episodes.

Screening

Postpartum depression is treatable, but the women must first be identified. Mothers may not seek help for postpartum depression due to any number of reasons, including a lack of knowledge regarding this devastating illness and/or because of the tremendous stigma attached to mental illness. Also, women may fear that if they are diagnosed with postpartum depression, child welfare authorities may take their infants.

Women should be screened for postpartum depression periodically during the first year after delivery, with an additional screening following the first year [5]. The standard practice of screening just one time during the early postpartum period (i.e., at 6 weeks' postpartum) may not detect postpartum depression that develops later. Because a woman is adjusting well during the early postpartum period does not mean she will not develop postpartum depression sometime later during the first 18 months after birth. Without repeated screenings, a mother may fall through the cracks in the health care system. Prior to screening women for postpartum depression, health care providers need to dispel the idealized myths of motherhood and provide a trusting environment in which women can feel free to discuss any negative feelings or thoughts they may be experiencing.

The Postpartum Depression Screening Scale (PDSS) is a survey available to clinicians for screening [9]. This self-report scale consists of 35 items that assess the presence, severity, and type of postpartum depressive symptoms. It has a five-point Likert response format in which women are asked to respond to statements about how they have been feeling since delivery. The response options range from 1 = strongly disagree, to 5 = strongly agree (Table 1). Agreement with a statement indicates the mother is experiencing that depressive symptom. The PDSS consists of seven symptoms content scales: Sleeping/Eating Disturbances, Loss of Self, Anxiety/Insecurity, Guilt/Shame, Emotional Lability, Mental Confusion, and Suicidal Thoughts. The range of possible scores is 35–175. A cutoff score of 80 or above indicates a positive screen for postpartum depression and the need to refer the mother for a formal diagnostic evaluation by a mental health clinician. Using this cutoff score of 80, Beck and Gable [9] reported the PDSS had a sensitivity of 94% and a specificity of 98%.

Table 1 Postpartum depression screening scale: selected items by dimension^a

During the past 2 weeks I...
Sleeping/eating disturbances
No. 1: I had trouble sleeping even when my baby was asleep
No. 8: I lost my appetite
Loss of self
No. 19: I did not know who I was anymore
No. 5: I was afraid that I would never be my normal self again
Anxiety/insecurity
No. 23: I felt all alone
No. 9: I felt really overwhelmed
Guilt/shame
No. 20: I felt guilty because I could not feel as much love for my baby as I should
No. 27: I felt like I had to hide what I was thinking or feeling toward the baby
Emotional lability
No. 3: I felt like my emotions were on a roller coaster
No. 31: I felt full of anger ready to explode
Mental confusion
No. 11: I could not concentrate on anything
No. 4: I felt like I was losing my mind
Suicidal thoughts
No. 14: I started thinking I would be better off dead
No. 28: I felt that my baby would be better off without me

^aSelected items from the PDSS copyright ©2002, by Western Psychological Services. Reprinted by permission of the publisher, Western Psychological Services, 12031 Wilshire Boulevard, Los Angeles, California, 90025 (www.wpspublish.com) Not to be reprinted in whole or in part for any additional purpose without the expressed, written permission of the publisher. All rights reserved

The Edinburgh Postnatal Depression Scale (EPDS) is a second instrument that has been developed to screen for depression [45]. It consists of 10 items in a Likert format that assess the following common depressive symptoms: inability to laugh or look forward to things with enjoyment, feeling scared or panicky, feeling like “things have gotten on top of me,” difficulty sleeping, and feeling sad. Using the EPDS cutoff, reported sensitivity (86%) and specificity (78%) have been reported by Cox et al. [45].

The Edinburgh Postnatal Depression Scale’s 10 items assess depression in general. None of the items is written in the context of new motherhood. With a sample of 150 new mothers, when using the published recommended cutoff points for major depression, the PDSS achieved a sensitivity of 94% and specificity of 98% while the Edinburgh Postpartum Depression Scale’s sensitivity was 78% and specificity was 99% [46]. Formal diagnosis of postpartum depression can be made by conducting a Structured Clinical Interview for DSM-IV Axis I Disorders (SCID) [47].

Brief Overview of Central Nervous System Anatomy and Physiology in Relation to Postpartum Depression

As discussed earlier in this chapter, the etiology of postpartum depression is currently unknown and likely to be multifactorial. With a focus on the brain specifically, it is important to consider how nutrients can affect the basic structure of the nerve cell and the surrounding neurochemical environment. Nerve cells or neurons are arranged in a highly organized fashion and collections of neurons comprise different functional areas of the brain including vision, hearing, memory, speech, emotions, and mood. A nutrient deficit can negatively influence the communication between nerve cells (i.e., neurotransmission) and have a collective negative effect on different functional areas of the brain including the regulation of mood and emotional response. The following sections outline the basic principles of neuroscience and review evidence of the role of key nutrients that may play a role in neurophysiological processes related to postpartum depression.

Nerve Impulse Conduction

The nerve cell or neuron is comprised of the cell body, dendrites, and an axon. The dendrites receive communications from other cells and have extensive branched projections that serve to maximize cellular signaling. Information received by the dendrites is sent to the body of the cell, where the nucleus of the cell passes information on to the axon. The axon of the cell also has branching at the terminal end, and it is at this end that the one nerve cell communicates with the next (Fig. 2). The point of communication between the terminal end of one nerve cell and the dendrite projection of another is referred to as the synapse. Neuronal cell excitation and inhibition typically occur by direct or indirect mechanisms that involve the activation of ion channels that are regulated by membrane-bound protein channels. For example, the activation of an ion channel, like chloride, results in an intercellular influx of ions with a negative charge, resulting in inhibition of the neuron. Conversely, ion channels that allow the flow of positive ions typically result in excitation of the neuron [48]. Inhibition and excitation of neurons is stimulated via the release of chemicals called neurotransmitters (produced in the axon terminal) and it is these that have a major influence on brain activity. Impulse transmission is expedited via a phospholipid-based sheath that covers the neurons, the myelin sheath. The myelin acts as a barrier for signal transmission and causes a “hopping” of transmission signals between myelinated areas. This “hopping” effect, or saltatory conduction, speeds the rate of impulse transmission [48]. Nutrient deficits interfering with the release of important cellular signals or the formation of myelin could have a profoundly negative impact on cellular communication.

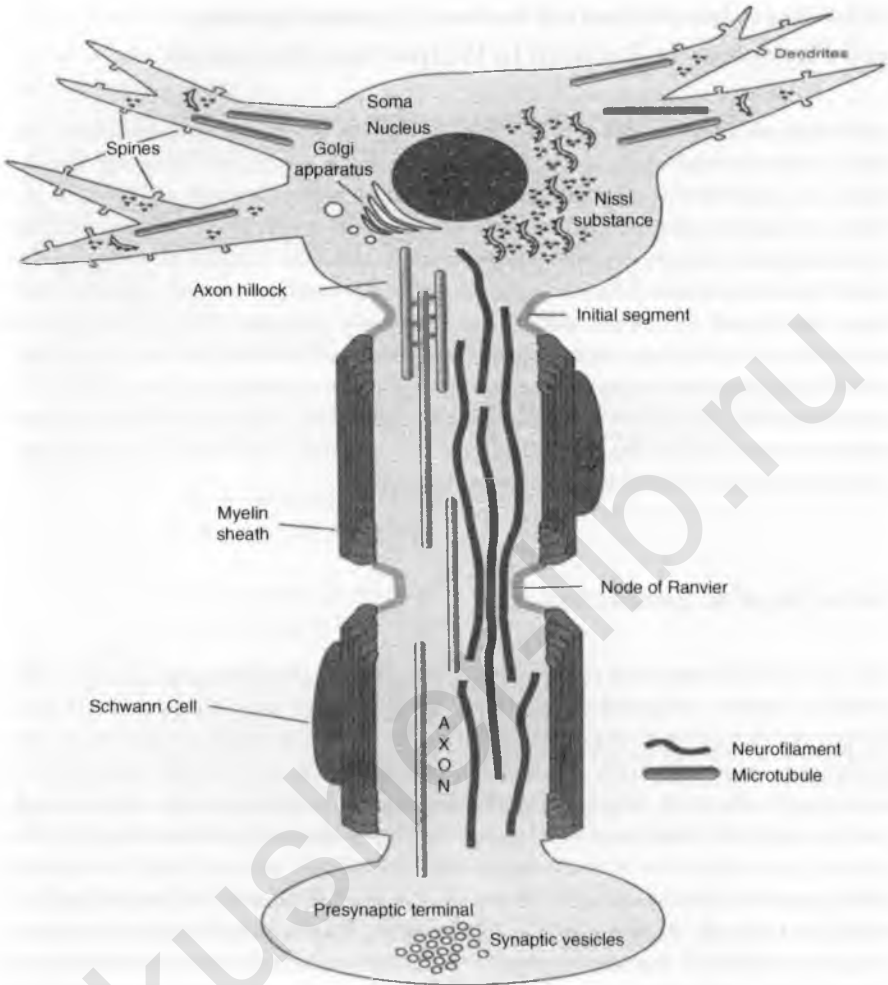


Fig. 2 Anatomy of a neuron [52]

Neuroanatomy Relating to Mood and Emotions

The cerebral cortex is comprised of two distinct tissue layers, the gray and white matter. The cortex surrounds the entire perimeter of the brain, comprising 80% of the volume of the human brain [49]. In the gray matter, blood vessels are present as well as neuronal cell bodies. The white matter of the brain is composed of the nerve axons connected to the cell bodies in the gray matter. Different areas of the cortex are responsible for receiving and processing stimuli. The four functional areas of the cerebral cortex include motor, sensory, visual, and auditory (Fig. 3). The primary functional areas of the cerebral cortex process initial sensory information and the

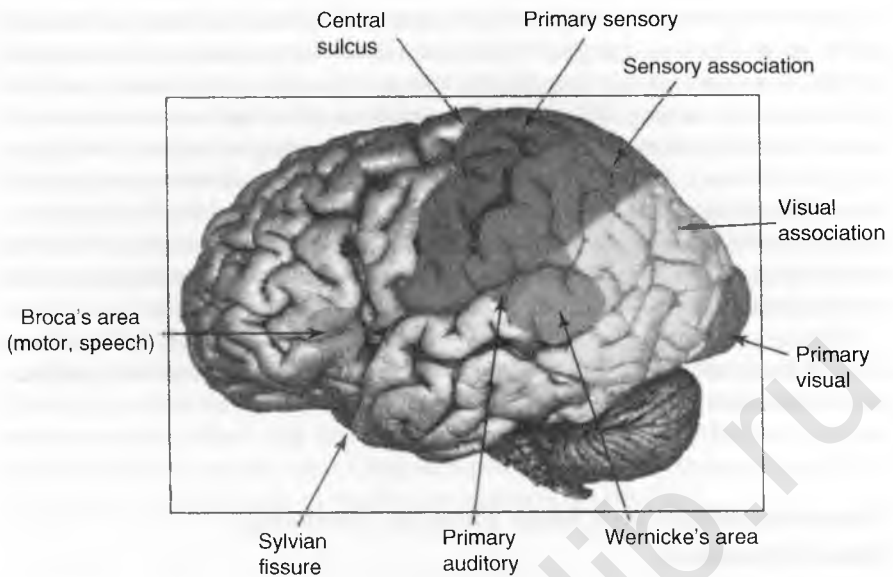


Fig. 3 Areas of the cortex responsible for receiving and processing stimuli

secondary and tertiary areas are responsible for association and processing. For example, visual information is sent to the primary visual cortex and processing related to assessment of shape, color, and categorization occur in secondary and tertiary visual areas.

Newer evidence suggests that memory occurs in various regions of the cortex and is dependent upon the type of sensory stimulus. These regions of visual, motor, sensory, or visual cortex then communicate with central brain structures.

The central brain structures are generally referred to as the brainstem, which is categorized into three main components: diencephalon, midbrain, and hindbrain. The diencephalon is comprised of three thalamic regions: epithalamus, thalamus, and hypothalamus. The thalamus is a very important relay station for the brain's cerebral cortex. The majority of sensory information is first sent to the thalamus before the information is relayed to the appropriate cortical area. The hypothalamus is involved in all aspects of motivated behavior or function including feeding, sexual, sleeping, emotional, temperature regulation, endocrine, and movement [49].

The midbrain consists of many structures. As examples, two important structures, the superior and inferior colliculi, are involved in visual and auditory processing. The superior colliculi receive projections from the retina and are involved in regulating behaviors related to visual stimuli. The inferior colliculi receive auditory information and regulate auditory-related behaviors [49]. For example, the sound of a phone ringing stimulates the auditory cortex, and it is the inferior colliculus that orients the individual to the phone and prompts the behavior to walk toward the phone.

Last, the forebrain extends from the brainstem and is made up largely of the limbic system and the basal ganglia. Studies using functional magnetic resonance imaging have demonstrated that the forebrain is highly specialized for working memory involved in new learning [50]. The central structures of the forebrain are commonly referred to as the limbic system, composed of the hippocampus, septum, and cingulate gyrus. Memory, new learning, and emotions are functions attributed to the limbic system. The limbic system has a central role in spatial behavior [49]. The basal ganglia include the putamen, globus pallidus, and caudate nucleus, and are involved in motor responses that require sequencing and smooth execution. These structures are also involved in habit learning and storage of older learned information.

From an anatomical standpoint, alterations in the function of the limbic system are most likely to cause disturbances in emotion and mood associated with postpartum depression.

Neurotransmitters and Brain Function Including Mood Regulation

The proper balance of neurotransmitters is important to maintaining normal brain chemistry and function. Behavior, mood, learning, and memory are just a few of the important functions requiring proper neurotransmission. Different cells have varying levels of the enzymes involved in the production of the neurotransmitters. The availability of different enzymes in the presynaptic membrane controls the type and quantity of neurotransmitter produced. Numerous neurotransmitters influence the complex chemical communicating systems in the brain. The monoamines, acetylcholine, amino acids, and peptides comprise the majority of the neurotransmitters [51].

Dopamine, norepinephrine, epinephrine, and serotonin are referred to as monoamines due to the existence of one amine group in their molecular structure. Dopamine, norepinephrine, and epinephrine comprise the catecholamine group of monoamines. Dopamine, norepinephrine, and epinephrine are produced via the same biochemical pathway referred to as the dopaminergic pathway [51]. In this pathway, tyrosine is converted to l-dopa, an intermediate in the biochemical pathway, via the enzyme tyrosine hydroxylase [51].

Serotonin is classified as an indolamine produced by the serotonergic pathway. In a manner similar to the dopaminergic pathway, the serotonergic pathway begins with an amino acid, in this case tryptophan [51]. The conversion of tryptophan to the next intermediary requires tryptophan hydroxylase. In both the dopaminergic and serotonergic pathways, tyrosine hydroxylase and tryptophan hydroxylase, respectively, are present in limited amounts. Therefore, it is the enzymes and not the availability of tyrosine or tryptophan that are the limiting factors for the production of these monoamines. Working memory involved in new learning has been attributed to dopamine in the prefrontal cortex (mesencephalic region) [52]. Norepinephrine is thought to

play an important role in stimulating processes involved in attention. Low dopamine and serotonin have been associated with depression and psychomotor slowing, which affects motivational processes. Drugs that alter the reuptake of these monoamines have been shown to elevate mood. The drug class called monoamine reuptake inhibitors (MAOI) are typically the first line of treatment in patients experiencing depression and postpartum depression [53, 54].

Acetylcholine is produced from acetyl CoA and choline, and it is synthesized through the action of choline acetyltransferase in the cholinergic pathway. Deficits in the production of acetylcholine are associated with learning and long-term memory deficits [55]. Acetylcholine also appears to have a role in maintaining normal motor activity [55].

The amino acids involved in neurotransmission can have either excitatory or inhibitory actions on nerve signal transmission. Glutamate and aspartate are the main excitatory amino acids and gamma amino butyric acid (GABA) and glycine are main inhibitory amino acids. Long-term potentiation in the hippocampus related to memory has been shown to require a reduction in GABA [56].

Inflammation and Mood

Major depression has been associated with the up-regulation of the inflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and cyclooxygenase-2 (COX-2) in two recent meta-analyses [13, 14]. Interleukin-6 is a pro-inflammatory cytokine produced by host immune cells related to tissue damage and other stressful events. Tumor necrosis factor- α is produced by host immune cells and serves to regulate immune and inflammatory processes. Lastly, COX-2 is a well-known inflammatory agent associated with inflammation and pain. Further research is necessary at the neural level to better understand the observed associations between these key inflammatory proteins and major depression. Given that prenatal depression is one of the strongest risk factors for postpartum depression [26–28], similar elevations in inflammatory cytokines are likely, yet remain unexplored. Further work is needed to advance our understanding of the complex interrelationships between inflammation, neurotransmission, and postpartum depressive symptomatology.

Role of Nutrition in Postpartum Depression

Carbohydrates

Carbohydrates (i.e., bread, cereal, rice, potatoes, pasta, beans) play a vital role in delivering energy to the body and can influence mood. Carbohydrates are the brain's primary source of energy, making adequate dietary intake important to postpartum

mental health. The delicate balance between carbohydrate and insulin can also affect mood. Balanced and consistent carbohydrate intake throughout the day can help ensure this balance between carbohydrates and insulin. Insulin increases markedly throughout the course of a normal pregnancy, and levels fall dramatically after delivery. Although the mechanism requires elucidation, it has been hypothesized that this drop in insulin levels following delivery may induce depression through a reduction in serotonin production [57]. Crowther et al. [58] demonstrated in a large randomized clinical trial that women with gestational diabetes mellitus (GDM) who received individualized dietary advice had lower rates of postpartum depression compared to those women with GDM receiving standard care. In contrast, in a large cohort investigation that included 865 Japanese women and 122 with postpartum depression, no significant association was reported between glycemic load and postpartum depression [59]. Overall, evidence is mixed regarding hypothesized associations, thus warranting further investigation.

Protein

Protein (meat, poultry, fish eggs, cheese, nuts, legumes) can play a role in mood regulation. During the postpartum period, women should ensure that they are consuming an adequate amount of protein, especially as a full complement of the essential amino acids. While protein intake in pregnancies of women who are consuming a full range of foods is generally not a concern, women who are depressed may not be eating normally. Women who are breastfeeding should pay particular attention to their protein intake, as protein needs are the same as during pregnancy. A full complement of all the essential amino acids will help ensure the synthesis of neurotransmitters. As reviewed in the section on neurotransmitters, the amino acids can have a direct impact on neurotransmission. Glutamate, aspartate, GABA, and glycine can be excitatory or inhibitory with respect to neurotransmission, depending upon the amino acid of interest. The essential amino acid tryptophan stimulates the production of serotonin, which plays an important role in the regulation of anger, aggression, body temperature, mood, sleep, sexuality, and appetite.

Fat/Omega-3 Fatty Acids: Docosahexaenoic Acid

Docosahexaenoic acid (DHA, 22:6n-3) has a central role in regulating the biophysical properties of neural membranes [60]. Based upon animal studies, specific regions of the brain, including the cerebral cortex, synapses, and retinal rod photoreceptors, have a particularly high DHA concentration [60–62]. Studies conducted in animals provide evidence for disturbances in brain development of offspring relating to DHA deficiency induced during the gestational period [56, 63–66]. In the United States and Canada, maternal intake of DHA, found in cold-water marine

fish, is far below the current recommended level of 300 mg/day during pregnancy [67–71], which raises concern for maternal health and infant neurodevelopment, as developmental advantages have been reported for infants of mothers who consumed DHA during pregnancy [72–74].

The Role of DHA in Neurotransmission

DHA deficiency during gestation in rats decreases dopamine production [66, 75] in the brain, which in turn induces behavioral disturbances resulting in decreased learning ability in their offspring. These findings are of particular interest because they link DHA deficiency, subsequent altered brain development, and impaired functional status. Conversely, the offspring of rats deficient in DHA during the gestational period exhibit an increase in acetylcholine [65] and GABA [56] production. Adequate levels of dopamine are necessary for mood elevation and for learning processes. Alternatively, acetylcholine and GABA appear to be increased in DHA deficiency. Learning, long-term memory, and motor activity have been linked to acetylcholine, and it is unknown currently how such alterations affect mood and emotions. All of the observed alterations of the brain's neurochemical profile provide a compelling basis for further exploration regarding DHA deficiency and the CNS.

DHA and Inflammation

DHA and other n-3 long-chain polyunsaturated fatty acids (LC-PUFAs) are known to act as anti-inflammatory modulators [76–83]. The typical Western diet is high in n-6 LC-PUFAs and these pro-inflammatory fatty acids are therefore more often incorporated into inflammatory cell phospholipids, making them more readily available for cellular signaling and biosynthesis [84]. In brief, excess n-6 LC-PUFAs result in pro-inflammatory 2-series prostaglandins, as opposed to the anti-inflammatory 3-series prostaglandins that would otherwise be derived from n-3 LC-PUFAs [85]. Related to these processes, supplementation with n-3 LC-PUFAs results in downregulation of inflammatory mediators including IL-6, TNF- α , COX-2, and many other related proteins [76–83, 85]. Taken together, the downregulation of mediators by the n-3 LC-PUFAs and the association of these proteins with major depression warrant further investigation into the potential mechanisms.

Although multiple reports have provided evidence of an inverse relationship between DHA intake and depression [86], few investigations have focused directly on postpartum depression specifically [87–91]. Hibbeln [87] conducted a meta-analysis of 23 countries that used the EPDS to screen for depression, and reported that the DHA content of mother's milk and seafood consumption rates were associated with lower prevalence rates of postpartum depression.

Otto et al. [88] investigated plasma phospholipid DHA in 112 women at delivery and at 32 weeks postpartum. The EPDS was given to the women at the 32-week

time point to assess postpartum depression. There was an inverse relationship between DHA status and depressive symptoms.

De Vriese et al. [89] conducted a similar investigation of maternal DHA status immediately following delivery. DHA and total n-3 fatty acids were significantly lower in the women who developed postpartum depression compared to the women who did not. Judge and colleagues conducted a pilot investigation of the role of DHA in preventing risk for postpartum depression [90]. Women were randomized to receive placebo or fish oil capsules from 24 to 40 weeks gestation, and maternal DHA status and depressive symptoms were followed using the Postpartum Depression Screening Scale from 2 weeks' to 6 months' postpartum. Participants in the fish oil group had lower depression scores compared to the placebo group and experienced less anxiety/insecurity, emotional lability, and loss of self.

In contrast, in a study of 865 Japanese women, Miyake et al. [91] investigated risk of postpartum depression related to dietary fatty acid intake. Again, the EPDS was used to evaluate postpartum depression and diet history questionnaires were self-administered to measure dietary fatty acid intake. There were no significant relationships between dietary fish consumption or n-3 fatty acid intake and postpartum depression. Likewise, Browne et al. [92] investigated maternal fish consumption and plasma DHA status after birth in relation to postpartum depression diagnosed using the Composite International Diagnostic Interview. There were no associations between maternal fish consumption during pregnancy or maternal DHA status following delivery and depressive symptoms in the postpartum period.

In conclusion, although the evidence exists to support the notion that DHA status may have a protective effect in the prevention of postpartum depression [87–90], further investigations are necessary to better define this relationship in light of some of the more recent conflicting reports [91, 92] that have failed to provide evidence to support this idea. To date, although DHA appears to help prevent postpartum depression, it has not been found to be beneficial in the treatment of postpartum depression [93, 94]. Future investigations should focus on dose–response relationships in the treatment of postpartum depression, as well as expand investigations to include measures of baseline DHA status [86].

Micronutrients and Postpartum Depression

Iron

Iron is a component of hemoglobin in red blood cells (RBCs) and as such, an iron-deficient diet can result in iron deficiency anemia characterized by the production of RBCs that do not contain a full complement of hemoglobin and are inefficient at delivering oxygen to cells. Pregnancy and childbirth place women at risk for iron deficiency anemia due to a marked blood volume expansion during pregnancy, increased maternal needs, fetal requirements, and blood loss associated with childbirth. Iron deficiency anemia is the most common nutritional deficiency in the

United States and the world, affecting 7.8 million adolescent girls and women of childbearing age [95].

Although the role of iron status remains unclear with respect to postpartum depression, current investigations point to increased risk for postpartum depression in women who have anemia [96, 97]. Corwin et al. [96] measured hemoglobin levels at 7, 14, and 28 days' postpartum, and depressive symptoms using the Center for Epidemiological Studies-Depressive Symptomatology Scale (CES-D) at 28 days' postpartum. Hemoglobin levels on day 7 were negatively correlated with CES-D scores obtained on day 28 postpartum. Further, Beard et al. [97] demonstrated that iron treatment resulted in a 25% improvement in previously iron-deficient mothers' depression and stress scales. Anemic mothers who did not receive iron treatment did not display improvements in depression or stress scales. Considering the reported associations between iron and postpartum depression, Sheikh et al. evaluated the efficacy of early iron supplementation on postpartum depression in a cohort of women with postpartum depression [98]. Early iron supplementation significantly improved symptoms of postpartum depression by 42.8%. Collectively, these results support continued education and monitoring of iron status during the postpartum period.

Folic Acid

Folate deficiency has been associated with problems in nerve development and function, and has classically been thought to pose more of a risk to fetuses, infants, and children who are growing; however, recent reports have linked folate deficiency with depression [99–103]. Neural tube defects have been associated with inadequate folate intake prior to conception and during pregnancy [95]. Excellent sources of folate include liver, yeast, asparagus, spinach, oranges, legumes, and fortified cereals/grain products [95]. During the postpartum period, folate needs are 400 mcg/day unless the woman is breastfeeding, which increases the need to 500 mcg/day [95].

Folate deficiency has been linked to depression in several investigations [104–108]. Although the mechanism is unknown at this time, folate has been hypothesized to be related to serotonin production involving S-adenosylmethionine (SAME), a major methyl donor formed from methionine, which is formed during regeneration of homocysteine. To date, no significant associations have been reported for folate and postpartum depression [100–102]. The current food folate fortification programs in the USA makes dietary folate deficiency an unlikely culprit in current rates for postpartum depression.

Riboflavin/Vitamin B₂

Riboflavin is important in the formation of key enzymes necessary for energy production via the citric acid cycle/electron transport chain. Based upon this role,

adequate riboflavin intake during pregnancy and the postpartum period could be beneficial to maternal energy level and mood. Milk is the best source of riboflavin in the North American diet [95], with liver, red meat, poultry, fish, whole grains, enriched breads and cereals, asparagus, broccoli, mushrooms, and green leafy vegetables identified as other excellent sources. During the postpartum period, riboflavin needs are similar to those prior to pregnancy: 1.1 mg/day [95]. The riboflavin requirement for breastfeeding women is 1.6 mg/day, greater than that for pregnant women.

To our knowledge, there is only one report for the role of riboflavin in postpartum depression. Miyake et al. [100] reported that pregnant women with riboflavin consumption in the third quartile were independently related to a decreased risk for postpartum depression. It has been hypothesized that riboflavin coenzymes are involved in the regeneration of homocysteine, which is involved in serotonin production [102]. Collectively, no significant relationship has been reported between riboflavin supplementation and postpartum depression [101].

Vitamin B₁₂

Vitamin B₁₂ is necessary for the maintenance of myelin, which insulates nerves and affects neurotransmission [95]. Although dietary B₁₂ deficiencies are rare due to efficient recycling, strict vegetarians and individuals with decreased appetite/anorexia should consider supplementing their diet. Neurological symptoms associated with deficiency include numbness and tingling, abnormalities in gait, memory loss, and disorientation. Vitamin B₁₂ is found almost exclusively in animal products. Fortified cereal and grain products provide an alternative for those individuals who do not consume animal products. Although vitamin B₁₂ is important to CNS functions, no associations have been reported for vitamin B₁₂ and depression [103] or postpartum depression [100, 103].

Pyridoxine/Vitamin B₆

Inadequate dietary intake of vitamin B₆ leads to decreased production of pyridoxal phosphate, a key compound in the metabolism of all energy nutrients. This vitamin is also important for the synthesis of nonessential amino acids, which in turn effect the production of both important neurotransmitters, and the lipids that comprise myelin in nerve tissue [95]. Deficiency causes neurological symptoms including depression, headaches, confusion, numbness and tingling in the extremities, and seizures [95]. Vitamin B₆ is found in a variety of foods including chicken, fish, pork, organ meats, whole-wheat products, brown rice, soybeans, sunflower seeds, bananas, broccoli, and spinach [95]. During the postpartum period, women require 1.3 mg of B₆ daily if not breastfeeding. Breastfeeding women need 2 mg/day of B₆.

Few investigations have been conducted investigating the role of B₆ in depression; however, an inverse association between plasma B₆ levels and depressive symptoms has been reported [109]. With respect to postpartum depression, only one investigation has included the assessment of the association with B₆, and reported no measurable association with postpartum depression [100]. Further work is necessary to determine if a definitive relationship exists between B₆ status and postpartum depression, however, evidence to this point does not support an association [101].

Breastfeeding

Breastfeeding is known to be very beneficial to both mother and infant, and recent reports suggest that it may reduce risk for postpartum depression in women by reducing stress [110–115]. Although the majority of investigations point to breastfeeding as protective in postpartum depression, results are equivocal, as other investigations have reported no relationship between depressive symptoms and breastfeeding [116–118]. As earlier described, infants of mothers with postpartum depression are at risk for cognitive and emotional impairments [40–44], and breastfeeding can help protect infants against these negative outcomes. Breastfed infants of depressed mothers exhibited decreased depressive symptoms compared to those who were bottle-fed [119].

Antidepressants and Breastfeeding

The clinicians of breastfeeding women diagnosed with postpartum depression must consider the different treatment options for their patients, including antidepressants, hormonal therapy, or psychotherapy. In situations where the postpartum depression requires antidepressants, the safety of the nursing infant must be considered. Antidepressants taken during breastfeeding can induce adverse symptoms in the infant. The antidepressants that have been particularly problematic are nefazodone [120], citalopram [121], doxepin [122, 123], and fluoxetine [124, 125]. Given the negative infant outcomes associated with maternal antidepressant therapies, the US Food and Drug Administration (FDA) has not approved any antidepressant for use during lactation [53]. Alternatively, depression during the postpartum period can impair maternal–infant interactions [126], which in turn negatively affect infant cognitive development [127], emotional development [127], anxiety, and self-esteem [128]. In some cases, the clinician may decide that the potential benefits of maternal antidepressant therapy outweigh the risks, in which case paroxetine, sertraline, and nortriptyline should be considered for use first, as these have been investigated and are reportedly without adverse infant-related outcomes [53].

Effect of Postpartum Depression on Breastfeeding Success

Given the benefits of breastfeeding for both mother and infant, breastfeeding mothers with postpartum depression may benefit from this choice of feeding. However, the additional demands of breastfeeding could also be overwhelming for women experiencing postpartum depression, and care should be taken to support mothers deciding to formula feed. Those women who decide to breastfeed will likely need additional support to foster the continuation of breastfeeding during this difficult time. Although breastfeeding may reduce depressive symptoms during the postpartum period, mothers with depressive symptoms are more likely to discontinue breastfeeding [129–134]. Referrals to area lactation consultants and breastfeeding support groups such as La Leche League can be extremely helpful to mothers with PPD who are interested in continuing breastfeeding.

Conclusion

Postpartum depression is a treatable mood disorder that often goes undetected. The symptoms of postpartum depression can have a profound impact on maternal–infant bonding as well as other family dynamics. Infants of mothers with postpartum depression are more likely to experience delayed cognitive and emotional development. Postpartum depression can occur any time throughout the first 18 months' postpartum, with the highest prevalence occurring during the first 3 months. The etiology of postpartum depression is currently unknown, but is thought to be a complex problem that includes biochemical, genetic, psychosocial, and situational life-stress factors. Postpartum depression appears to transcend cultural background, as it affects women throughout the world; however, it appears to affect more women of low socioeconomic status compared with women who are more affluent. Although there are multiple risk factors that place women at risk for postpartum depression, prenatal depression is in the foreground as placing women at the highest risk. Women with postpartum depression suffer from an overwhelming feeling of loss of control. Screening is key to treating postpartum depression, as many women go undetected. Screenings should be repeated throughout the first 18 postpartum months because postpartum depression can develop at any point.

Nutrients play key roles in maintaining a healthy CNS, including serving as structural components of brain tissue, altering neurochemical properties of membranes involved in neurotransmission, as precursors in the formation of neurotransmitters, serving directly as neurotransmitters, and modulating inflammatory expression. A well-balanced diet comprised of adequate carbohydrates, protein, and fat will help ensure a steady source of fuel to the brain. Key nutrients including omega-3 fatty acids, iron, folate, riboflavin, and vitamin B₆ have been implicated in depression and/or postpartum depression, and care should be taken to ensure adequate intakes of these nutrients for women during pregnancy and the postpartum period.

Last, although breastfeeding may be beneficial to both mother and infant, care should be taken to support women in making the decision that is best for them. Women suffering from postpartum depression are at an increased risk for breastfeeding cessation and require additional support for long-term breastfeeding success.

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Diabetes in Pregnancy: Worldwide Perspective

I-Lynn Lee and Louise Maple-Brown

Keywords Gestational diabetes · Diabetes in pregnancy · Prevalence · Trends · Pre-conception counselling

Key Points

- Diabetes in pregnancy has become one of the most common health complications of pregnancy worldwide with an increasing trend in prevalence over time.
- There is a lack of a uniform approach to screening and diagnosis of DIP contributing to the challenges in estimating the true prevalence of worldwide DIP.
- Ethnic differences in DIP prevalence contribute to the wide variation in DIP prevalence between countries and within countries with multi-ethnic populations.
- There is an increasing burden of type 2 diabetes in pregnancy, which is associated with high maternal and fetal morbidity.
- Preconception counseling and optimisation of glycaemic control in women with pre-existing diabetes is crucial in minimising complications associated with DIP.
- Postpartum diabetes testing in women with recent gestational diabetes is an excellent opportunity to educate women about planning future pregnancies and optimising their health.

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Introduction

As the prevalence of obesity and diabetes worldwide increases, affecting all age groups, diabetes in pregnancy (DIP) is becoming one of the most common health complications of pregnancy [1]. DIP comprises of pre-existing Type 1 diabetes (T1DM), Type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM). GDM has been described as carbohydrate intolerance of varying degree of severity with onset of first recognition during pregnancy [2]. This may inevitably include undiagnosed pre-existing T2DM.

Prevalence of Dip

Methodological Challenges in Estimations of GDM Global Prevalence

It has been historically challenging to estimate the true prevalence of worldwide DIP due to several methodological challenges, which include the lack of a uniform approach to screening and diagnosis of DIP [3]. The screening approaches for GDM differ from country to country, within some countries, and over time. These approaches can also vary from universal or routine screening for all pregnant women to selective screening among high-risk women [3]. The screening methods employed are determined by the country's own diabetes or health association, or local health society, or its regional obstetric organisation. The country or region's resources to cope with the burden of the disease may also impact the method employed.

The diagnostic criteria for GDM historically have been an issue of contention. The debate has evolved over time as evidence for adverse effects of even mild hyperglycaemia in pregnancy emerged. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study was a large ($n = 23,216$) multinational epidemiologic study of pregnant women with untreated mild glucose intolerance which showed a continuous glucose relationship with adverse outcomes for fetal macrosomia, cord C-peptide, and neonatal adiposity. These relationships were importantly independent of potential confounders such as maternal age, obesity, race/ethnicity, and family history [4]. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus panel concluded that single-step testing is recommended for all pregnant women at 24–28 weeks' gestation. The group recommended that the 75-g oral glucose tolerance test should be used as the test for GDM diagnosed with any one abnormal value being diagnostic. The panel agreed on glucose values with an odds ratios of 1.75 for various perinatal risks from the HAPO Study compared to mean glucose values at each testing time. Hence, the plasma glucose thresholds recommended by IADPSG are fasting ≥ 5.1 mmol/l (92 mg/dl) or 1-h ≥ 10 mmol/l (180 mg/dl) or 2-h ≥ 8.5 mmol/l (153 mg/dl) [5].

Underlying Shifts in Demographic Factors Affect Trends in GDM Prevalence

Another important factor to consider, in addition to varied screening approaches and diagnostic criteria, is that of underlying population characteristics that may impact the trends in GDM prevalence across studies [3]. The key population characteristics and major risk factors for GDM are race/ethnicity and advancing maternal age.

That the prevalence of GDM varies with maternal ethnicity has been well described in countries with multi-ethnic populations such as USA, Canada, and Australia [6, 7]. In Australia, women born in South Asia had the greatest risk, with odds of developing GDM more than four times greater than women born in Australia and New Zealand [6]. In the USA, the prevalence of GDM was higher among Asian and Hispanic women, intermediate among African-American women, and lower among non-Hispanic white women [7]. It has also been well established that indigenous women in Australia, Canada, New Zealand, and the United States have a higher risk of DIP, particularly T2DM, compared with other women in the same country [8]. There has also been an increase in the proportion of births to women from minority populations in the USA, Australia, and Canada. In Australia, 28.1% of mothers who gave birth in 2010 were born in countries other than Australia compared to 22.1% in 2001; and 12.7% of women who gave birth were born in an Asian country in 2010 compared to 7.7% of women in 2001 [9, 10]. In the United States in 2012, Asian or Pacific Islander women aged 35–39 had the highest birth rate of 19.7 births per 1000 women [11]. These demographic trends impact the increased prevalence of diabetes.

It is well established that age is a major risk factor for GDM, and hence when increasing GDM prevalence is described over time in a population, increasing maternal age could be a partial contributing factor [3]. There has been an increasing trend in the average age of women at first birth over the past four decades in the USA. The first birth rate for women in the USA aged 35–39 has increased steadily from 1970 to 2006, decreased from 2006 to 2010, and increased again in both 2011 and 2012 [11]. The first birth rate for women aged 40–44 has more than doubled from 1990 to 2012. Hence, an age-standardised prevalence estimate may provide further insight when prevalence estimates of GDM are compared across populations.

Global Prevalence of GDM

Despite the methodological challenges described above, a comprehensive review in 2016 provided an overview of the global prevalence of GDM based on data published in the past decade. There were data from 77 eligible studies from 36 countries, with countries such as the USA, Canada, Australia, China, and India having multiple published studies. Conversely, other developing countries in Africa and

South/Central America have few published prevalence studies. The Middle East and North Africa had the highest prevalence of GDM with a median estimate of 12.9% (range 8.4–24.5%) followed by Southeast Asia, Western Pacific, South and Central America, Africa, and North America and the Caribbean (median prevalence 11.7, 11.7, 11.2, 8.9, and 7.0%, respectively). Europe has the lowest prevalence with a median value of 5.8%; range 1.8–22.3%. Different countries have used different diagnostic criteria with variations of prevalence within regions [3].

The widest prevalence variation was reported in the Western Pacific region, with a prevalence of 4.5% in Japan compared to 25.1% in Singapore. Japan's diagnostic criteria were based on both the Japanese Society of Gynecology and Obstetrics 1984 criteria and the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria, whereas the Singapore study was based solely on the IADPSG criteria. The least variation was observed in the North America and Caribbean region, with GDM prevalence estimations to range from 6.5% in Canada (Canadian Diabetes Association criteria) to 11.9% in Barbados (IADPSG criteria) [3].

A systematic review by Guariguata et al. of 47 studies from 34 countries calculated age-specific prevalence of hyperglycaemia first-detected in pregnancy (HIP consisting of GDM, T1DM, and T2DM) in women 20–49 years in 2013 [12]. The review further adjusted for heterogeneity in screening method and blood glucose diagnostic threshold in studies to align with recent published diagnostic criteria by World Health Organisation for HIP [13]. It was estimated that there was a crude prevalence of 16.9% in 127.1 million live births to women aged 20–49 affected by hyperglycaemia in 2013. The highest crude prevalence of HIP was reported to be in the South-East Asia Region at 23.1% of live births, followed by the Middle East and North Africa Region with 22.3%. The majority (91.6%) of HIP occurred in low and middle-income countries. Low-income countries were accountable for 71.5% of cases of undiagnosed T2DM compared with 34.1% in high income countries [12].

Guariguata et al. further reported an age-standardised worldwide prevalence of HIP at 14.8% with additional country-specific estimates. The United Arab Emirates had the highest age-standardised prevalence of HIP at 36.8% (crude prevalence 40.4%) of women 20–49 years, followed by Norway (31.1%), India (27.5%), and the Netherlands (27.2%). The lowest age-standardised prevalence occurred in Japan at 4.0%. There was an enormous burden of the disease in Asia in 2013, with 5.7 million cases in India and 1.2 million in China [12].

Population Groups at Risk of DIP

The wide variation in prevalence of DIP between countries contributes to the ethnic differences in prevalence of DIP within countries with multi-ethnic populations. In the USA, Hispanic, African-American, Native American, and Asian women are at higher risk for GDM than non-Hispanic white women [7, 14]. In Europe, GDM is more prevalent among Asian women [15]. In Australia, GDM is more common in indigenous women [16, 17] and women from Asia and middle-eastern countries

[18]. GDM has been reported to be more common in women living in urban than rural areas in India [19]. This could be attributed to the change from traditional to modern lifestyles in low-income countries [20].

T2DM and GDM may be prevalent in Asian countries at a lower BMI than Western populations. Yajnik et al. have described the “thin-fat” babies in India using detailed anthropometric measurements of Indian babies compared to Western babies born in Southampton, UK; Indian babies were born of lower birth weights and ponderal index, but with thicker subscapular skin-fold, indicative of excess fat [21]. This was described in the context of high prevalence of maternal malnutrition in rural areas of India. Hence the intrauterine environment may predispose the offspring to a tendency to lay down fat that may continue into adult life and contribute to obesity [22].

Trends in Prevalence

Despite the methodological difficulties in assessing the trends of DIP prevalence, it remains important to assess prevalence from population-based studies to understand the trends over time.

In the United States, a study using the National Hospital Discharge Survey, comprised of 59 million births over 16 years, reported a 122% increase in GDM prevalence from 1989–1990 to 2003–2004. There was a relative increase of 94% among white women (2.2% in 1989–1990 to 4.2% in 2003–2004). There was an even larger relative increase in GDM among black women of 110% (0.6% in 1989–1990 to 2.1% in 2003–2004) occurring in a younger age group of younger than 25 years [23]. A large retrospective study of 175,000 women aged 13–58 in years from 1999 through 2005 in all Kaiser Permanente hospitals in southern California reported that there was no change in age- and race-adjusted prevalence of GDM from 7.5 per 100 in 1999 to 7.4 per 100 in 2005. On the other hand, this study reported a doubling of age- and race/adjusted prevalence of pre-existing diabetes from 0.81 per 100 in 1999 to 1.82 per 100 in 2005 ($P_{\text{trend}} < 0.001$) [14]. In general, over this same time period there was an increasing trend in the prevalence of GDM in the USA. The estimated increase varied greatly from 0 to 220%, depending on the composition of the denominator (screened plus unscreened women vs. screened women only) and the method of case identification (hospital discharge diagnostic codes vs. consistent glucose thresholds to blood glucose test results from laboratory databases) [14, 24–29].

In Australia, several studies have reported an increase in prevalence of GDM by 27% to 88% between 1988 and 2008 [6, 16, 30, 31]. Only one study adjusted for age, and recognised that over the study period, there were increased numbers of Australian-born women of non-Caucasian ethnicities whose parents were born elsewhere, and this was not adjusted for in the analysis [30].

In the province of Ontario in Canada, the prevalence of GDM increased by 12% from 1995 to 2002 [32] as compared to a 61% increase in the province of Manitoba

from 1985 to 2004 [33]. As the study from Ontario was based on administrative data that did not record maternal ethnicity, the differences in prevalence of GDM by race/ethnicity were not examined [32]. The study from Manitoba showed a smaller increase in GDM prevalence among First Nation women of 19% compared to 67% among non-First Nation women, although the prevalence of GDM was still higher in First Nation women (8.1%) compared to non-First Nation (3.0%) women in 2004 [33].

Increasing Burden of Type 2 Diabetes in Pregnancy

The combination of a high prevalence of obesity together with later childbearing ages has led to an increase in the prevalence of T2DM complicating pregnancy. This is of concern, as T2DM in pregnancy is associated with increased maternal morbidity and perinatal mortality [34]. The long-term effects of T2DM in pregnancy were reported from studies of Pima Indians, demonstrating an increased risk of obesity and diabetes in their offspring [35].

In Australia, the proportion of T2DM within cohorts with pre-existing DIP has been reported to have increased from 20% in 1989–1998, to 36% in 1998–2001, to 55% in 2003–2004 [36–38]. A survey of 10 Australian teaching hospitals reported that among those with pre-existing DIP, the proportion with T2DM (55%) had exceeded that of T1DM in pregnancy (45%) [38]. Nationally, pre-existing T2DM affects about 0.3% of pregnancies [17]. Rates of T2DM in pregnancy are up to ten-fold higher among Aboriginal women than the general Australian population [17], with the prevalence of T2DM in Aboriginal women living in the Northern Territory reported to be 4% in 2013 [39]. A Japanese study reported a three-fold increase in pre-existing DIP (T1DM and T2DM) between 1971 and 1993, with more than two-thirds of the cohort having T2DM in pregnancy [40]. There has been an increasing number of studies of T2DM in pregnancy from high-income countries, where there used to be more focus on pre-gestational type 1 diabetes, identifying that women with T2DM comprise a significant proportion of pregnancies [41–44].

Maternal Morbidity Associated with T2DM in Pregnancy

The micro- and macrovascular complications associated with T2DM contribute to the maternal morbidity in pregnancy. A Japanese study involving women with a longer duration of T1DM in pregnancy than the women with T2DM in pregnancy (11.5 vs. 5.6 years) reported a similar prevalence of maternal complications between the two groups [40]. Retinopathy has been reported to worsen in pregnant women with T1DM and T2DM [45]. Women with diabetic nephropathy during pregnancy have higher rates of preterm birth, intrauterine growth restriction, and pre-eclampsia [34]. Women with moderate to severe renal insufficiency have more than a 40% chance of accelerated progression of their diabetic nephropathy in pregnancy [46].

In women with pre-existing nephropathy, up to 51% will develop pregnancy-induced hypertensive disorders in pregnancy [34]. Independent of nephropathy, up to 10–15% and 20% of pregnancies complicated by T2DM could develop pregnancy-related hypertension and pre-eclampsia, respectively [47, 48]. Although women with T2DM are more likely to have ischaemic heart disease (IHD), data on IHD in T2DM in pregnancy is lacking [34]. The risk of obstetric complications such as miscarriages, pre-term labour, urinary tract infection, polyhydramnios, postpartum haemorrhage, birth injury, and emergency caesarean sections is increased in pregnancies complicated by T2DM [43, 49, 50].

Fetal Mortality and Morbidity

Perinatal mortality is also significantly higher in infants born to mothers with T2DM compared to the general population. Several studies have reported that the perinatal mortality of pregnancies with T2DM was higher than that of T1DM [42, 47]. A French multicenter survey reported that women whose first trimester HbA1c was elevated (>8%) had an almost four times higher rate of perinatal mortality (9.2 vs. 2.5%; OR 3.9; 95% CI 1.5–9.7, $p < 0.005$) compared to those with first trimester HbA1c < 8% [49].

The congenital malformations associated with infants born to mothers with diabetes most commonly involve the cardiovascular, neurological, facial, gastrointestinal, and genitourinary systems [34]. The risk of congenital anomalies has been reported to be 2.9–13% in women with pre-existing DIP [37, 42, 49, 51], which is 2 and 10 times that of the rate in pregnancies in the general population. The most common perinatal complication of infants born to mothers with diabetes is “large for gestational age” (LGA); rates of which have been reported as high as 56% of pregnancies complicated by pre-existing diabetes [47]. This contributes to the neonatal morbidity and mortality associated with pre-existing DIP.

Lack of Pre-Conception Counselling

Despite increasing awareness of complications associated with T2DM in pregnancy and the importance of prepregnancy glycaemic control, pregnancies in women with diabetes remain poorly planned [52, 53]. A cross-sectional French multi-centre study reported that 24% of women with T2DM received pre-conception care [49]. The pre-conception counselling rate in an Australia survey was documented in about 36% of T2DM pregnancies [37]. There is strong evidence that pre-conception planning improves the outcomes of pre-gestational diabetes in mainly T1DM pregnancies, with similar results for T2DM pregnancies [50, 54–56]. It has been shown that women with pre-existing diabetes whose first trimester HbA1c was elevated (>8%) had higher rates of major congenital malformation and preterm delivery than

those with first trimester HbA1c <8% [49]. A meta-analysis of 14 studies that included women with T1DM and T2DM in pregnancy reported that the pooled rate of major anomalies was lower among pre-conception care recipients (2.1%) than non-recipients (6.5%) (RR 0.36, 95% CI 0.22–0.59) [54].

Besides pre-conception glycaemic control, pre-conception folate supplementation is also crucial, and has been shown to reduce neural tube defects [57, 58]. Women with pre-existing diabetes have rates of folic acid supplementation reported to be as low as 22–45% [38, 53, 56]. All women with T2DM should be advised to commence folate supplementation prior to conception.

Women with T2DM may have other comorbidities such as hyperlipidaemia and hypertension, and hence may be on cholesterol-lowering or anti-hypertensive medications. This is of concern as statins are associated with fetal malformation and angiotensin converting enzyme (ACE) inhibitor are contra-indicated in the second and third trimesters of pregnancy, as they may interfere with normal fetal renal development causing oligohydramnios, fetal growth retardation, pulmonary hypoplasia, neonatal renal failure, and death [59, 60]. Therefore, statins and ACE inhibitors should be ceased during the pre-conception period, and ACE inhibitors could be replaced with alternative agents such as nifedipine, atenolol, or methyldopa. This adds further weight to the importance of pre-conception counselling in women with pre-existing diabetes, as it is an important opportunity to optimise glycaemic control, screen for complications of diabetes, ensure folate supplementation, and rationalise pre-existing medications.

Management and Prevention of GDM

Intensive treatment of GDM with dietary advice and insulin therapy has been shown to reduce the risk of serious perinatal morbidity for death, shoulder dystocia, nerve palsy, and bone fracture in the infant. Although treatment was associated with reduced risk of macrosomia or LGA, it was also associated with an increase in special care unit admission and induction of labour rates. When standard care was compared to intensive treatment, risk of developing pre-eclampsia was reduced, but caesarean section rates were not significantly reduced [61]. The effects of treatment on the long-term outcomes of mother and offspring remain unclear.

The first-line treatment for GDM involves glucose monitoring, medical nutritional therapy (MNT), and exercise. If glycaemic targets are not met, insulin may be initiated [62]. There have been randomised controlled trials that support the efficacy and short-term safety of glyburide [63] and metformin [64–66] for the treatment of GDM. However, both agents have been shown to cross the placenta and long-term safety data are not available [67].

There are multiple challenges in providing MNT to populations who are of low-income with limited resources. Firstly, socioeconomic factors have been shown to have a significant impact on nutrient intake and food-purchasing patterns. Energy-dense, nutrient-poor foods cost much less than nutrient-rich foods, and hence con-

tribute disproportionately to energy availability in a person of low income [68, 69]. A diet high in refined carbohydrates and low in fresh fruit and vegetables has been reported in an Aboriginal population of low socioeconomic background living in a remote region of northern Australian [69]. This adds challenges to providing MNT to women with DIP from resource-poor countries globally. These settings may also involve population groups at increased risk of GDM and T2DM. Secondly, lack of food security for some economically marginalised groups can be another major challenge in providing MNT to women with DIP. If the woman eats only one meal a day, it may be challenging to achieve tight glycaemic control through the day [70]. Thirdly, low-income countries are associated with higher rates of physical inactivity, which is another cornerstone in MNT [71]. These challenges can contribute to the complexity of managing DIP with MNT in resource-poor settings.

There have been conflicting results on effective ways to prevent GDM. A meta-analysis in 2011 showed that combined lifestyle intervention (physical activity with healthy eating) was associated with reduced gestational weight gain (GWG), but not with improvement in perinatal outcomes or significant reduction in GDM rates [72]. A recent Finnish study reported that lifestyle intervention was effective in reducing the incidence of GDM by 39% in obese women with a previous history of GDM [73]. Other large randomised controlled trials have shown that lifestyle interventions did not achieve a reduction in the GDM incidence [74–76].

Management of Pre-Gestational Diabetes in Pregnancy

It is recommended that women in their reproductive age with diabetes need to be educated and counselled about the potential outcomes and risk of DIP, dangers of unplanned pregnancy, and the benefits of good glycaemic control in the pre-conception period. Where feasible, women should be advised to continue with contraception until tight glycaemic control is achieved [34]. Pre-conception counselling is an opportune period to review and optimise all oral medications, including statins and ACE inhibitors. Alternative anti-hypertensives such as atenolol, nifedipine, or methyldopa could be initiated to achieve a target BP < 130/80 mmHg. Healthy eating and exercise are recommended, with an aim to meet healthy prepregnancy body mass index. Education regarding smoking cessation and healthy alcohol consumption is also recommended. Women on metformin should be checked for vitamin B₁₂ deficiency [77].

Insulin is the preferred medication for management of pre-existing DIP. Tight glycaemic control prior to and during pregnancy requires regular monitoring, as insulin resistance may vary through pregnancy. There is an increased risk of hypoglycaemia with tight glycaemic control that is associated with intrauterine growth restriction [62]. Implementation of rapid glycaemic control has been associated with precipitating worsening of retinopathy in women with pre-existing retinopathy [45]. Hence, tight glycaemic control needs to be carefully balanced with risk of hypoglycaemic events. Unplanned pregnancies in the setting of suboptimal control

in T2DM will require frequent monitoring to intensify management of diabetes, comorbidities, detailed fetal surveillance, and appropriate timing and mode of delivery [34].

Postpartum Diabetes Screening and Progression from GDM to T2DM

Women with GDM have a sevenfold increased risk of developing overt diabetes mellitus and dysglycaemia (impaired fasting glucose or impaired glucose tolerance) later in life compared to women without GDM [78]. Hence, a diagnosis of GDM may reflect a transient unmasking of an underlying predisposition of diabetes, induced by the metabolic changes of pregnancy, that disappears after delivery [79]. Alternatively the diagnosis may reflect pre-existing glucose intolerance or T2DM that was first detected in pregnancy. A postpartum oral glucose tolerance test (OGTT) at 6–12 weeks is thus recommended in order to risk stratify this group of at-risk women [62]. The postpartum check is also an excellent opportunity to intervene early, educate the woman about planning future pregnancies, and optimise health.

Despite the importance of postpartum diabetes screening, there are generally low worldwide postpartum screening rates for women with GDM, varying between 35% and 65% [55]. Predictors of postpartum screening include older age, Asian or Hispanic race/ethnicity, higher education, earlier GDM diagnosis, use of diabetes medications during pregnancy, and more provider contacts after delivery. Obesity and higher parity were independently associated with lower screening performance [80]. Studies have reported higher postpartum testing rates when patients were proactively contacted via phone calls or education programs or sent postal reminders [55, 81]. A physician-based reminder system has also been shown to be an effective way to improve postpartum screening rates [82]. Strategies to improve postpartum screening need to be channeled in a multi-level approach where both patients and physicians are targeted.

Conclusion

DIP is the most common complication of pregnancy, and is associated with adverse short- and long-term perinatal complications. The prevalence of DIP in recent years has increased worldwide, perpetuating the vicious cycle of obesity and diabetes. Screening and early detection of DIP among high-risk groups can improve outcomes. Tight glycaemic control with lifestyle modification and insulin are cornerstones in the management of DIP. Close fetal monitoring, and appropriate mode and timing of delivery, contribute to improved perinatal outcomes. As obesity is the

driving force of GDM and T2DM in pregnancy, a public health focus on the prevention of obesity is recommended through population measures on a global scale. Strategies to prevent obesity and diabetes should include a life course approach that covers pre-conception, in-utero, childhood, adolescence, and adulthood.

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Nutrition and Maternal Survival in Low and Middle Income Countries

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Keywords Maternal mortality · Causes · Pregnancy · Micronutrients · Anemia · Vitamins · Supplementation · Morbidity · Nutrition

Key Points

- Undernutrition in pregnancy, including low body mass index, short stature and micronutrient deficiencies, represents an underlying vulnerability that may lead to increased maternal morbidity and mortality in LMIC.
- Anemia especially severe, in pregnancy, has been consistently linked with maternal mortality, albeit based on observational studies.
- In populations with low dietary intake of calcium, daily calcium supplementation at 1.5–2 g can prevent pre-eclampsia and is recommended.
- Three large vitamin A supplementation trials do not support universal antenatal use, except in high-burden vitamin A-deficient settings.
- Adolescent pregnancy is common in LMIC (low and middle income countries), and girls enter pregnancy with inadequate nutritional stores and may stop growing, thus missing their opportunity to fulfill their growth potential. Young mothers are at increased risk of maternal mortality, obstructed delivery, and C-section delivery.
- Antenatal nutrition support including supplementation with calcium, iron-folic acid, and balanced energy protein in undernourished contexts has the potential to impact pregnancy health and birth outcomes, when delivered at scale using robust ANC delivery platforms.

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Introduction

The United Nations' fifth Millennium Development Goal (MDG) of improving maternal health and reducing maternal mortality by 75% was unmet, yet there was global progress. The maternal mortality ratio declined from 385 in 1990 to 213 deaths per 100,000 live births by 2013, a decline of 44% [1–3]; the success was higher in South Asia compared with sub-Saharan Africa (64% vs. 49% decline). Globally, 71% of births were attended by skilled birth attendants, and the number of women who received four antenatal care visits also increased. The number of maternal deaths, although lower, was 303,000 in 2015, with 99% of the burden in LMIC. Many countries of sub-Saharan Africa and South Asia continue to harbor a high burden. Reducing mortality related to complications of pregnancy, labor, and delivery continues to be a priority and to receive attention globally. The previous *Lancet* series on maternal survival [4–8] was a call to focus action on the high burden of maternal mortality in the developing world. The series also provided a critical overview of known strategies that were most likely to exert an impact. Much progress was made applying these strategies to address the global burden of maternal morbidity and mortality. Consensus on the kind of focused approaches and the necessary tools and strategies known to work to reduce maternal death by addressing obstetric complications, be it through increasing facility-based deliveries, skilled attendants or emergency obstetric care, or by meeting unmet obstetric need, has been a prime focus of the Safe Motherhood Initiative and the Maternal Survival Series steering group [9].

The Way Forward

Two recent major publications are likely to influence the way forward for continued improved maternal health for achieving the Sustainable Development Goal-3 global target of less than 70 maternal deaths per 100,000 livebirths and no country having a ratio greater than 140 by 2030. First, the new 2016 *Lancet* series on maternal health takes a refreshingly novel and more comprehensive view on maternal health and acknowledges the changing causes of maternal morbidity and mortality. These include the demographic and epidemiologic transition, and continued increasing diversity and divergence in the burden caused in part by lack of equity not only related to access, but also quality of health care. The series also calls for focus on adolescents and social determinants of maternal health and the increasing need for integrating maternal and newborn actions. The “next generation” maternal health recognizes the impact of global factors and movements including urbanization and climate change, but also technological and health systems innovation from mobile health to data revolutions, that will all play a role in changing the landscape of maternal health globally. The series also calls for implementing and assessing routine provision of care, in addition to emergency care, with recommendations for

services focusing on antenatal care, including nutritional interventions. These strategies can align with the new WHO antenatal care (ANC) guidelines [10] in which 39 evidence-based nutrition, health, and other guidelines address pregnancy-related preventable morbidity and mortality. To emphasize the need for adequate antenatal care, the WHO increased the number of scheduled ANC contacts to a minimum of eight. Together, many of these recommendations address the provision of nutrition services, including supplements and counseling, and further highlight the importance of supporting nutritional care to promote maternal and newborn health and outcomes.

Fully recognizing the importance of effective antenatal, intrapartum, and postpartum health care and nutrition and the changing needs addressing maternal and infant health, this chapter examines the evidence for the specific role of nutrition in contributing to improving maternal health and survival in LMIC. In their commentary in the *Lancet Maternal Health* series, Ceschia and Horton [11] call out maternal nutrition, saying that it “remains a marginal concern for most countries.” Poor nutrition is often referred to in the same broad context as economic development, poverty, low education, and poor access to medical care [9]—factors that are known to be underlying contributors to the burden of maternal mortality and that are likely to take much longer to address. Another prevailing notion that was challenged in this series is that “it is hard to prevent maternal health risks—because every pregnancy faces a risk.” Rigorous evidence suggests that nutrition interventions can reduce the burden of life-threatening morbidities that result in maternal death, especially in many underserved settings of the world, where health care access is poor and maternal malnutrition is high. The new set of ANC guidelines include a number of evidence-based recommendations for nutrition interventions and care [11].

Antenatal nutrition support has the potential to impact pregnancy health and birth outcomes, when delivered at scale using robust ANC delivery platforms. Maternal health is increasingly reliant on providing adequate care and support throughout pregnancy. This chapter examines nutrition interventions and strategies and provides the biologic basis, rationale, and empirical evidence for the impact of nutrition in ameliorating the risk of maternal mortality in underserved populations of the world.

Causes of Maternal Mortality and the Link with Nutrition

The International Classification of Diseases (ICD-10) defines maternal death as “death of a woman while pregnant or within 42 days of the end of pregnancy, irrespective of the 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” [12]. Deaths from both direct (resulting from obstetric complications of pregnancy) and indirect causes (resulting from previous existing diseases or diseases that developed during pregnancy) are included in calculating maternal mortality. However, measuring maternal mortality is complex due to the lack of adequate

data on the timing and cause of deaths in many regions of the world. WHO, in collaboration with other agencies, recently published global estimates of, and trends in, maternal mortality noting declining rates worldwide as described above. The major causes of maternal mortality, with the caveat that causes are not well known, continue to be hemorrhage (27.1%), hypertension (14.0%), sepsis (10.7%), abortive outcomes (7.9%), and embolism and other direct causes (12.8%) [13, 14]. Deaths from indirect causes continue to contribute the most to maternal deaths, with about 70% being due to a preexisting condition including HIV/AIDS, although misclassification continues to be a challenge [14]. Obstructed labor, previously listed as a cause of maternal mortality, may be assigned other causes such as hemorrhage or sepsis; 2.8% of maternal deaths may be accounted for by complications of delivery or obstructed labor. Regional variation in the causes of maternal deaths continue to be noted, with hemorrhage-related deaths being higher in sub-Saharan Africa, sepsis in South Asia, and hypertensive disorders in Latin America and the Caribbean [13]. Worldwide, indirect causes continue to be high with HIV/AIDS contributing the highest burden in Africa and Latin America.

Nutrition Condition of Women of Reproductive Age in Low-Income Settings

Undernutrition, inadequate dietary intake, and micronutrient deficiencies in women of reproductive age (15–45 years), including pregnant women, are common in many low-income countries. The prevalence of low body mass index (BMI), defined as weight for height squared <18.5 , has declined globally from 14.6% to 9.7% [15]; nevertheless, it continues to be prevalent in South Asia, with 24% women being thin. In many settings, high BMI (>25 kg/m²) is also on the rise, and this also has implications for maternal and pregnancy-related health outcomes [15]. Maternal short stature (height <145 cm or <150 cm) continues to be high in many countries, especially in South and Southeast Asia, where it ranges from 40–70% of the population [16]. Nutrition and environmental factors throughout life, including in the first 1000 days, as well as during adolescence, influence linear growth and attained stature in adulthood [17, 18]. There is a very strong socioeconomic gradient when mean increases in height of adult men and women is examined among birth cohorts from 1930 to 1980, with mean population height in low-income countries or low-wealth quintiles remaining stable. However, in upper middle/high-income or high-wealth quintiles, populations have experienced an increase in height over time [18, 19]. The importance of maternal height and its link to pregnancy-related outcomes is described later in this chapter.

Dietary intakes, especially during pregnancy, may not be sufficient to meet the increased requirements for a pregnancy. For example, dietary survey data from many regions of the world show that maternal intakes are lower than the requirements for key nutrients such as iron, zinc, calcium, and vitamin A [20]. Subsequently, maternal micronutrient deficiencies are high in many LMIC, with the global

prevalence rates of iron deficiency anemia, vitamin A (serum retinol $<0.7 \mu\text{mol/l}$), and iodine (median urinary iodine concentration $<100 \mu\text{g/l}$) deficiencies estimated at 19.2%, 15.3%, and 28.5% [21]. The prevalence of maternal anemia in many countries in South Asia and sub-Saharan Africa ranges from 40–60% [22].

The sections that follow describe the evidence linking maternal nutrition deficiencies to maternal mortality. Specifically, the association between anemia and maternal mortality and hemorrhage is examined, including the efficacy of iron supplementation and other interventions in reducing maternal anemia. The role of calcium and antioxidants in the prevention of hypertensive disease and preeclampsia, and the efficacy of magnesium sulfate in the prevention of eclampsia are reviewed, as well as the link between sepsis and infection and maternal vitamin A and zinc deficiencies. Finally, causes of obstructed labor and nutrition factors related to maternal stunting, with focus on growth in childhood and adolescence, are discussed.

A. Maternal Anemia and Maternal Mortality

It is estimated that 533 million women 15–45 years of age have anemia, with the prevalence rate being 29% in 2011, down by very little from 33% in 1995. The World Health Assembly goals for reducing anemia in women of reproductive age to below 50% by 2025 may not be achieved, with 182 countries being off target according to the recent Global Nutrition Report [23]. The WHO's recommendations for iron-folic acid supplementation and deworming during pregnancy are described in detail in Box 1 [10].

Box 1 WHO ANC Guidelines Related to Maternal Anemia and Iron [10]

- Daily oral iron (30–60 mg) and folic acid supplementation is recommended to prevent maternal anemia, puerperal sepsis, low birth weight, and preterm birth
- Where anemia (Hb $< 110 \text{ g/L}$) is 40% or more, 60 mg of elemental iron is recommended
- If a woman is diagnosed with anemia during pregnancy, her daily iron should be increased to 120 mg until her Hb rises to 110 g/L or more
- In low-anemia prevalence settings ($<20\%$), intermittent supplementation, i.e. oral iron (120 mg) and folic acid (2800 μg) once per week, is recommended
- Anemia assessment in pregnancy is recommended using full blood count testing. If not available, testing with hemoglobinometer is recommended over the Hb color scale method
- In endemic settings, deworming and malaria treatment is recommended

The relationship between maternal anemia and the risk of mortality was examined in two previous reviews [24, 25]. No randomized controlled trials to date provide data on the impact of iron supplementation on maternal mortality as the outcome. The likelihood of such trials being conducted remains low, mainly due to ethical and feasibility considerations. Observational studies conducted in Africa and

Asia, primarily among pregnant women presenting at hospitals, provide evidence for the association between hemoglobin concentration, upon admission at a hospital or clinic, and maternal mortality. None of these studies provides information on iron deficiency per se or the proportion of anemia attributable to iron deficiency. Anemia, especially severe, can arise from multiple causes including malaria (mainly *Plasmodium falciparum*), hookworm, vitamin deficiencies, and chronic infections such as HIV. However, as reported in the review by Brabin et al. [25], *P. falciparum* malaria as an etiology of anemia may be less important in leading to maternal death. In holoendemic malarious settings, an estimated 9 versus 41 deaths per 100,000 are due to malaria-related severe anemia compared with non-malarial anemia deaths among primigravidae [25]. Similarly, the contribution of HIV as a cause to maternal deaths is low, at 2% even in sub-Saharan Africa [14].

Severe anemia has long been considered to be associated with an increased risk of maternal mortality [24, 25], and the population attributable risk is provided by categories of anemia (Table 1) [25]. Severe anemia (normally defined as hemoglobin [Hb] <70 g/L) can result in circulatory decompensation and increased cardiac output at rest. The added stress of labor and blood loss, whether normal or excessive, can lead to circulatory shock and death. In most settings, however, the prevalence of mild-to-moderate (70–110 g/L) tends to be much higher than that of severe anemia [26]. Data from 10 studies were examined to determine the relationship between Hb concentration and case fatality (Murray-Kolb, unpublished data). This association was used to model the decrease in proportion of maternal deaths with a unit increase in Hb concentration. The WHO prevalence estimates for anemia were converted to mean Hb concentrations, assuming a normal distribution. These values were further adjusted to reflect a distribution of Hb for iron deficiency anemia, assuming that iron deficiency contributes to 50% of anemia globally [27]. Using relative risk estimates from published studies, an odds ratio estimate of 0.71 (95% confidence interval [CI]: 0.62, 0.89) was calculated, indicating a decrease of 29% in the odds of maternal death with every 10 g/L increase in the population in mean Hb concentration. Antenatal iron supplementation at dosages ranging between 60 and 120 mg/day and duration between 10 and 12 weeks has been shown to increase Hb concentrations by about 80–140 g/L [27]. Thus, antenatal iron supplementation would be an important strategy for combating the risk of anemia-related maternal mortality in the developing world. Although iron deficiency is the main cause of anemia, other etiologies such as malarial infection, hookworm, or chronic diseases can also contribute to severe anemia [22]. A note of caution with respect to the

Table 1 Relative risk and population attributable ratio (PAR) of maternal mortality for moderate and severe maternal anemia

	Relative risk	95% CI	PAR	PAR
Population prevalence of anemia			5%	20%
Moderate anemia (Hb 40–80 g/L)	1.35	0.92, 2.00	0.017	0.065
Severe anemia (Hb 27–47 g/L)	3.51	2.05, 6.00	0.111	0.334

Adapted from Brabin BJ, Hakimi M, Pelletier D. An analysis of anemia and pregnancy-related maternal mortality. *J Nutr.* 2001;131:604S–615S

anemia-maternal mortality relationship; confounding and bias cannot be overruled, since data examining this relationship were derived solely from observational studies of women who may have presented to the hospital with multiple morbidities, and whose Hb was assessed at the time of booking and not in early or mid-pregnancy.

Recent studies that were not part of the previous reviews (as mentioned above) have also linked maternal anemia to the risk of maternal mortality and morbidity. In a small case-control study in Ghana, anemic women (defined as Hb < 80 g/L) experienced more deaths (5/157) compared with age- and parity-matched controls (0/152) with Hb > 109 g/L [28]. Anemic cases that were treated in this study (treatment unspecified) had an increase in median Hb from 65 to 95 g/L. In a second small study from India ($n = 447$ pregnancies), Hb was assessed as part of an antenatal exam (gestational age unspecified) [29]. While too small to examine mortality as an outcome, this study showed that subjects with Hb < 89 g/L had a four- to six-fold higher risk of prolonged labor compared with those with Hb > 110 g/L. Similarly, the risk for cesarean section and “operative” vaginal delivery was higher by about the same magnitude. Both studies were observational, with low sample sizes, and failed to adjust for confounding variables. The lack of adjustment for confounding is problematic, as illustrated by a recent study of women with HIV in Tanzania [30]. Data in this study were analyzed linking anemia during pregnancy to female mortality. While the relative hazards for both all-cause and AIDS-specific mortality increased with increasing severity of anemia, adjustment attenuated the magnitude of the risk and reduced the differential in the excess risk between moderate and severe anemia. Although these were not maternal deaths per se, and the median follow-up period represented in the analysis was 5.9 years (interquartile range: 3.8–6.7 years), this study showed an increased risk of mortality related to anemia among HIV-infected women.

Hemorrhage contributes to 30–40% of maternal deaths in Africa and Asia, where the burden of maternal mortality is the highest [13]. While underlying anemia is considered to exacerbate the deleterious effect of postpartum hemorrhage (PPH) and death due to this cause, there are no empirical data to support this claim. In a series of 40 PPH deaths that occurred between April 1982 and April 2002 in rural India, hospital records indicated that 47.5% had severe anemia (Hb < 70 g/L) at the time of admission, and another 45% had Hb between 70 and 90 g/L [31]. However, without controls, it is hard to predict mortality due to PPH among non-anemic women.

It has long been considered that anemia may also increase the risk of PPH [32, 33], although data supporting this are scant. The main causes of PPH include uterine atony, placental retention, trauma, and coagulopathy [34]. The few existing studies that have examined the risk of PPH by level of anemia indicate a weak association (Table 2). Among emergency room patients admitted to a hospital in Auckland, New Zealand, between January and August of 1966, of 1743 anemic women, 159 suffered from PPH compared with 15 out of 170 non-anemic women, suggesting no difference in the risk of PPH by anemia status [35]. More recently, Geelhoed et al. [28], using a cohort design in two sub-district hospitals in Ghana, compared the risk of PPH among 157 severely anemic (Hb < 80 g/L) and 152 non-anemic pregnant women (Hb \geq 109 g/L) matched for age and parity and found no difference. On the

other hand, Tsu [36] in a multivariate logistic regression analysis, after adjusting for other risk factors such as maternal age, parity, and antenatal hospitalization, reported that Zimbabwean women with PPH after normal vaginal deliveries were more likely to be anemic compared to those who did not experience PPH. In a study conducted in a hospital in Nigeria among 101 women who developed PPH and 107 controls, there was no difference in the prevalence of anemia measured during pregnancy [37]. Finally, in a hospital study, 374 cases of PPH were derived from 9598 vaginal deliveries and matched to controls (ratio: 1:3) [38]. Cases had a significantly higher hematocrit (not lower) compared with controls at admission. There was no association between antenatal anemia and uterine atony, an important cause of PPH in a tertiary care hospital-based study in Pakistan [40]. One study in Tanzania measured blood loss during delivery using an alkaline hematin method and showed a dose-response relationship between Hb concentration during pregnancy and volume of blood loss, with more anemic women having a higher volume of blood loss [41], but the study was not powered to examine PPH. Lastly, a double-blind, cluster randomized controlled trial of supplementation with different combinations of micronutrients during pregnancy in rural Nepal showed that iron-folic acid vs. placebo significantly reduced the risk of intrapartum hemorrhage, defined as self-reported excessive bleeding that resulted in unconsciousness (Table 2) [39]. Although an RCT, because the symptoms were assessed via maternal recall, further research is needed to establish more direct evidence of a benefit.

Table 2 Risk of postpartum hemorrhage and maternal anemia

Reference	Population			
Risk of PPH: cohort studies		Anemic	Nonanemic	<i>P</i> value
[35] ^a	Auckland, New Zealand, booked emergency patients, 1743 anemic vs. 170 non-anemic women	10.8%	8.8%	NS
[28] ^b	157 severely anemic and 152 non-anemic Ghanaian women	11.3%	12.1%	NS
Risk of anemia: case-control studies		Cases	Controls	<i>P</i> value
[36] ^c	151 cases of PPH and 299 controls	39.6%	19.0%	0.05
[37] ^d	101 cases of PPH and 107 controls	5.9%	4.7%	NS
[38] Hct, mean \pm SD	374 cases and 1122 controls	36.6 \pm 2.1	35.6 \pm 2.3	0.01
RCT of iron-folic acid supplementation: risk of PPH		Placebo	Iron-folic acid	RR (95% CI)
[39]	Rural Nepal, 828 pregnant women receiving active placebo vs. 737 receiving iron-folic acid	5.4%	3.3%	0.59 (0.35, 0.98)

PPH postpartum hemorrhage, NS not significant, Hct hematocrit

^aAnemia defined as Hb < 105 g/L and/or hematocrit <35% or Hb > 105 g/L, but blood film showing aniso-cytosis, microcytosis, and hypochromia

^bAnemia defined as Hb < 80 g/L and non-anemic women had Hb \geq 109 g/L

^cHb < 120 g/L

^dAnemia was undefined

A recent Cochrane review [27] of iron supplementation vs. no supplementation found a reduction in maternal puerperal infections. In four trials that included 4374 women, the relative risk (RR), with 95% confidence interval (CI) was 0.68 (0.50, 0.92). The same review showed no impact on postpartum hemorrhage (RR 0.93, 95% CI 0.59, 1.49) but the number of trials was also limited ($n = 4$), and included a smaller sample of pregnant women ($n = 1488$).

In summary, study results are suggestive of neither an increased risk of mortality due to PPH as a result of underlying anemia nor an increased risk of PPH due to maternal anemia during pregnancy. However, the association between maternal mortality and anemia remains consistent, albeit derived from observational studies. In addition, antenatal iron-folic acid supplementation is likely to impact other outcomes, such as reduction in low birth weight and preterm delivery, and improved infant iron stores.

Despite WHO recommendations and national policies for iron-folic acid supplementation, programs have failed to effectively reduce the prevalence of maternal anemia in many regions of the world. Previous data from Demographic and Health Surveys (DHS) reveal low rates of any antenatal iron use in LMIC, with the proportion of women taking at least 90 tablets, an amount recommended during pregnancy, being even lower in many countries (Fig. 1) [42].

The major barrier to effective supplementation programs that remains problematic is the supply chains for iron-folic acid tablets [42]. Despite the prevailing belief that side-effects of high-dose iron (generally 60 mg) may result in low adherence rates, the recent Cochrane review [27] found virtually no effect on the risk of any side effects, including constipation, heartburn, and vomiting and there was even some evidence of lowered diarrheal symptoms due to supplementation. In a country such as Malawi, with one of the highest maternal mortality ratios (984/100,000 live births), women consider anemia to be a maternal health concern [43]. Similarly, perceptions of improvement in physical well-being and alleviation of symptoms of fatigue and poor appetite with iron use would be helpful to use as messages in efforts aimed at promoting antenatal iron supplement use [42].

B. Nutrition and Hypertensive Disease of Pregnancy

Historically, observations that Mayan Indians who consume a traditional diet of corn soaked in lime had high calcium intakes [44], and Ethiopian women whose diets contain high amounts of calcium have low rates of preeclampsia [45] support the role of calcium in reducing hypertensive disorders of pregnancy. A dietary deficit in calcium is postulated to cause an increase in blood pressure due to stimulation of the parathyroid gland and release of parathyroid hormone, resulting in movement of calcium intracellularly in vascular smooth muscles and causing an intensified reactivity and vasoconstriction [46]. A review of the numerous epidemiologic and clinical data and the series of trials that were conducted is beyond the scope of this chapter. However, a six-center WHO trial of calcium supplementation among

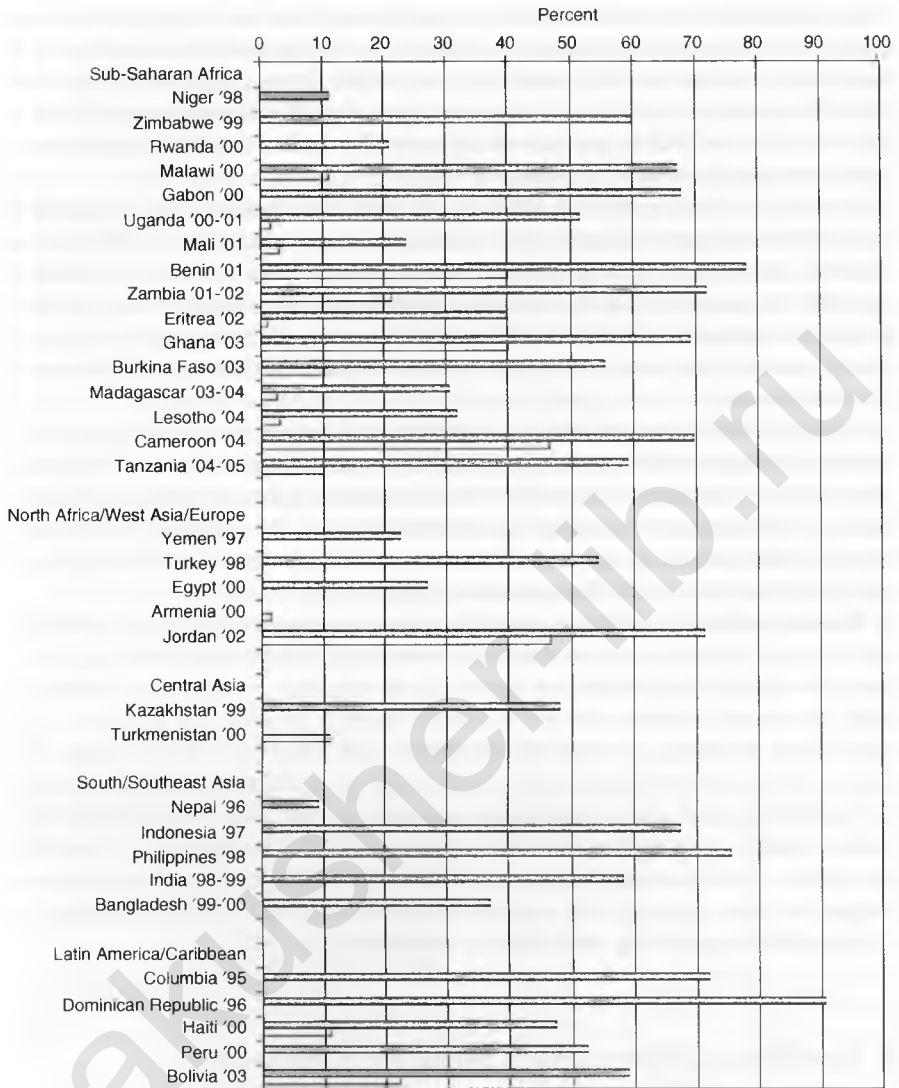


Fig. 1 Percent of women who reported taking iron supplements [any (grey bars) and 90+ tablets (light bars)] during a previous pregnancy in the past 3–5 years. Data on prevalence of consumption of 90+ tablets were not available for many countries. Adapted from Demographic and Health surveys and Mukuria A, Abouafia C, Themme A. The context of women's health: results from the Demographic and Health Surveys, 1994–2001. Comparative Reports no. 11. Calverton, MD: ORC Macro; 2005

women consuming a low-calcium diet (<600 mg/day) supports the evidence of benefit. This study showed no effect of calcium supplementation on preeclampsia or hypertension, but significantly reduced the incidence of eclampsia (alone) and severe hypertension (defined as a systolic blood pressure ≥ 160 or a diastolic blood pressure ≥ 110 mm Hg) [47].

The WHO does have a “context-specific” recommendation of calcium supplementation (1.5–2 g daily) in populations with low dietary calcium intake to reduce the risk of pre-eclampsia [10]. Evidence provided in a Cochrane systematic review of 13 randomized clinical trials involving 15,730 pregnant women was used to make this recommendation [48]. The meta-analysis showed reductions of 35% and 55% in the risk of high blood pressure (RR = 0.65, 95% CI: 0.53–0.81) and preeclampsia (RR = 0.45, 95% CI: 0.31, 0.65), respectively, as a result of daily 1–2 g of calcium supplementation during pregnancy [48]. The effects were higher among those with low baseline calcium intake. Based on data from four trials, a composite outcome of maternal death or serious morbidity was reduced by 20% (RR = 0.80, 95% CI: 0.65, 0.97). Maternal death was reported as an outcome in a recent multicenter, double-blind, placebo-controlled trial of daily 1.5 g calcium, starting from before 20 weeks of gestation among women with low intake of calcium [47]. This trial, while not powered to show an impact on maternal mortality, reported 1/4151 and 6/4161 maternal deaths in the calcium and placebo arms, respectively (RR = 0.17, 95% CI: 0.03–0.76).

While evidence exists that calcium supplementation during pregnancy is an economical and safe way of reducing the risk of preeclampsia, especially among women with low calcium intakes [48], translating guidelines into practice is a challenge, [49] as the high dosage of calcium recommended is costly and poses constraints for programmatic scale-up and high adherence [50]. The recent WHO guideline recognizes this and recommends breaking up the supplement into three doses, but negative interactions between iron and calcium also exist [10]. There is intriguing, albeit insufficient evidence, from a subset of 10 trials which shows a significant reduction in pre-eclampsia and gestational hypertension with lower dose (<1 g) calcium supplementation, but these findings may be biased, as pregnancies in these trials were selected to be high risk for preeclampsia. Further research is needed in determining the impact of low-dose calcium supplementation in low-calcium-intake populations.

It should be noted that the use of magnesium sulfate, an anticonvulsant, among women with symptoms of pre-eclampsia (hypertension and proteinuria) for the prevention of seizures in women with eclampsia is routine in obstetric care and delivery facilities in LMICs. Oxidative stress has been proposed to have a potential role in the two-stage model of pre-eclampsia [51–53]. The first stage in this model is reduced placental perfusion, resulting from abnormal implantation or other pathologies. The second stage involves the maternal hypertensive/inflammatory response that may be influenced by environmental factors and oxidative stress [54]. Trophoblastic cells

isolated from the placenta of pre-eclamptic women have increased superoxide generation and decreased superoxide dismutase activity, supporting the hypothesis that increased oxidative stress plays a role in the pathology for pre-eclamptic placentae [55]. In a small randomized, placebo-controlled trial, daily vitamin C (100 mg) and E (400 IU) from 16 to 22 weeks of gestation significantly reduced the risk of pre-eclampsia [56]. The plasminogen activator inhibitor ratio (PA1:PA2), which is elevated in pre-eclampsia, significantly decreased due to supplementation, suggesting a reduction in endothelial activation and placental dysfunction. Subsequently, however, a larger trial among 2410 women at risk of pre-eclampsia failed to replicate these results [57]. Daily supplementation with vitamins C and E provided at the same dosages used in the previous trial failed to affect the incidence of pre-eclampsia (15 vs. 16% in the placebo group). Two other trials also failed to show a difference in the risk of pre-eclampsia between those who received vitamins C and E supplementation compared with placebo [58, 59]. Two separate Cochrane reviews of vitamin E [60] and C [61] supplementation found no evidence of benefit for reducing the risk of pre-eclampsia or eclampsia. The meta-analyses combined 14 studies among 20,878 women and found RR (95% CI) of 0.91 (0.79, 1.06) for pre-eclampsia. Thus, at present the use of antioxidants during pregnancy does not appear to hold merit for either preventing eclampsia among high-risk women, or as a prophylaxis for preventing the risk of pre-eclampsia during pregnancy. The recent WHO antenatal care guideline states that vitamin E and C supplementation of women to improve maternal and perinatal outcomes is not recommended for pregnant women [10].

C. Vitamin A, Maternal Mortality, and Infection

Vitamin A deficiency, defined as a serum retinol $<0.70 \mu\text{mol/L}$, affects 15.3% and clinical night blindness affects 7.8% of pregnant women worldwide [21]. Vitamin A deficiency can reduce immunocompetence and resistance to severe infection, while vitamin A maintains the integrity of epithelial and endothelial cells and preserves natural killer cell activity. While the relationship between vitamin A deficiency and childhood morbidity and mortality is well established, few studies provide the link between vitamin A deficiency and infection in pregnancy [62]. An early trial conducted in the 1930s in England showed that maternal vitamin A supplementation in later pregnancy through the first week postpartum reduced the occurrence of puerperal sepsis [63], a finding replicated in the 1990s among Indonesian women [64] in a study in which a 78% reduction in puerperal infection, assessed by the occurrence of fever in the first 10 days postpartum following supplementation, was seen.

A large randomized trial of weekly vitamin A or beta-carotene (7000 μg retinol equivalents each) supplementation to about 45,000 women 15–45 years of age in rural Nepal showed a 40–50% reduction, respectively, in all cause pregnancy-related mortality relative to a placebo, although cause-specific mortality using verbal autopsy data provided no information for type of maternal causes of death that were affected [65].

Pregnant women who experienced night blindness, representing a subgroup at high risk, experienced a significantly increased risk of pregnancy-related (42 days) and two-year-postpartum mortality in the placebo group compared to non-night-blind women or night-blind women who received either vitamin A or beta-carotene [66]. Moreover, causes of death among night-blind women were more likely (RR = 5, 95% CI: 2.2–10.6) to be infection-related. Biologically plausible mechanisms for the vitamin A effect are described by Faisel and Pittrof [34]. The trial in Nepal reported a reduction in the length of labor (by 1.5 h among primiparas and 50 min in multiparas) associated with vitamin A supplementation [67]. The hematopoietic activity of vitamin A is well known and vitamin A may act by reducing anemia, one of the known causes of maternal deaths. Subsequently, in the 2000s, two replicate placebo-controlled cluster-randomized trials were conducted in Ghana and Bangladesh to test if vitamin A supplementation reduced the risk of maternal mortality in these contexts [68, 69]. Neither trial showed a significant reduction in maternal deaths. The Bangladesh trial supplemented women only in pregnancy and included a beta-carotene arm in addition to vitamin A [69], whereas the Ghana trial was conducted among women of reproductive age, but only tested vitamin A [68]. These trials completed almost 10 years after the Nepal study, found lower mortality rates of 362 and 231 per 100,000 pregnancies in Ghana and Nepal, respectively (compared to a mortality rate of 704 in the placebo group in the trial in Nepal), and maternal vitamin A deficiency in these populations was also less common. A meta-analysis of weekly vitamin A supplementation on pregnancy-related mortality that included all three trials, involving a total of 205,000 women of reproductive age and 163,000 pregnancies, revealed an overall null impact on the primary outcome of pregnancy-related mortality (RR: 0.86, 95% CI: 0.60, 1.24) [70]. It is likely that as maternal mortality declined globally, any protective effect of vitamin A on causes of mortality related to infection or sepsis may have attenuated. Yet, the current WHO ANC recommendation is to supplement pregnant women in areas where vitamin A deficiency is a severe public health problem to prevent night blindness [10]. Vitamin A deficiency is considered severe if $\geq 20\%$ of pregnant women have serum retinol of $< 0.70 \mu\text{mol/L}$, or of public health significance if $\geq 5\%$ women have a history of night blindness in a recent pregnancy within 3–5 years. Few countries have policies and programs of vitamin A supplementation during pregnancy, and work is needed to promote such programs in high-burden settings.

Zinc and Infection

The role of zinc in reproductive health is well established in animal models and in small observational studies in humans, yet trials have shown limited impact on pregnancy and maternal health outcomes [71, 72]. A recent meta-analysis of 21 trials that included over 17,000 women from low- and middle-income countries found that zinc supplementation had no impact on the risk of maternal infections (RR 1.06, 95% CI 0.74, 1.53, based on three trials) [73]. The evidence for other outcomes such as C-sections or pre-eclampsia was also lacking. It is likely that

supplementation trials have failed to show efficacy, perhaps due to inadequate sample size, or because the studies were conducted in populations that were not likely to be zinc deficient, or that they did not provide adequate levels of zinc. Thus, it is not clear if zinc supplementation in pregnancy can result in a decrease in pregnancy-related infection or other adverse outcomes. Currently, WHO does not recommend zinc supplementation for pregnant women [10].

D. Maternal Height, Nutritional Status, and Dysfunctional Labor

Unlike in high-income settings, where it is no longer a cause of maternal mortality, obstructed labor was reported to be an underlying cause in 8% of maternal deaths globally in 2013, a statistic that has not changed much since 1990 when 9% of maternal deaths were attributed to this cause [74]. The inverse relationship between maternal height and the risk of dystocia (difficult labor) due to cephalopelvic disproportion (CPD) due to a disparity between the dimensions of the fetal head and maternal pelvis, or assisted/caesarean-section deliveries, is frequently described but is weak. A meta-analysis of nine studies found low sensitivity and specificity of low maternal height (<20th percentile) in predicting the risk of dystocia [75]. Further, the relationship between maternal height and dystocia appears to be relative and not absolute. Height in the analysis was expressed in percentiles and, thus, the absolute value of a twentieth percentile differed in different populations, despite the risk of dystocia at that cut-off being of the same magnitude. In practical terms, therefore, using a single value of height as a cut-off is not appropriate for predicting the risk of dysfunctional labor. In an earlier WHO meta-analysis that included 16 studies, the odds of nonspontaneous deliveries, including cesarean section, was 60% higher among women in the lowest height quartile compared with those in the highest quartile [76].

The size of the fetus is also a cofactor in this relationship. Harrison [77] showed that the risk of operative delivery was associated with both maternal height and the size of the baby; low maternal height and high birth weight increased the risk of operative delivery (Fig. 2). In Nepal, the risk relationship between maternal height and birth asphyxia (defined using self-reported symptoms and an algorithm) was modified by the size of the newborn at birth [78].

However, maternal height, which is correlated with uterine volume, is a strong predictor of birth weight, and thus it is unlikely that the shortest women would produce truly large babies. In a meta-analysis, short maternal stature was reported to increase the risk of small-for-gestational age and preterm births by two to threefold [16]. Evidence that interventions such as food supplementation or multiple micronutrient supplementation during pregnancy, aimed at improving birth weight in malnourished settings, can increase the risk of CPD or obstructed labor, however, is not conclusive. There was no evidence of an increased risk of CPD or complications in delivery in an antenatal food supplementation trial in the Gambia in which birth-weight increases ranged from 100 to 200 g [79]. The largest increase in head

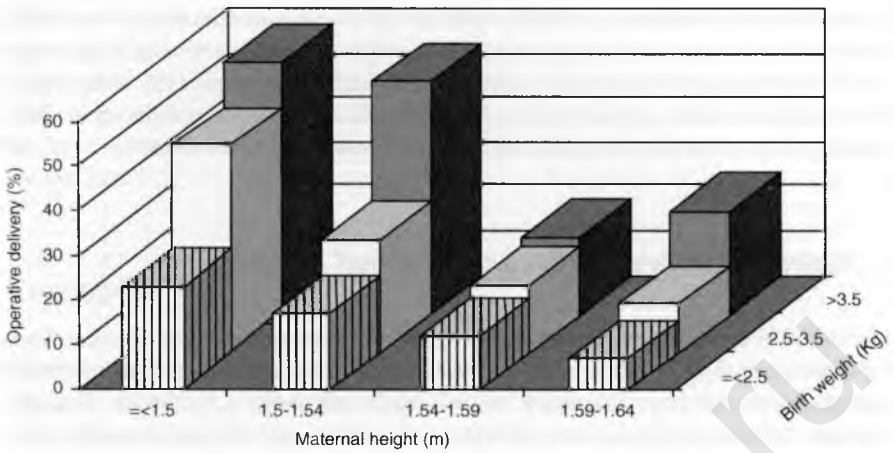


Fig. 2 Rate of operative delivery by maternal height and birth weight. Adapted from Dujardin B, Van Cutsem R, Lambrechts T. The value of maternal height as a risk factor for dystocia: a meta-analysis. *Trop Med Intern Health*. 1996;4:510-21

circumference, where head size was more strongly correlated with CPD than birth weight per se [24], was only 3 mm. This translates to an increase of only 1 mm in diameter, which is unlikely to raise the prevalence of CPD. Perinatal mortality was reduced due to maternal supplementation, further attesting to the lack of evidence for any harmful outcome as a result of the increase in birth weight but rather a benefit [80]. In a meta-analysis of 17 trials of daily supplementation with multiple micronutrients versus iron-folic acid as standard of care there were small increments in birth weight but no impact on neonatal mortality, adverse or beneficial [81].

Addressing the problem of short maternal stature and stunting is important for improving reproductive health in the developing world. However, few interventions are known to influence maternal height. Food supplementation between 6 and 24 or even up to 36 months of age may promote accelerated linear growth, but interventions beyond this period do not show further benefit [82]. Interventions during school age or adolescence appear to only modulate onset of menarche [7], although further research is needed. Based on adoption studies, relocation from environments that give rise to stunting may promote catch-up growth, but only among younger children (< 2 years old) [24, 82]. In older adopted children, accelerated maturation (early onset of menarche) resulted in a shorter growth period that led to little overall benefit in terms of attained height. Based on data from nine European countries, mean age at menarche has decreased in Europe by 44 days (range 18-58 days) as indicated by follow-ups of 5-year birth cohorts (youngest cohort: 1915-1919, oldest cohort: 1960-1964) [83]. Simultaneously, European women have grown taller over time, from 0.42 to 0.98 cm per 5-year birth cohort. However, women grew 0.31 cm taller when menarche occurred a year later, due to the later closure of the epiphyseal plates of the long bones following onset of menarche. Change in mean population height (in both men and women) has also been examined and compared between low-, middle-,

and high-income countries, and within countries by socioeconomic strata. These data show increases in mean population height in richer countries, whereas it has stagnated over time in both men and women in low-income countries [19]. Underlying this are factors related to the environment and nutrition and health conditions in these settings, and within countries, the disparity in these by wealth levels [19].

E. Maternal Undernutrition and Maternal Mortality

The risk of maternal mortality related to undernutrition or wasting malnutrition has not been examined in many studies. While it is commonly assumed that women who die each year from pregnancy-related causes are likely to be “short, thin, and anemic” [84], empirical data to support that an underlying factor is wasting malnutrition are lacking. A recent historical account of increase in maternal mortality following short-term economic crises in six German villages was attributed to nutritional stress [85]. A tenfold increase in the staple, rye, resulted in an increase in maternal mortality a year later; the increase was higher among those not engaged in agricultural work and during 2–6 weeks after childbirth, when mothers were most prone to infections and indirect obstetrical causes of maternal death.

Two prospective studies using large cohorts of pregnant women at risk of maternal morbidity and mortality have examined undernutrition using a nutritional status indicator of mid-upper arm circumference (MUAC), an indicator of thinness, adjusted for socioeconomic and other confounders. In rural Nepal, in an analysis of risk factors collected during the first half of gestation among ~22,000 pregnant women, maternal MUAC was significantly and independently associated with the risk of maternal mortality in a multivariate analysis [86]. For each 1-cm increase in maternal first-trimester MUAC, the risk of maternal death decreased by 24% (adjusted OR = 0.76, 95% CI: 0.67, 0.87). In rural Bangladesh, a similar study of risk factors of obstetric complications showed low MUAC (<21.5 cm) to increase the risk of hemorrhage and sepsis morbidity and near-misses by 12% and 16%, respectively, after adjusting for other factors [87].

There are no data to show that improving maternal nutrition via food (also referred to as balanced energy-protein) supplementation either during or prior to pregnancy results in an improvement in maternal survival. Currently, the WHO antenatal care guideline [10] recommends daily supplementation with balanced energy and protein supplementation in undernourished populations to reduce the risk of stillbirths and small-for-gestational age babies. If implemented at scale, such an intervention is likely to also impact maternal health and survival. For the developed world and countries in transition, a growing concern is the rising prevalence of overweight and obesity in pregnancy [88]. WHO estimates that 9–25% of women in developed countries are obese. Obesity in pregnancy may increase the risk of early miscarriage by 20–25% and pre-eclampsia and gestational diabetes mellitus by approximately five- to six-fold. It may also be associated with the increased risk for stillbirth, cesarean section, macrosomia, or preterm birth [88].

With low- and middle-income countries and countries in transition now witnessing overweight and obesity, food supplementation and micronutrient interventions during pregnancy will need to be considered in light of this expanding global problem. WHO's antenatal care guidelines include recommendations for counseling about healthy eating and keeping physically active during pregnancy to prevent excessive weight gain [10].

Conclusion

Although anemia is no longer a direct cause of maternal mortality, it may still complicate deaths due to hemorrhage. The burden of maternal anemia is high in Asia and Africa. Programmatic action for antenatal iron supplementation—and in endemic settings, for deworming and intermittent prophylaxis and treatment of malaria—needs to be heightened in many regions where the rates of maternal anemia are high. Calcium supplementation in populations with low intakes of dietary calcium can reduce the risk of pre-eclampsia, although the recommended high dosage for supplementation poses programmatic challenges and there are no large-scale programs providing daily calcium during pregnancy. Maternal vitamin A supplementation does not reduce the risk of pregnancy-related mortality; however, supplementation with vitamin A is recommended in areas where vitamin A deficiency is a severe public health problem to prevent night blindness, a condition associated with an increased risk of pregnancy-related mortality. Overall, there appears to be a role for nutrition interventions in improving maternal health and survival in low- and middle-income countries, but antenatal care programs with strong nutritional components that reach a high proportion of pregnancies need strengthening before a substantial impact can be achieved.

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Domestic Violence During Pregnancy and Its Effects on Birth Weight: Perspective from Nepal

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Keywords Abuse · Domestic violence · Intimate partner violence · Nutrition · Low birth weight

Key Points

- Domestic violence during pregnancy is reported as a significant public health problem especially in low income countries.
- The well-documented adverse consequences of violence during pregnancy on birth outcomes are miscarriage, a late entry into prenatal care, stillbirth, premature labor and birth, fetal injury, and low birth weight (LBW) of the baby.
- Birth weight is a major predictor of infant growth and survival, and it is linked with early mortality and morbidity of the baby.
- In the context of low income countries, among all causes, domestic violence during pregnancy is one of the main causes of low birth weight babies.
- The risks for domestic violence need to be identified, assessed, and protection should be implemented in all countries, especially during pregnancy.
- Elimination of domestic violence is one of the best strategies to have a healthy and well-nourished baby.

Introduction

Domestic violence (DV) is a major public health issue, especially in the context of a developing nation like Nepal. Women experience DV irrespective of their age, and this is associated with long-term adverse health outcomes, leading to increases in mortality and morbidity for the women. As defined by the World Health

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Organization (WHO) [1], DV comprises physical acts of violence within the family, including sexual coercion, physical threats, psychological abuse, and controlling actions such as imposing physical isolation and controlling access to information and services. These acts of violence are related to gender-based discrimination and are concerns for human rights throughout the world [2]. The Declaration on the Elimination of Violence Against Women, accepted by the United Nations General Assembly in 1993, defines violence against women as “any act of gender-based violence that results in, or is likely to result in, physical, sexual, or psychological harm or suffering to women, including threats of such acts, coercion or arbitrary deprivation of liberty, whether occurring in public or private life” [3]. DV consists of physical, sexual, and psychological violence occurring in the family, which is comprised of, but is not limited to, beating, sexual abuse, dowry-related violence, marital rape, female genital mutilation, and other harmful traditional practices. The violence against women is mainly a result of a traditionally unbalanced power distribution between men and women, leading to male domination and injustice to the woman, which ultimately prevents the development of the woman [3].

In Nepal, DV is considered an action or an absence of legitimate action, committed against members of the family, which gives rise to torture, pain, stress, suffering, and discrimination [4]. In 2009, the Ministry of Law and Justice in Nepal recognized DV as one form of gender-based violence and defined it as “any form of physical, mental, sexual, or economic harm perpetrated by one person on another with whom he or she has a family relationship, including acts of reprimand or emotional harm” [5]. DV is common during pregnancy, which has profound adverse effects not only on the maternal physical, psychological, reproductive, and sexual health but also on child health [6, 7]. Unlike the developed world, DV against women in Nepal is mostly committed by their partners and in-laws [8, 9]. Management of DV is a health service priority because it greatly affects the health of the women who are living in abusive relationships as well as their newly born babies [10, 11].

Forms of Domestic Violence

Physical Abuse

It is an abuse committed with the intention of giving physical torture which consists of slapping, beating, arms twisting, stabbing, strangling, burning, choking, kicking, threatening with sharp objects, killing, and other harmful traditional practices like female genital mutilation and widowhood abuse [12]. The chemical attacks, like acid attacks, are also one of the forms of physical abuse in DV. In acid attacks, acid is thrown at the victims, especially targeting their faces, causing burns, scarring skin, and sometimes even dissolving the bones [13, 14].

Sexual Abuse

Sexual abuse, according to WHO, is “any sexual act, attempt to obtain a sexual act, unwanted sexual comments or advances against a person’s sexuality using coercion, by any person regardless of their relationship to the victim” [15]. This includes forceful sex through threats, coercion, enforced prostitution, and any undesirable sexual act.

Psychological Abuse

Psychological abuse is comprised of acts intended to coerce or terrify the victims to undermine their self-esteem. These types of behaviors can be threats of rejection, confinement, surveillance, verbal abuse, mental torture, all attempts to control the victim’s autonomy [16].

Emotional Abuse

Emotional abuse includes anything that causes fear, embarrassment, continued pressure and taunts, loneliness, and humiliation. Emotional abuse can include threatening the victim with injury or harm, terrorizing them by saying that their life is in danger if they attempt to abandon the relationship, isolating them from other people, and humiliating them in public. The restriction of the victim’s access to financial resources, education, job, or health care is also an emotional abuse [17].

Economic Abuse

This is a type of violence when one intimate partner has control over the other partner’s access to economic belongings [18]. Acts like denial of funds and rightful income, exploitation, and control of access to whether health care, food, or necessities that can be accessed fall under economic abuse.

Magnitude of Domestic Violence

Globally, approximately one in every three women has experienced either physical and/or sexual, intimate partner or non-partner, violence in their lifetime. However, these acts of violence are overlooked most of the time in almost all societies of the world [19]. The

global estimate shows 13–61% of women between 15 and 49 years of age experience violence by their intimate partners [10]. A comprehensive picture of the patterns of intimate partner violence and sexual violence in low- and middle-income countries was presented by a WHO multinational study on women's health and domestic violence against women. This reflected that 15–71% of women had experienced physical and/or sexual violence by their intimate partner at some point in their lifespan [20].

Even after the country's 10-year-long internal battle has settled, each year, thousands of women are still facing violence in Nepal [21]. DV accounts for over 80% of the total incidence of violence against women in Nepal. In the majority of these cases, perpetrators are not strangers to the women but are part of their own family. This reflects that even the home is not a secure place for women [22]. A situation analysis of violence against women in Nepal revealed that 93% of women were exposed to mental and emotional torture, 82% were beaten, 30% were raped, 28% were forced into prostitution, and 64% reported polygamy [23].

Burden of Domestic Violence During Pregnancy

DV during pregnancy is present everywhere, regardless of economic status, social status, ethnicity, religion, urban or rural residence, and Nation. According to global statistics of the WHO Multinational Study, about 1–28% of women have experienced physical abuse during pregnancy [10]. In addition, a study of 10 different countries revealed that more than 5% of pregnant women were physically abused during at least one pregnancy in most of the settings [20]. Violence during pregnancy was 38% in Pakistan, with 24% comprised of emotional violence and 14% of sexual and physical violence; 5% of women had a new onset of violence during pregnancy, and 51% of the women were abused either prior to pregnancy or during pregnancy [24]. A study conducted among postnatal mothers in Nepal showed that DV during pregnancy was a frequent event, especially physical and emotional abuse. Additionally, 42% of these women also reported sexual abuse during pregnancy [25]. The study showed that, among 33% of the pregnant women who experienced DV during pregnancy, 23% reported physical, 13% reported sexual, and 47% reported psychological violence [26]. Although the figures show a wide variation in incidence, they indicate that DV among pregnant women is prevalent, and there is an emergent need for both understanding and developing appropriate interventions in the health care system to tackle DV during pregnancy.

Responsible Factors for Domestic Violence in the Context of the Developing Nation

In the low-income countries, many factors contribute to domestic violence: patriarchal society, discriminatory laws, conservative social practice, unforgiving religion, hostile traditions, economic dependency, lack of awareness, lack of skills,

unemployment, orthodox upbringing, dowry-related issues, and control over reproductive roles of women. The highly prevalent poverty and illiteracy worsen the situation. The case of domestic violence is considered a “family matter,” which usually does not involve external and legal interventions. Therefore, many cases remain unreported and hidden in the society [22].

The fear of various socio-cultural and traditional values plays a role in underreporting of DV. The fear of further abuse from husband and other family members, fear of ruining the family reputation, fear of being marginalized by the society, fear of being left alone if family relations break, lack of faith in the justice system, and affection towards husband and family despite abuse are some of the factors that make a woman hesitant to report DV [27]. These factors are frequently reported as major contributors for the rising prevalence of domestic violence in underdeveloped societies.

As most women in the developing nations depend upon their husbands and in-laws economically and emotionally, they become most vulnerable to violence in the family [26]. At the root of domestic violence in many developing countries are the dowry system, polygamy practices, women accused of being witches, and property conflict [22]. The preference for male children in the family also encourages domestic violence in pregnancy, as women who repeatedly give birth to female children often become victims of violence.

Consequences of Domestic Violence During Pregnancy

If women are abused during the perinatal period, it can have serious direct and indirect detrimental effects for both mothers and their infants. Infection, miscarriage, a late entry into prenatal care, stillbirth, premature labor and birth, fetal injury, low birth weight (LBW), and increased perinatal and neonatal death are some of the adverse health outcomes for DV during pregnancy [26, 28, 29]. DV during pregnancy is an attack on not just one, but two lives. DV during pregnancy not only causes LBW and stillbirth for babies, but it also predisposes the pregnant woman to depression and substance abuse [30]. In a prospective observational study, Yost et al. demonstrated that physical abuse during pregnancy is associated with neonatal death and verbal abuse is associated with LBW [31]. There are also the risks of abortion, miscarriage, stillbirth, preterm delivery, and low birth weight, which are increased by intimate partner violence in pregnancy. Intimate partner violence and sexual violence are both associated with increased vulnerability to HIV [19].

Because abuse has been regarded as a private matter by women, help is often not sought from health care providers following the violence. Also, awareness regarding gender-based violence was found to be very low among health care providers, which made it difficult for them to address the problem, and often results in more serious complications [26].

Other adverse health conditions associated with abuse during pregnancy include poor perinatal weight gain, anemia, antepartum bleeding, and infections. Since DV is associated with increased morbidity and mortality for both mother and growing

fetus, it is essential that evidence or suspicion of any kind of abuse during pregnancy should be systematically and routinely investigated [32]. Further evidence of abuse during pregnancy comes from a study in Egypt that reported significantly higher numbers of unfavorable pregnancy outcomes (miscarriage, preterm labor, and premature rupture of membrane) as well as detrimental effects to the fetus or neonates including fetal distress, fetal death, and LBW [33].

Domestic Violence and Low Birth Weight

LBW has been defined as a baby weight of less than 2500 g (5.5 pounds) at birth [34]. LBW of a baby can be due either to preterm birth (birth before 37 weeks of gestation) or due to restricted fetal (intrauterine) growth [35]. Worldwide, about 16% of the live births, or around 20 million infants per year, are LBW [36]. The incidence of LBW is less than 10% in the developed countries, whereas it is in the range of 15 to 30% of total births in developing countries [37]. In Nepal, around 14% babies were born LBW, as reported by a hospital-based study in 2013 [38], whereas in rural Nepal, up to 43% may be LBW due to micronutrient deficiencies [39]. There are various maternal, fetal, and medical factors related to the delivery of LBW babies. In the context of the developing world, among all causes, domestic violence during pregnancy is one of the main causes of LBW babies.

Various studies from different parts of the world have shown associations between physical violence and LBW or preterm births [40–42]. Some studies have found modest increases in risk of LBW among women who experienced intimate partner violence during pregnancy [43, 44]. Systematic reviews on this reveal that adverse outcomes like low birth weight were significantly higher among abused women [32]. Likewise, a study in Timor Leste showed that women reporting physical violence, compared to non-abused women, were more likely to use traditional contraceptive methods, report sexually transmitted infections, terminate a pregnancy, and have LBW infants [45]. Furthermore, a study in Iran showed that women who had a history of abuse by intimate partners had 1.9 increased risk of premature rupture of membranes and 2.9 increased risk of having an LBW baby than those women who did not experience any kind of violence from by their partners [46]. Similarly, the infants exposed to intimate partner violence (IPV) had a 31% increase in the odds of experiencing adverse outcomes compared with the infants without known IPV exposure. IPV exposure was associated with low birth weight and neonatal hospitalization [47]. Abuse during pregnancy was identified as a significant risk factor of LBW, low maternal weight gain, anemia, smoking, and use of alcohol or drugs, and it was associated with delayed prenatal care also [43].

The effects of psychological violence are less documented compared to physical violence. A study was carried out in the United States to assess the effects of psychological violence among the women who had no history of physical abuse. It showed that abuse that was limited to threatening the pregnant woman was associ-

ated with adverse birth outcomes. Women experiencing threats at any occasion during pregnancy had twice the risk of having LBW babies [48].

Abused women are more likely to have risk factors such as smoking, substance use, and poor obstetric history, all of which are associated with LBW. Indeed, poor obstetric history by itself is a known risk factor for LBW. Importantly, the harmful effects of smoking and substance use on the weight of the baby have been confirmed by many studies and are well documented [29, 49–54]. Substance abuse may be an underlying factor for domestic violence that results in LBW [55]. An Indian study identified that abused women were less likely to get antenatal care and they also did not receive home visits by health workers [56]. All of these factors are potential contributing factors for LBW.

In the context of Nepal, due to social tradition, women usually eat their meals only after feeding all the family members. This tradition reflects, in part, the historical status of women in Nepal's culture. Indeed, when these traditions and practices are shouldered on the pregnant woman, she often becomes a victim of domestic violence. Sometimes, there will be insufficient food left for the pregnant woman, and nutritional needs may not be met. If this repeatedly occurs during pregnancy, it can result in insufficient nutrition, leading to anemia and other kinds of malnutrition. This will directly affect the growing fetus of the abused mothers. It has been well documented throughout history that restriction or limited access to food coupled with lack of antenatal care account for LBW. Developing countries like Nepal have a very high burden of domestic violence during pregnancy, and intervention efforts to prevent and control it, are limited. On the other hand, LBW is also higher in Nepal due to other factors besides violence during pregnancy, highlighted previously in this chapter. It is a very pertinent issue to address, though studies focused on this issue are not concrete, due to limited resources and incomplete studies.

Prevention and Control Measures for Domestic Violence During Pregnancy

DV is increasing like an epidemic and is not only causing physical trauma to victims, but it is also responsible for multiple chronic diseases. Despite these facts, there is a considerable lag in dealing with these problems in health care settings of developing nations like Nepal. Many women are only getting care for injuries they present with, but hidden and unseen injuries and causes of those traumas are not addressed [57]. The risks for DV should be identified and protection against these risks needs to be identified, assessed, and implemented in all countries. Indeed, we must recognize and tackle the factors which are encouraging domestic violence, including IPV. Primary prevention strategies should focus on adolescents, to prevent and to protect them from all types of violence, including IPV. Alcohol is one of the main culprits often associated with DV, so the consumption of alcohol should be discouraged to lessen its harmful effects on violence and to help prevent violence.

Various modifiable risk factors should be targeted, such as reducing tolerance to violence, enhancing literacy among women, incorporating laws that address DV, and implementing gender-equitable policies [58].

Moreover, the prevalence of DV, its adverse health consequences, and lack of self-disclosure of violence makes it very important to screen women routinely in the health care settings. Importantly, information on support services and safety planning should also be offered during the health care visits [11]. Screening for domestic violence during pregnancy is an important tool for preventing maternal and fetal adverse effects that result from it. Antenatal care visits provide excellent opportunities to identify the pregnant women who are victims of violence. Antenatal care settings can many times be the only point of contact between an abused pregnant woman and health care settings. Additionally, these settings are also important for providing required health services, information, and support throughout the period of pregnancy.

The most important tested intervention is empowerment counselling for the abused pregnant women. This is the type of counselling which provides information about the violence, estimates the danger to pregnant women by identifying risks and preventive options, and helps formulate a safety plan in discussions with the victims. This tested and proven intervention has helped to reduce psychological and physical abuse leading to improvement of overall physical and mental health of women [59–61]. There is increasing evidence from the review of violence interventions that support interventions in domestic violence can be very beneficial. It is also evident that psychological interventions have a role in treating domestic violence. Since no trials of screening programs have focused on morbidity and mortality, more research is needed here [62]. According to the WHO, there should be efforts to address maternal and newborn health needs, and the programs and policies should include issues of violence against women, adolescent health, and HIV/AIDS as key elements to prevent these problems. The health care providers who are currently working in settings like family planning, prenatal, postnatal, and delivery care should be taught and trained regarding the adverse health consequences of domestic violence and appropriate response regarding care of victims. At the very least, adequate information regarding violence should be provided to health care providers so that they can be aware of the possibility of violence during the patient's perinatal period, especially in poor-resource settings [63]. These professionals should be trained to recognize signs of possible abuse and be instructed in reporting procedures.

Conclusion

To conclude, domestic violence is a social phenomenon. It is a global public health problem. Foremost, society should be well informed and educated regarding the issues of gender equality and violence. They should be made aware regarding the adverse effects of violence to mother and baby, and know the ways to reduce them. Women should be equally educated and empowered to resist violent behavior in the

family so that they will be able to raise their voice against violence and fight for their right. Only if a mother can take care of herself and protect herself against violence, will she be able to care for the growing fetus in her womb properly. This is very essential for meeting the demands of the growing fetus and mitigating the problems of LBW due to violence. Elimination of violence is the best strategy to having a healthy and well-nourished baby.

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