Nutrition and Health
Series Editor: Adrianne Bendich · Connie W. Bales

Rajkumar Rajendram
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Vinood B. Patel *Editors*

Diet, Nutrition, and Fetal Programming

Humana Press

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Nutrition and Health
ISBN 978-3-319-60287-5 ISBN 978-3-319-60289-9 (eBook)
DOI 10.1007/978-3-319-60289-9

Library of Congress Control Number: 2017943959

Printed on acid-free paper

This Humana Press imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

The exposure of the fetus to adverse nutritional conditions has long-term effects, which can then extend into adulthood. These include increased rates of cardiovascular disease, diabetes, and metabolic syndrome. Some cancer rates are also reported to increase, and there is evidence that neurological deficiencies occur in adults who were previously exposed to nutritional inadequacies in utero.

There are complex interrelationships between these aforementioned conditions and their causative mechanisms. These include deficient receptor-post-receptor signaling, endocrine imbalance, defective DNA methylation, and alterations in other pathways. It is highly probable that many scientific processes are intertwined in a multifaceted way, impacting on the fetus and then the adult. Understanding these causative events, effects, and long-term outcomes means that there are windows of opportunity throughout the life cycle where diet and nutrition can be monitored, controlled, or rectified where necessary. However, presently there is no coherent text that reviews the wide-ranging effects of adverse fetal nutrition and beyond. This is addressed in the present book *Diet, Nutrition, and Fetal Programming*, which has over 40 detailed chapters ranging from molecular biochemistry to epidemiology. Coverage includes international aspects, ethnicity, famines, malnutrition (general and specific), maternal stress, fetal growth restriction, birth weights, biomarkers, myogenesis, fibrogenesis, adipogenesis, gametogenesis, nephrogenesis, food preferences, physiology, immunology, endocrinology, neuroendocrinology, hepatology, the pancreas, the cardiovascular system, obesity, metabolic syndrome, neuropsychiatric disorders, cognition, sleep, food preferences, high-fat diets, junk food diets, fish and fish oil, n-3 fatty acids, taurine, caffeine, telomere biology, knockouts, microRNAs, and many other areas too numerous to list here.

Contributors are authors of international and national standing, leaders in the field, and trendsetters. Emerging fields of science and important discoveries are also incorporated in *Diet, Nutrition, and Fetal Programming*.

This book is designed for nutritionists and dietitians, public health scientists, medical doctors, midwives, obstetricians, pediatricians, epidemiologists, health-care professionals of various disciplines, and policy makers. It is designed for teachers and lecturers, undergraduates and graduates, researchers, and professors.

London, UK

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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 patients' 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 editors, 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 and emerging 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.

Diet, Nutrition, and Fetal Programming, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, is a most timely and very welcome addition to the Nutrition and Health Series and fully exemplifies the series' goals. The term "fetal programming" was first proposed by Drs. David Barker and Charles N. Hales in 2001 following their in-depth examination of epidemiological data that pointed to poor maternal nutrition during fetal development increasing the risk of a number of chronic diseases in the offspring over their lifetime. Subsequently, the topic of fetal programming and the mechanisms that result in this phenomenon has been linked to another field of research called epigenetics; this volume brings together these two fields, and thus an objective, up-to-date volume on these topics is very timely. There is new attention being given to developmental biology, including embryology, that has contributed to the fetal programming hypothesis, also known as the fetal origins hypothesis, or the developmental origins of health and disease (DOHaD). The hypothesis suggests that conditions very early in development in utero can, through epigenesis, leave lasting alterations on the fetus that may affect its susceptibility to diseases with onsets that may occur many decades later.

The editors of this volume are experts in their respective fields and represent the medical profession as well as the academic research community. Dr. Rajkumar Rajendram is an intensive care physician, anesthetist, and perioperative physician. He was trained in general medicine and intensive care in Oxford, and he attained membership in the Royal College of Physicians (MRCP) in 2004. Dr. Rajendram then trained in anesthesia and intensive care in the Central School of Anesthesia, London Deanery, and became a fellow of the Royal College of Anaesthetists (FRCA) in 2009. He is one of the first intensivists to become a fellow of the faculty of intensive care medicine (FFICM). Dr. Rajendram

recognized that nutritional support was a fundamental aspect of critical care, and, as a visiting lecturer in the Nutritional Sciences Research Division of King's College London, he has published over 150 textbook chapters, review articles, peer-reviewed papers, and abstracts. Professor Victor R. Preedy is a senior member of King's College London where he is a professor of nutritional biochemistry. He is also director of the Genomics Centre and a member of the School of Medicine. He is a member of the Royal College of Pathologists and a fellow of the Royal Society of Biology, the Royal College of Pathologists, the Royal Society for Public Health, and, in 2012, the Royal Society of Chemistry. Dr. Vinood B. Patel is a senior lecturer in clinical biochemistry at the University of Westminster and honorary fellow at King's College London. Dr. Patel obtained his degree in pharmacology from the University of Portsmouth and his Ph.D. in protein metabolism from King's College London and completed postdoctoral research at Wake Forest University School of Medicine. Dr. Patel is a recognized leader in alcohol research and was involved in several NIH-funded biomedical grants related to alcoholic liver disease. Dr. Patel has edited biomedical books in the area of nutrition and health and disease prevention and has published over 160 articles.

The 42 chapters within this clinically important as well as basic research-oriented volume provide the reader with a comprehensive examination of the growing acknowledgment that environmental exposures during the fetal period can affect the fetus' health throughout life. The global prevalence and consequences of maternal malnutrition and primary fetal environmental exposure affect the health of the mother, the length of the pregnancy, as well as the health and growth of the fetus. One critical example, which is captured in the recent book edited by this volume's editors, entitled *Nutrition and Diet in Maternal Diabetes*, shows that gestational diabetes (GDM), and in fact, any maternal hyperglycemia, is associated with complications such as increased birth weight, macrosomia, cesarean birth, and preterm birth. Women who are diagnosed with GDM have a significantly increased risk of developing type 2 diabetes within 10 years, and the offspring also have an increased risk of diabetes. GDM also increases the risk of preeclampsia and other adverse birth outcomes.

This comprehensive volume is organized into eight sections that include chapters on general considerations of maternal diet and health and the fetus followed by an in-depth examination of the effects of maternal undernutrition and protein restriction. Part III reviews the effects of obesity, high-fat diet, and junk food on fetal outcomes, and Part IV includes chapters on specific dietary components including fish and its fatty acids, folate, taurine, and tryptophan. The fifth part contains chapters that look at data on fetal programming effects in different countries, and the sixth part looks at the data with respect to effects seen in childhood and adolescence. New research that describes the biochemical and genetic mechanisms involved in fetal programming is discussed in the seventh part, and the last part provides readers with relevant resources.

Part I: Maternal Diet, Health, and the Fetus – General Considerations

The first section, containing six chapters, begins with two chapters that examine associations between maternal stress, nutritional status, and fetal responses to these critical environmental factors. The first chapter informs us that there is a large literature and active research area that suggests that certain exposures in the prenatal period may have lasting effects on the behavior and physiology of the child. Prenatal diet and nutrition is one area of focus, and another area of research includes the examination of the role of prenatal stress and its effects on fetal and infant health and development. Chapter 1 describes the well-researched historical events where both maternal stress and poor nutrition occurred together. In the Dutch Hunger Winter of 1944–1945, the women who were pregnant during that period have been followed for many decades to understand the long-term effects on their physiology and that of subsequent generations. Gestational exposure to the Dutch famine has been linked to psychological and metabolic changes in the offspring later in life. Similar findings have been reported in studies of

pregnancies during the Great Leap Forward Famine in China from 1959 to 1961. In both cases, the physiological changes observed in offspring are frequently attributed to the substantial caloric and micronutrient deficiencies that fetuses experienced during these natural experiments. However, we learn that, in addition to nutritional status, maternal stress and stress physiology are an important coexisting factor. The constant military threat, limited food rations, displacement, and general upheaval would have placed a serious psychological burden on the pregnant woman and affected fetal programming. The chapter provides many examples where low socioeconomic status is adversely associated with nutritionally poor diets, food insecurity, and heightened psychosocial stress, and the authors suggest that poor diet may serve as a proxy for stress exposure and vice versa. Poor diet and nutritional deficiencies may confound the negative effects of exposure to psychosocial stress but may also interact with or modify the effects of stress. Chapter 2 examines the effects of modern diets and maternal nutritional status on the fetus' ability to cope with stressful environments during growth and maturation and into adulthood. Poor prenatal metabolic/nutritional environments can lead to altered fetal programming of neural circuitry that may result in adverse adult stress responses The chapter reviews the effects of epigenetic alterations during fetal development and the altered roles of the limbic system and the hypothalamic-pituitary-adrenal (HPA) axis. The strong relationship between stress and heart disease, high blood pressure, and the development of affective disorders, such as anxiety and depression, and the new data on the effects of maternal obesity are also examined.

Chapter 3 links fetal nutritional status with brain development and cognition as these can be modified by nutrient and gene interactions through epigenetics. Cognition refers to the mental ability to process and retrieve new information using functions which include attention, memory, thinking, learning, and perception. DNA methylation is an epigenetic mechanism that requires dietary nutrients, including folate, vitamin B12, and vitamin B6, that are needed for biochemical reactions whereby methyl groups are donated to DNA nucleotides and thus modify the regulation of gene expression. The chapter, which includes nearly 100 relevant references and 7 informative figures and tables, reviews the epigenetic modifications that mediate DNA methylation, disrupt cell-signaling molecules, and increase neurotoxins in the brain which may adversely affect cognitive function.

The next three chapters examine the effects of maternal nutritional status before and during pregnancy on fetal programming. Chapter 4 looks at the importance of exercise, normal maternal body mass index (BMI), and strength on the development of the fetus as well as the beneficial effects of exercise on maternal health before, during, and after pregnancy. Physical activity and cardiorespiratory fitness both produce significant cardiovascular health benefits. During pregnancy, regular physical activity has been shown to help maintain physical fitness, decrease gestational weight gain, and reduce the risk of developing gestational diabetes and potentially preeclampsia. The chapter examines the research linking infant birth weight and subsequent child weight from exercising mothers versus sedentary mothers. Chapter 5 describes the factors that influence the development of fetal growth retardation. We learn that fetal growth restriction (FGR) affects up to 10% of live-born infants worldwide. Using global norms, approximately 10% of term infants in developed countries are small for gestational age (SGA) compared to 23% of term infants in developing countries. Normal fetal growth is a multifactorial process that is dependent on genetic background, endocrine milieu, and appropriate placental function. FGR is defined as the failure of a fetus to reach its growth potential according to gestational age and gender. FGR is a risk factor for hypertension, hyperlipidemia, coronary heart disease, and diabetes mellitus in adulthood. The chapter reviews the maternal factors, such as age, alcohol consumption, smoking, diastolic blood pressure, and diet, that strongly modify embryonic growth trajectories early in pregnancy. First trimester embryonic growth has been related to subsequent fetal growth in the second and third trimesters of pregnancy, as well as to adverse pregnancy outcomes including preterm delivery and SGA infants. With regard to fetal programming and epigenetic factors, the genome-wide differential DNA methylation of all known imprinted genes in normal and FGR placentas has been analyzed. The data point to differential methylation changes that occur in FGR throughout the genomic regions, including genes actively expressed in the placenta. Analyses

of genome-wide methylation patterns in normal, SGA, and FGR human placentas show that certain methylation patterns are associated with infant growth. The final chapter in this section examines the importance of fetal brain sensitivity to insulin. Chapter 6 describes the use of a new technology, fetal magnetoencephalography (fMEG), which is a noninvasive technique which enables a direct measurement of fetal neuronal activity in utero. Maternal postprandial exposure to insulin showed a direct effect on fetal brain responses. This is an important new area of fetal programming research.

Part II: Maternal Undernutrition and Protein Restriction – Effects on Fetus

Part II also contains six chapters, and the first three chapters examine the effects of overall maternal undernutrition, and the last three chapters look at specific protein restriction and the effects on fetal programming. Chapters 7, 8, and 9 review the importance of the cascade of events that follow fetal exposure to maternal undernutrition. Undernutrition can alter both maternal and fetal concentrations of many hormones including insulin, insulin-like growth factors, thyroid hormones, leptin, cortisol, and glucocorticoids. Because some maternal hormones can cross the placenta, the fetal endocrine response to undernutrition reflects the activity of both maternal and fetal endocrine glands, as reviewed in Chap. 7. Reduction in availability of nutrients during fetal development programs the endocrine pancreas and insulin-sensitive tissues, and the malnourished offspring may be born with defects in their β-cell and insulin-sensitive tissues. Chapter 8 continues to explore the effects of maternal undernutrition during critical periods of fetal development that affects the development of visceral obesity later in life. Prenatal undernutrition particularly during the later stages of gestation can induce differential signals in adipose tissue in such a way that lipid storing capacity is increased. The consequent increased adiposity can result in elevated inflammatory responses and associated metabolic disturbances during gestation and throughout the infant's lifespan. Chapter 9 examines the direct epigenetic mechanisms underlying the aberrant expression of hepatic genes in malnourished offspring that persist into adulthood. The neonatal liver is sensitive to oxidative stress associated with maternal undernutrition and this can result in epigenetic changes. Thus the liver is another tissue that is adversely affected by maternal undernutrition and can also result in metabolic dysfunctions that last throughout the lifetime of the child.

Chapters 10, 11, and 12 concentrate on the effects of maternal protein malnutrition on fetal programming of the heart, kidney, and brain. Protein malnutrition in utero is strongly associated with intrauterine growth retardation. Reduced growth in fetal life and small birth weight, along with accelerated growth in childhood, are associated with a greater risk of coronary heart disease in adult life and increased risk of hypertension and type 2 diabetes. Chapter 10 reviews the studies that indicate that exposure to low protein in utero adversely affects heart cell number (cardiomyocyte number). Additionally, neonate's fetal growth restriction is associated with an increase in aortic intima-media thickness, which can hinder the movement of blood through the heart. The chapter reviews the data from animal models and human survey studies that show an increased risk of cardiovascular disease and direct heart effects that are associated with epigenetic changes that were initiated under an environment of maternal protein malnutrition. Related to the changes in the cardiovascular system are the effects of low maternal protein on the kidneys. Chapter 11 provides compelling evidence of the association of maternal low-protein ingestion with low nephron number in the fetus that is directly related to the development of arterial hypertension and kidney dysfunction in adulthood and aging. Chapter 12 looks at the effects of maternal protein deficiency on the brain. Protein restriction during the prenatal period that is followed by low birth weight is associated with the development of neurological and psychiatric diseases. Substantial evidence from studies in animals and in humans shows that gestational and early postnatal dietary protein restriction influence cognitive performance and can lead to behavioral abnormalities and disorders in memory and learning. The chapter clearly explains

that, in humans, the greatest time period of vulnerability of the brain and other components of the CNS occurs from the second third of pregnancy through the first year of life; the peak of brain growth occurs during pregnancy, and over 25% of the brain's weight at birth is attained during this time period. Thus, maternal protein deficiency can have an irreversible impact on the brain development of the fetus.

Part III: Effects of Obesity, High-Fat Diet, and Junk Food on Fetal Outcomes

As indicated in earlier chapters, there is a growing awareness of the negative impact of maternal obesity and overweight on fetal programming. The six chapters in Part III examine some of these impacts and the effects of certain dietary components on fetal health. The first two chapters, Chaps. 13 and 14, provide an overview of the effects of obesity during pregnancy. Maternal obesity increases the risk of many adverse events including, but not limited to, thromboembolic complications, gestational diabetes, hypertension, maternal hemorrhage, and infection. There is also increased risk for spontaneous miscarriage, fetal malformations, fetal macrosomia, stillbirth, and preterm delivery. Other complications that are associated with maternal obesity are reviewed including greater need for cesarean delivery and respiratory risks with anesthesia. Chapter 13 also examines the potential opportunities to reduce these risks with diet, exercise, and bariatric surgery prior to pregnancy and reviews the inconsistent data from the USA and UK. With regard to fetal programming, maternal obesity is associated with infants who have an increased risk of overweight and obesity, insulin resistance, and diabetes in childhood and adulthood. Chapter 14 describes the molecular effects of maternal obesity and its many consequences. Maternal obesity further increases inflammatory cytokines, insulin, and lipids compared to that found in normal pregnancy. Maternal obesity also affects placental vascularity, metabolism, and/or nutrient transport function leading to alterations in fetal growth, metabolism, and organ development. Maternal obesity is linked to an increased incidence of offspring metabolic dysregulation including obesity, hyperglycemia, hyperinsulinemia, hyperlipidemia, type 2 diabetes, and cardiovascular disease. These changes are due to gene-environment interactions in utero which produce epigenetically induced changes in gene expression. The chapter reviews the current research using small and large animal models including sheep that suggest that maternal obesity can initiate fetal programming events that have adverse effects on her offspring as well as her offspring's children.

Chapter 15 reviews the role of ethnicity on the development of maternal obesity and its consequences. The chapter tabulates the prevalence rates of many chronic diseases and links these to the risk of maternal obesity, gestational diabetes, and many of the other adverse effects noted above. The chapter indicates that cardiovascular disease, diabetes, and asthma all occur at differing prevalence rates among people of different ethnicities. Coronary artery disease is up to two times more common among South Asians compared to Europeans, and type 2 diabetes is almost four times more common in South Asians. Diabetes is also more common in Filipinos, Hispanics, Chinese, Middle Easterners, North Africans, South and Central Americans, and people from the western Pacific region than seen in Europeans. Black individuals have a consistently higher prevalence of hypertension, diabetes, and stroke compared to white populations. The authors note that the etiology of stroke differs according to ethnicity. Western populations are more likely to experience emboli originating from the heart or extracranial large arteries compared to Asian populations where small-vessel occlusion or intracranial atherosclerosis occurs more frequently. Emerging evidence suggests that the associations between obesity and adverse pregnancy outcomes may also be additive in some ethnicities. Obesity is a stronger risk factor for maternal gestational diabetes in Asian compared to Caucasian women. Obesity is also more strongly associated with preeclampsia in Latino compared to Caucasian women. This unique

chapter, with 100 important references and 4 excellent figures, provides valuable data to help in assessing the role of fetal programming balanced against ethnic and country environmental factors.

Chapter 16 looks at the molecular mechanisms involved in the liver's metabolism during fetal development and points out the main and recent findings on the role of microRNAs in modulating hepatic metabolism in the offspring of obese mothers or mothers consuming a high-fat diet during important periods of fetal and neonatal development including pregnancy and lactation. The liver regulates many vital physiological processes. The functions are reviewed including processing nutrients after intestinal absorption, synthesis and excretion of metabolites, detoxification of xenobiotics, modulation of lipid and glucose metabolism, and energy homeostasis. The eight figures and tables help to explain the findings from the recent animal model studies.

Chapters 17 and 18 describe the findings from animal models that examine the mechanism and potential for diets that are high in fats and carbohydrates to affect fetal programming events and lifelong outcomes. Chapter 17 reviews the effects of maternal high-fat diet during gestation and/or lactation on the mother and on stress-related neurodevelopment and behavior in her offspring. The chapter includes descriptions of animal models using maternal high-fat diet exposure and their impacts on physiological, behavioral, and epigenetic outcomes observed in offspring. Chapter 18 looks at the impact of maternal junk food diets during pregnancy and/or lactation on the developing offspring in well-described animal models. Maternal junk food diets have been shown to result in increased fat mass and heighted preference for fat and sugar intake through the offspring's life course. More recent studies focus on defining the biological mechanisms driving these effects and have identified the developing fat cell, or adipocyte, and the central neural network that regulates the response to reward as major targets. It has been demonstrated that maternal junk food intake results in an activation of lipogenic pathways in fetal and neonatal fat depots, which leads to early accumulation of excess fat tissue and persistently increases the capacity of the fat depots to store fat. In parallel, exposure to maternal junk food diets also leads to permanent alterations in the structure and function of the reward pathways in the brain that appear to differ between males and females.

Part IV: Specific Dietary Components

Seven chapters review specific components of the maternal diet including fish; fish oil; n-3 fatty acids; folate, vitamin B12, choline, and other methyl donors; taurine; tryptophan; and caffeine. Chapters 19, 20, and 21 look at a number of the functions that have been attributed to the consumption of fish that are the major source of long-chain n-3 fatty acids. Chapter 19 presents a balanced perspective on the plusses and minuses of fish consumption during pregnancy and provides the reader with four comprehensive tables that outline the relevant studies. We learn that fish is the primary dietary source of n-3 long-chain polyunsaturated fatty acids and a rich source of protein, selenium, iodine, and vitamin D but is also a major source of exposure to methylmercury (MeHg) and other environmental pollutants. In utero exposure to nutrients and toxicants found in the same fish might act on the exact same end points with opposite effects. Overall, evidence on the association of maternal fish consumption during pregnancy with child health outcomes has been largely inconsistent. However, in 2014, the US FDA and Environmental Protection Agency updated their advice on fish consumption for women of childbearing age, encouraging women who are pregnant, breastfeeding, or likely to become pregnant to consume more fish but no more than three servings per week to limit fetal exposure to MeHg. The European Food Safety Authority (EFSA) has also reported recently that the benefits from fish consumption of up to three to four servings per week during pregnancy could outweigh the risks associated with MeHg exposure. Chapter 19 looks at fish oil supplementation during pregnancy and outcomes. The supplements contain no or very low levels of the contaminants found in whole fish. The chapter describes the evidence that fatty acids may alter the epigenome, although studies in healthy humans

and experiments in animals have shown variable long-term metabolic and gene function responses to fish oil supplementation during pregnancy. Detailed descriptions of models showing the potential effects of fish oil on epigenetic alterations of RNAs especially with regard to insulin resistance are included. Chapter 20 describes the clinical data that show that n-3 fatty acid consumption in adults reduces systolic and diastolic blood pressure as well as resting heart rate. The reduced heart rate is thought to be due to direct effects on cardiac electrophysiology as well as indirect pathways involving the heart muscle. The n-3 fatty acids also may be involved in programming the fetus' blood pressure as maternal docosahexaenoic acid (DHA), a major long-chain n-3 fatty acid, is readily transferred via the placenta to the fetus and later is an important component of breast milk and is rapidly accumulated in the synapses during fetal development and early postnatal life. DHA comprises 30% of the phospholipid fatty acids within the brain's cortex and 15% within the hypothalamus, a key brain center that controls blood pressure. Relevant survey and intervention studies are tabulated. Chapter 21 reviews the experimental and clinical studies that point to the intrauterine environment as a predictor of neonatal blood pressure. Underlying mechanisms include alterations in fetal kidney function and damage to the nephron's vasculature. Maternal malnutrition can reduce nitric oxide-dependent vasodilatation and microvascular density as well as total peripheral resistance. The n-3 fatty acids have the potential to lower blood pressure in offspring of supplemented mothers during pregnancy and lactation. The laboratory animal studies as well as human survey and intervention studies are discussed and tabulated.

Chapter 22 looks closely at the role of one carbon metabolism, maternal deficiencies, and fetal programming via DNA methylation and regulation of gene expression. This complex metabolic network is regulated by a number of genes and requires micronutrients including folate; vitamins B12, B6, and B2; and choline. Folate, vitamin B12, and choline are methyl donors, which are involved in the synthesis of the precursor of S-adenosylmethionine, the universal donor of methyl groups needed for DNA methylation. Deficiencies in these nutrients can alter the epigenetic regulation of gene expression. The chapter highlights animal studies, human association studies, and interventional studies and finds consistent evidence that maternal status of nutrients required for efficient one carbon metabolism affects many metabolic factors in the offspring including low B12 and increased homocysteine related to adverse cardiovascular outcomes, low folate status and reduced cognitive performance in offspring, and low folate status and significant increased risk of neural tube defects.

The next two chapters examine the effects of two different amino acids, taurine and tryptophan. We learn in Chap. 23 that taurine is a sulfur-containing amino acid that has multiple cellular and molecular functions mainly associated with the conjugation of bile acids, cellular osmoregulation, energy storage, the absorption of intestinal fat, glucose metabolism, antioxidant function, neurotransmission, and cytoprotective effects during cell development and survival. In adults, taurine is nonessential and is synthesized in the liver and adipose tissue from ingested methionine and cysteine. In humans, taurine is the most abundant amino acid found in the developing brain, skeletal muscle, liver, spinal cord, retina, pancreas, heart, white blood cells, platelets, and placenta and is found in breast milk as well. The fetus cannot synthesize taurine and maternal taurine deficiency, either from protein restriction or, as seen in the animal models described, by maternal diabetes, affects fetal development of the endocrine pancreas. The pancreatic changes during fetal and neonatal life increase the risk of the offspring developing diabetes, obesity, and hypertension. The chapter includes 92 relevant references and important figures that help the reader understand the findings in this unique chapter. Chapter 24 describes the role of nutrition, with emphasis on tryptophan, in fetal development. Tryptophan is an essential amino acid and therefore cannot be synthesized within the body and must be consumed as part of the normal dietary intake. Tryptophan is the precursor of serotonin, a neurotransmitter synthesized mainly in the central nervous system and, as discussed below, also in the endocrine pancreas. Tryptophan is involved in the regulation of several body functions including the growth and maturation of specific developing brain regions and secretion of hormones such as growth hormone and gonadotropins.

The final chapter in this part, Chap. 25, discusses the data linking caffeine consumption with fetal programming. Caffeine is a methylxanthine alkaloid that is widely present in coffee, tea, soft drinks, foods, and some prescription drugs. Many studies have reported that caffeine ingestion can enhance mood and alertness, awareness, attention, and reaction time. The chapter, containing over 120 references, objectively reviews the correlation between prenatal caffeine ingestion and intrauterine growth retardation (IUGR) and agrees that the data are inconsistent and many human survey findings remain controversial. Different doses of caffeine ingested, clinically insignificant magnitudes of IUGR, and other confounding factors including the age and health condition of the pregnant woman may be possible reasons for the conflicting results. Therefore, the chapter concentrates on data from animal experiments that suggest an association between certain adverse developmental events and prenatal caffeine ingestion.

Part V: International Aspects and Policies

Five chapters examine the contrasting effects of maternal malnutrition in different countries around the world including India and Africa as well as Ireland and Japan. Chapter 26 posits that famine or severe maternal malnutrition does not provide molecular evidence that epigenetic changes caused by starvation or other environmental influences are part of an ordered predictable (or programmed) response. The environmental influence could cause random and nonspecific stochastic effects on individual cells within the organism. Somatic and germ cells with favorable epigenotypes and/or genotypes could then be selected on the basis of their ability to survive and proliferate in the mother in the prevailing negative environmental circumstances. The chapter reviews the survey data linking famines in Europe and China with adverse health outcomes in males born during these times and examines data from animal studies where embryonic loss can be documented. However, at present, there are no definitive findings of an effect on the genome of the offspring born during a famine and limited data of an epigenetic effect.

Chapter 27 describes strategies reducing pregnancy risks in malnourished women in India. The chapter authors emphasize that appropriate nutrition, in particular, during adolescence, pregnancy, and lactation, affects the growth and development of the fetus, thereby translating into healthy statistics for birth outcomes, childhood health, and long-term health and economic benefits, and concentrate their review on the dual issues of under- and overnutrition seen in today's population of Indian women of childbearing potential. According to the Indian National Family Health Survey in 2005–2006, the prevalence of undernourished women, based on a body mass index (BMI) less than 18.5 kg/m^2, was 36.5%, and nearly half of the women had a BMI less than 17 kg/m^2, pointing to the widespread prevalence of moderate to severe undernutrition. Moreover, the prevalence of anemia among women in their childbearing years, aged 15–49 years, ranges from 32.7% to 76.3% that is indicative of the wide variation across states in India. The overall prevalence of overweight women aged 15–49 years was 13%, with about 3% falling in the obese category (BMI greater than 30 kg/m^2). The chapter reviews over 40 years of national programs designed to provide key nutrients to malnourished women especially during pregnancy, taking into account cultural changes associated with urbanization and the research into fetal programming. Chapter 28 sensitively reviews the nutritional status of women in many of Africa's nations. Africa, like India, is also experiencing the paradox of escalating maternal hunger and obesity. The consequence is the birth of small, low-birth weight (LBW) neonates as well as large babies with fetal macrosomia. However, unlike India, the authors note that Africa is saddled with food insecurity arising from huge humanitarian crises, refugee and poverty situations, and emerging African cities where there is a growing risk of maternal obesity with micronutrient deficiencies as a result of overconsumption of fast foods. Babies adapt to maternal undernutrition by slowing their growth velocity, which leads to LBW, whereas babies of obese mothers adjust in favor

of high growth trajectory giving rise to macrosomia. Other critical issues include maternal infection with HIV, malaria, and other common infectious agents that can adversely affect fetal growth directly or through placental infection. Major factors that affect food availability include political instabilities and wars, poverty, lack of electricity and refrigeration, as well as sanitation issues, cultural factors including religions and tribal factors, and rural versus city life; all of these and other relevant factors are considered within the chapter.

Chapter 29 objectively examines the current status of birth outcomes in Ireland and describes the major nutrition-related issues of current public health concern; the chapter includes six informative tables and figure. The critical issues include maternal obesity; excessive gestational weight gain; increased risk of gestational diabetes; inadequate intake of folate before and during pregnancy; lower than recommended intakes of vitamin D, iron, and long-chain polyunsaturated acids; and higher than recommended intake of alcohol prior to and during pregnancy. For each issue, the chapter describes the extent of the problem and any Irish-based interventions to improve the situation. National policies and clinical guidelines relating to each issue are also discussed. Chapter 30 objectively describes current issues in Japan. In contrast to Ireland, female obesity does not appear to be a significant issue during pregnancy in Japan. However, over the last 20 years, the proportion of low-birth weight infants in Japan has exceeded that of other developed countries. The desire of young Japanese women to be thin has been identified as an underlying cause. The chapter reports on the literature review of 50 relevant Japanese studies of pregnancy outcomes. A recent review in 2014 reported that the proportion of LBW (1500–2499 g) babies in Japan is consistently increasing. The National Health Survey in 2013 reported that both men and women at childbearing age (20–39 years) had a higher energy intake but a lower vitamin intake than in 2003. These data substantiate the increasing concern about the components of the diets of teenagers especially young women and highlight the importance of education about nutrition and health in early life. Several vitamin deficiencies are reviewed, and there is an in-depth review of studies involving exposure to mercury, PCBs, and other contaminants and their effects on pregnancy outcomes. Research on fetal programming in Japanese populations is in its infancy.

Part VI: Effects of Fetal Programming in Childhood and Adulthood

Five chapters examine specific aspects of fetal programming during childhood and beyond. Chapter 31 reviews the classical growth curves that are based on population studies of gestational age and gender and have been in use for many decades. The chapter then looks at the more recent, new customized growth criteria that incorporate variables, such as mother's height, parity, and initial weight, in addition to gender and gestational age, with the aim of better assessing a child's true growth potential. However, we learn that the baby's gender and mother's parity, height, weight, and ethnicity can predict only about 20–35% of the neonate's birth weight. Since the 1990s, a number of customized growth curves have been developed including certain maternal biomarkers that appear to be better predictors of adverse fetal growth and development. Chapter 32 looks at the recent epidemiological and animal studies that have examined the effects of overnutrition during fetal development and subsequent offspring's risk of developing aspects of the metabolic syndrome including elevated blood pressure, hyperglycemia and excess adiposity, impaired insulin signaling and resistance, glucose intolerance, and hypertriglyceridemia. The chapter examines the associations between both under- and overnutrition during fetal development as well as maternal factors including gestational diabetes and subsequent metabolic diseases that may go beyond the first generation exposed to hyperglycemia in pregnancy. The chapter delves into the specific eating habits of children undernourished in utero and at increased risk for metabolic diseases. Chapter 33 examines both clinical and experimental data that indicate that exposure to fetal undernutrition may have programming effects on feeding

preferences and behaviors that can contribute to the development of diseases. Individuals born small for gestational age (SGA) have preferences toward highly caloric and palatable foods such as carbohydrates and fats and display altered eating behaviors. These behaviors can lead to small but persistent nutrient imbalances across the lifespan, increasing the risk of metabolic diseases in adult life. The chapter includes a detailed description of the parts of the brain that are involved in food choices. The hypothalamus is the central brain region involved in regulating appetite and guaranteeing the energy intake needed for survival. The pleasurable sensations associated with the intake of highly palatable foods that are usually rich in sugar and fat are controlled mostly by the mesocorticolimbic dopaminergic pathway, with inputs from other brain systems such as the opioids. Impulse control and decision-making processes, largely based on the prefrontal cortex, are important determinants of food choices. Adding to this complexity, the brain areas are enriched with receptors for peripheral hormones involved in energy intake and expenditure, such as insulin, leptin, and ghrelin, and therefore signals from the gastrointestinal tract and adipose tissue depots are able to modulate the central responses from the brain in a finely regulated fashion.

Chapter 34 provides a careful review of the relatively new data linking fetal undernutrition with alterations in bone and muscle structure and function. In the 1990s, researchers developed the theory that changes in early stages of bone development due to starvation and reduced provision of nutrition, minerals, and growth factors would lead to bone metabolic changes in adults. This theory was further elaborated in the following decade, when the pathogenesis of osteoporosis was described and a role was attributed to intrauterine programming, confirming the earlier analysis of growth in infancy and bone mass in adult life. Important connections were shown to exist between maternal life style, maternal body mass, and vitamin D dependence, which could predict bone mass in offspring and the risk of future fracture. In 2015, research confirmed that bone metabolic aberrations resulted from intrauterine macro- and micro-nutritional deprivation. The nine tables and figures provide evidence of the role of overall nutrition, specific nutrients, and timing of fetal exposures on bone development that affects bone growth and loss throughout life and may affect the next generation's bones as well.

Chapter 35 describes the unique consequences of fetal growth retardation (FGR) on the development of sleep patterns that begin in utero and continue to be programmed through early childhood. FGR is associated with increased risks of preterm birth, perinatal mortality, and short- and long-term morbidity. FGR is associated with a high risk of neurodevelopmental impairment, including motor and sensory deficits, cognitive and learning difficulties, and cerebral palsy. Underpinning these deficits, FGR is associated with altered brain structure with reduced total brain and cortical gray matter volume. Poor sleep in childhood is related to neurocognitive impairment and in adulthood to metabolic disorders and cardiovascular disease. The chapter examines the development of the phases of sleep from its origins in the fetus though childhood and the relevance of sleep patterns to cognition and other brain functions.

Part VII: Mechanisms of Programming

The final part of this comprehensive volume, containing six chapters, reviews the major laboratory studies, including in vivo models and in vitro findings that delve into the genetic and other molecular factors that are considered to have key roles in fetal programming involved in the development of metabolic diseases. Chapter 36 describes the new high-throughput experimental and computational technologies from the fields of genomics, transcriptomics, proteomics, and metabolomics and how these methodologies may provide potential predictive biomarkers of abnormal birth weight and also biomarkers of maternal diseases that can affect neonatal birth weight. This technical chapter describes the data linking specific genes with abnormal birth weight: IGF-I, IGF-II, ADCY5, CDKAL1, ADRB1, HMGA2, LCORL, CMPXM2, CLDN1, TXNDC5, LRP2, PHLDB2, LEP, and GCH1.

Proteins that have been proposed as abnormal birth weight biomarkers include IL-8, TNF-alpha, IFN-gamma, IL-10, alpha fetoprotein, free beta hCG, PAPP-A, MMP-9, VEGF, endothelin peptides, and A-FABP. Additionally, phospholipids, monoglycerides, and vitamin D3 metabolites are potential metabolic biomarkers of abnormal birth weight.

Chapters 37 and 38 look at pancreatic functions linked to fetal programming. Chapter 37 concentrates on the endocrine pancreas. The endocrine pancreas is impaired by nutritional restriction during the perinatal phase. The pancreatic islets are a key target of metabolic programming. Fetal and neonatal insulin secretion and insulin sensitivity are altered by maternal under- or overnutrition prior to and during pregnancy and lactation. The chapter reviews the well-characterized animal models and genes, transcription factors, and other bioactives that affect pancreatic islet cell function. Chapter 38 further provides insights into the complexity of pancreatic cells' functions. Pancreatic beta-cell development and function are influenced by locally produced GABA and serotonin. GABA has a direct inhibitory action on insulin secretion and a stimulatory action on glucagon secretion. During pregnancies associated with reduced fetal growth, long-term changes to beta-cell GABA receptors can persist in the offspring into adulthood, compromising normal glucose homeostasis. Serotonin receptors are also abundant on beta cells throughout life, and serotonin can promote glucose-stimulated insulin release. Intrauterine growth retardation results in altered serotonin receptor gene expression in the offspring due to epigenetic modifications. This could contribute to the increased risk of metabolic disease in offspring. The chapter reviews the major animal models and links these data to human functions of the pancreatic islets of Langerhans and the beta cells that synthesize neurotransmitter molecules including GABA and serotonin. These molecules have both autocrine and paracrine actions within individual islets that include beta-cell proliferation, survival, and glucose-stimulated insulin secretion. IUGR significantly increases the risk of metabolic diseases including type 2 diabetes that results from disturbances in pancreatic beta-cell functions in utero.

Chapter 39 examines the critical role of glucocorticoids in the transfer of nutrients through the placenta to the fetus and how untimely overexposure to this hormone can alter normal fetal programming. Maternal malnutrition invokes a stress response in the mother and fetus and that stress may further reduce food intake and expose the developing fetus to excess glucocorticoids. The chapter reviews the processes that could result in inappropriate timing of glucocorticoid exposure or excessive exposure that can restrict fetal growth and cause permanent structural, functional, and behavioral changes with adverse consequences later in life including, but not limited to, metabolic diseases. Chapter 40 discusses the role of gene knockouts in animal models in helping to elucidate the effects of maternal high-fat diets on fetal development. The chapter describes the removal of a mammalian gerontogene involved in the regulation of oxidative stress and in fat storage. Knocking out this gene in mice protected them from oxidative stress and from maternal diet-induced obesity resulting in overall improved health in the offspring.

Chapter 41 introduces the reader to the field of telomere biology and examines the effects of the fetal environment on telomere length that is associated with longevity. We learn that telomere biology is a highly evolutionarily conserved system that plays a central role in maintaining the integrity of the genome and cell. Telomere biology refers to the structure and function of two entities – telomeres, non-coding double-stranded repeats of guanine-rich tandem DNA sequences and shelterin protein structures that cap the ends of linear chromosomes, and telomerase, the reverse transcriptase enzyme that adds telomeric DNA to telomeres. Telomeres protect chromosomes from mistaken recognition by the DNA damage-repair system. As telomere length shortens, cells become senescent and die. Telomerase maintains telomere length and preserves healthy cell function. The chapter examines the hypothesis that a reduction in the initial (newborn) setting of telomere length and telomerase expression capacity confers greater susceptibility for earlier onset and faster progression of age-related disorders that manifest in later life. New data suggest that maternal nutritional status of folate, as an example, had a programming effect on fetal telomere length during pregnancy. The chapter includes

over 130 references and important tables and figures that help the reader to better understand this new area of fetal programming research.

Part VIII: Resources

The final chapter in this comprehensive volume, Chap. 42, contains a compilation of important resources for health professionals who are interested in learning more about nutritional aspects and consequences of fetal programming. The chapter includes lists of relevant journals, books, and references as well as websites of interest.

Conclusions

The above descriptions of the volume's 42 chapters attest to the depth of information provided by the 95 well-recognized and respected editors and chapter authors who come from more than 20 countries around the world and provide a unique perspective on the value of adequate nutritional status during the female's reproductive years, pregnancy, and lactation to help assure normal fetal programming of all aspects of fetal organ and systems development. The volume presents compelling evidence that inadequate maternal nutrition, both under- and overnutrition, as well as inadequate intake of vitamins, minerals, and other bioactive dietary components, can adversely affect the offspring throughout the lifespan and may even adversely affect the next generation. As many of the chapters reflect new findings in this area of research, each chapter includes fully defined abbreviations for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include over 200 detailed tables and informative figures; an extensive, detailed index; and more than 2700 up-to-date references that provide the reader with excellent sources of worthwhile information. Moreover, the final chapter contains a comprehensive list of web-based resources that will be of great value to the health provider as well as graduate and medical students.

In conclusion, *Diet, Nutrition, and Fetal Programming*, edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of maintaining optimal nutritional status for individuals during their reproductive years to help reduce the risk of the adverse effects of inadequate nutrition on the fetus that is manifest in damage to the fetal programming processes. Negative effects of fetal programming not only affect the fetus, neonate, and child but continue throughout life and may affect the next generation as well. The volume serves the reader as the benchmark in this complex area of interrelationships between maternal nutrition, be it undernutrition or more recently, with the increasing prevalence of obesity during reproductive years, overnutrition and the development of obesity, metabolic diseases, and many of the other chronic diseases of aging. The importance of diet quality including types and quantity of carbohydrates, dietary protein intakes and long-chain fatty acids, essential micronutrients, and other relevant dietary bioactive factors is reviewed in depth. The areas of genomics, proteomics, placental health, stress effects on glucocorticoid production, novel animal models including knockout models, and nutrients' and toxic dietary components' effects on cognition and other higher brain functions are clearly discussed so that students as well as practitioners can better understand the complexities of these issues as well as learn about the newest research in developing more sensitive and earlier diagnostic tools. The editors are applauded for their efforts to develop the most up-to-date, unique resource in the area of fetal programming and its effects on the health of the fetus and potentially their offspring. The volume authors aim to identify factors and mechanisms that have the potential to reduce the risk of the adverse effects

associated with maternal malnutrition that predispose the fetus to increased risk of chronic diseases during their life. The editors are to be congratulated on developing this volume that provides the reader with the most comprehensive compilation on fetal programming to date, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Series Editor Bio

Dr. Adrianne 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 that have developed the 80+ well-respected and highly recommended volumes in the Series.

In addition to *Diet*, *Nutrition*, *and Fetal Programming*, *edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel*, major new editions published in 2012–2017 include:

1. *Dietary Patterns and Whole Plant Foods in Aging and Disease*, edited as well as written by Mark L. Dreher, Ph.D., 2017
2. *Dietary Fiber in Health and Disease*, edited as well as written by Mark L. Dreher, Ph.D., 2017
3. *Clinical Aspects of Natural and Added Phosphorus in Foods*, edited by Orlando M. Gutierrez, Kamyar Kalantar-Zadenh, and Rajnish Mehrotra, 2017
4. *Nutrition and Diet in Maternal Diabetes*, edited by Rajendram Rajkumar, Victor R. Preedy, and Vinood B. Patel, 2017
5. *Nitrite and Nitrate in Human Health and Disease*, *Second Edition*, edited by Nathan S. Bryan and Joseph Loscalzo, 2017
6. *Nutrition in Lifestyle Medicine*, edited by James M. Rippe, 2017
7. *Nutrition Guide for Physicians and Related Healthcare Professionals*, *Second Edition*, edited by Norman J. Temple, Ted Wilson, and George A. Bray, 2016
8. *Clinical Aspects of Natural and Added Phosphorus in Foods*, edited by Orlando M. Gutiérrez, Kamyar Kalantar-Zadeh, and Rajnish Mehrotra, 2016
9. *L-Arginine in Clinical Nutrition*, edited by Vinood B. Patel, Victor R. Preedy, and Rajkumar Rajendram, 2016
10. *Mediterranean Diet: Impact on Health and Disease*, edited by Donato F. Romagnolo, Ph.D. and Ornella Selmin, Ph.D., 2016
11. *Nutrition Support for the Critically Ill*, edited by David S. Seres, MD and Charles W. Van Way, III, MD, 2016
12. *Nutrition in Cystic Fibrosis: A Guide for Clinicians*, edited by Elizabeth H. Yen, M.D. and Amanda R. Leonard, MPH, RD, CDE, 2016
13. *Preventive Nutrition: The Comprehensive Guide For Health Professionals*, *Fifth Edition*, edited by Adrianne Bendich, Ph.D. and Richard J. Deckelbaum, M.D., 2016
14. *Glutamine in Clinical Nutrition*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
15. *Nutrition and Bone Health*, *Second Edition*, edited by Michael F. Holick and Jeri W. Nieves, 2015

16. *Branched Chain Amino Acids in Clinical Nutrition*, *Volume II*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
17. *Branched Chain Amino Acids in Clinical Nutrition*, *Volume I*, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
18. *Fructose*, *High Fructose Corn Syrup*, *Sucrose and Health*, edited by James M. Rippe, 2014
19. *Handbook of Clinical Nutrition and Aging*, *Third Edition*, edited by Connie Watkins Bales, Julie L. Locher, and Edward Saltzman, 2014
20. *Nutrition and Pediatric Pulmonary Disease*, edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
21. *Integrative Weight Management*, edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin, and Dr. Laura E. Matarese, 2014
22. *Nutrition in Kidney Disease*, *Second Edition*, edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
23. *Handbook of Food Fortification and Health*, *Volume I*, edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
24. *Handbook of Food Fortification and Health*, *Volume II*, edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
25. *Diet Quality: An Evidence-Based Approach*, *Volume I*, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
26. *Diet Quality: An Evidence-Based Approach*, *Volume II*, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
27. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
28. *Nutrition in Infancy*, *Volume I*, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
29. *Nutrition in Infancy*, *Volume II*, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
30. *Carotenoids and Human Health*, edited by Dr. Sherry A. Tanumihardjo, 2013
31. *Bioactive Dietary Factors and Plant Extracts in Dermatology*, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
32. *Omega 6/3 Fatty Acids*, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson, and Dr. Sherma Zibadi, 2013
33. *Nutrition in Pediatric Pulmonary Disease*, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
34. *Nutrition and Diet in Menopause*, edited by Dr. Caroline J. Hollins Martin, Dr. Ronald Ross Watson, and Dr. Victor R. Preedy, 2013.
35. *Magnesium and Health*, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
36. *Alcohol*, *Nutrition and Health Consequences*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
37. *Nutritional Health*, *Strategies for Disease Prevention*, *Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
38. *Chocolate in Health and Nutrition*, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
39. *Iron Physiology and Pathophysiology in Humans*, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

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*, co-edited 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 and 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 co-authored 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 of American Women*.

Connie W. Bales, PhD, RD is 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 the impact of protein-enhanced meals on muscle quality, function, and other health indicators during obesity reduction in older adults with functional limitations. Dr. Bales has served on NIH and USDA grant review panels and is a member of the American Society for Nutrition's Medical Nutrition Council. Dr. Bales has edited three editions of the *Handbook of Clinical Nutrition in Aging and is Editor-in-Chief of the Journal of Nutrition in Gerontology and Geriatrics*.

Editors Bio

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Dr. Rajkumar Rajendram is a clinician scientist whose focus is on perioperative medicine, anesthesia, and intensive care. One of the many aspects of his role is fetal nutritional support through the management of maternal diabetes and nutrition. Dr. Rajendram graduated in 2001 with a distinction from Guy's, King's and St. Thomas Medical School in London. As an undergraduate, he was awarded several prizes, merits, and distinctions in preclinical and clinical subjects.

Dr. Rajendram began his postgraduate medical training in general medicine and intensive care in Oxford. He attained membership of the Royal College of Physicians (MRCP) in 2004 and completed specialist training in acute and general medicine in Oxford in 2010. Dr. Rajendram also trained in anesthesia and intensive care in London and became a fellow of the Royal College of Anaesthetists (FRCA) in 2009. He has completed advanced training in regional anesthesia and intensive care. He became a fellow of the Faculty of Intensive Care Medicine (FFICM) in 2013 and obtained the European diploma of intensive care medicine (EDIC) in 2014.

Dr. Rajendram returned to Oxford as a consultant in general medicine at the John Radcliffe Hospital, Oxford, before moving to the Royal Free London Hospitals as a consultant in intensive care, anesthesia, and perioperative medicine. He is currently a consultant in internal and perioperative medicine at King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Dr. Rajendram recognizes that nutritional support is a fundamental aspect of perioperative medicine. As a clinician scientist, he has therefore devoted significant time and effort into nutritional science research. As a visiting lecturer in the Division of Diabetes and Nutritional Sciences, King's College London, he has published over 100 textbook chapters, review articles, peer-reviewed papers, and abstracts.

Victor R. Preedy, BSc, **PhD**, **DSc**, **FRSB**, **FRSPH**, **FRCPath**, **FRSC**, is a senior staff member of the Faculty of Life Sciences and Medicine within King's College London. He is a member of the Division of Diabetes and Nutritional Sciences (research) and the Department of Nutrition and Dietetics (teaching). Additionally, Professor Preedy is the director of the Genomics Centre of King's College London.

Professor Preedy graduated in 1974 with an honors degree in biology and physiology with pharmacology. He gained his University of London Ph.D. in 1981. In 1992, he received his membership of the Royal College of Pathologists, and in 1993, he gained his second doctorate (D.Sc.), for his

outstanding contribution to protein metabolism in health and disease. Professor Preedy was elected as a fellow to the Institute of Biology in 1995 and to the Royal College of Pathologists in 2000. Since then, he has been elected as a fellow to the Royal Society for the Promotion of Health (2004) and the Royal Institute of Public Health (2004). In 2009, Professor Preedy became a fellow of the Royal Society for Public Health and, in 2012, a fellow of the Royal Society of Chemistry. Professor Preedy has carried out research at the National Heart Hospital (part of Imperial College London), the School of Pharmacy (now part of University College London), and the MRC Centre at Northwick Park Hospital. He has collaborated with research groups in Finland, Japan, Australia, the USA, and Germany. Professor Preedy has a long-standing interest in the science of health including the impact of nutrition on the various life stages. To his credit, Professor Preedy has published over 600 articles, which include peer-reviewed manuscripts based on original research, abstracts and symposium presentations, reviews, and numerous books and volumes.

Dr. **Vinood B. Patel, BSc**, **PhD**, **FRSC**, is a reader in clinical biochemistry at the University of Westminster and honorary fellow at King's College London. Dr. Patel graduated from the University of Portsmouth with a degree in pharmacology and completed his Ph.D. in protein metabolism from King's College London in 1997. His postdoctoral work was carried out at Wake Forest University Baptist Medical School studying structural-functional alterations to mitochondrial ribosomes, where he developed novel techniques to characterize their biophysical properties. Dr. Patel is a nationally and internationally recognized scientist, and in 2014, he was elected as a fellow to the Royal Society of Chemistry. He presently directs studies on metabolic pathways involved in tissue pathology particularly related to mitochondrial energy regulation and cell death. Research is being undertaken to study the role of nutrients, antioxidants, phytochemicals, iron, alcohol, and fatty acids in tissue pathology. Other areas of interest are identifying new biomarkers that can be used for diagnosis and prognosis of liver disease and understanding mitochondrial oxidative stress in Alzheimer's disease and gastrointestinal dysfunction in autism. Dr. Patel has edited biomedical books in the area of nutrition and health, disease prevention, autism, and biomarkers and has published over 150 articles.

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Acknowledgments

The development of this book is built upon the foundation of the excellent work provided by the staff of Humana and Springer Nature. In particular, we wish to acknowledge the outstanding support, advice, and great patience of the series editor, Dr. Adrianne Bendich; the developmental editor, Michael Griffin; and assistant editor, Samantha Lonuzzi.

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Part I
Maternal Diet, Health and the Fetus: General Considerations

Chapter 1
Prenatal Maternal Stress in Context: Maternal Stress Physiology, Immunology, Neuroendocrinology, Nutrition and Infant Development

Emily S. Barrett, Ana Vallejo Sefair, and Thomas G. O'Connor

Key Points

- Although typically studied individually, prenatal stress and dietary factors often covary and may affect the same developing body systems.
- There is an extensive body of literature on prenatal stress and infant development, with a heavy emphasis on the role of the hypothalamic-pituitary-adrenal axis.
- Prenatal stress has been linked to impaired prenatal growth followed by rapid postnatal catch-up growth.
- Stress may alter maternal prenatal immune function with downstream effects on the child's development.
- Children born to stressed mothers show long-lasting changes in brain activity, behavior, and temperament.
- Additional research is needed to explore the overlapping contributions of diet and stress in shaping infant developmental trajectories.

Keywords Prenatal stress • Anxiety • Pregnancy • Infant development • Fetal programming • HPA axis • Immune function • Neurodevelopment

Abbreviations

BBB	Blood brain barrier
CRH	Corticotropin releasing hormone
DoHaD	Developmental origins of health and disease
HPA	Hypothalamic-pituitary-adrenal

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R. Rajendram et al. (eds.), *Diet, Nutrition, and Fetal Programming*,
Nutrition and Health, DOI 10.1007/978-3-319-60289-9_1

Introduction

As evidenced by the current volume, there is a large and rapidly growing literature indicating that certain exposures in the prenatal period may have lasting effects on the behavior and biology of the child. Prenatal diet and nutrition is a particular focus of this volume. We seek to build upon and connect that literature to an equally large, but thus far largely separate, line of research suggesting that prenatal stress can also alter fetal and infant health and development in a manner consistent with a fetal programming hypothesis.

To date, surprisingly little research has explored the relationship between prenatal nutrition and stress in the context of infant development [1], however several lines of evidence suggest that this is an important future direction. First, maternal stress and poor nutrition often occur together. This overlap is most clearly illustrated in extreme cases such as the Dutch Hunger Winter of 1944–1945. The famine, which occurred due to military blockades during World War II, has been well-described, and individuals who gestated during that period have been followed for many decades to understand the long-term effects on their physiology (as well as that of subsequent generations) [2]. Gestational exposure to the Dutch famine has been linked to psychological [3] and metabolic [4] changes in the offspring later in life. Similar findings have been reported in studies of those who gestated during the Great Leap Forward Famine in China (1959–1961) [5, 6]. In both cases, the physiological changes observed in offspring are frequently attributed to the substantial caloric and micronutrient deficiencies that fetuses experienced during these tragic "natural experiments", however the role of stress (and stress physiology) is an important alternative explanation. With the constant military threat, limited food rations, displacement, and general upheaval, the psychological burden on the population, including pregnant women, is incontrovertible. The profound psychological distress suffered by mothers during these events could contribute to altered development in their gestating offspring; indeed, some of the earliest evidence suggesting a role of prenatal maternal stress on child health outcomes examined war as the source of psychological stress and ignored the associated nutritional deficiencies [7]. Similarly, animal models that examine fetal programming by extreme caloric restriction cannot rule out the possibility that psychological stress due to starvation confounds interpretation of the impact of diet on offspring outcomes.

It is not only in these extreme cases that stress and nutrition will likely be confounded. In daily life, under normative stressful circumstances, women may be less likely to choose healthy, nutrient rich foods [8]. Similarly, low socioeconomic status populations are disproportionately exposed to nutritionally poor (albeit often calorically rich) diets, food insecurity, and heightened psychosocial stress – suggesting that poor diet may serve as a proxy for stress exposure and vice versa. Furthermore, poor diet and nutritional deficiencies may not only be confounded by exposure to psychosocial stress, but may also interact with or modify the effects of stress. While we await the advent of multidisciplinary research that considers these exposures together [1], understanding the ways in which maternal stress may affect fetal development can inform studies of programming by diet and nutrition and vice versa can move both fields forward (Fig. 1.1). In this chapter, we review the ways in which prenatal stress (and associated constructs) alters infant behavioral and biological development; we highlight those areas for which there are particular parallels in the nutrition and stress literatures, with the goal of stimulating future research that adopts a more integrative, ecologically relevant model for human development.

Stressful situations can evoke a physiological cascade of hormone and neurotransmitter release, preparing the individual for "fight or flight". As part of this response, hypothalamic-pituitary-adrenal (HPA) axis activity is temporarily upregulated and levels of stress hormones, such as cortisol, rise to better respond to a stressor or challenge. This model applies also to pregnancy – accounting for the dominant role of HPA axis-related research on prenatal stress – although changes in the hormonal, endocrine, metabolic and immune systems in pregnancy complicate the model, especially in late pregnancy [9]. Understanding how and if maternal stress physiology alters fetal and child development

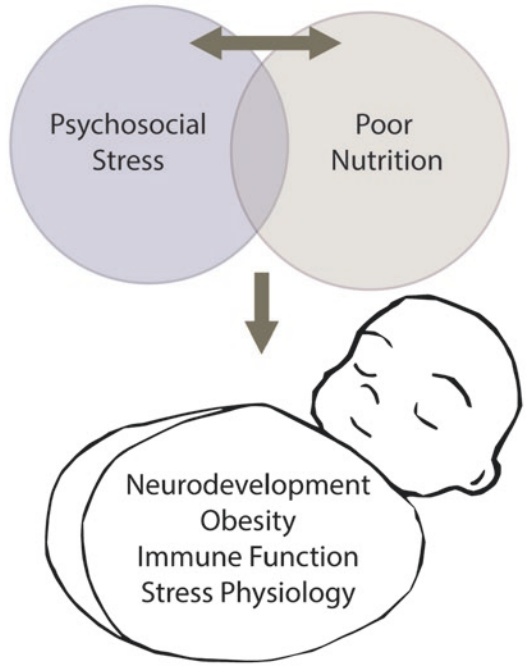

Fig. 1.1 Nutrition and stress may co-occur and interact to affect child outcomes

presents notable challenges. For example, normally during pregnancy, the placental barrier enzyme 11βHSD2 buffers the fetus from maternal stress hormones. This barrier is not impermeable, however, and there is evidence that in the face of heightened maternal stress, the enzyme may be down-regulated, allowing more cortisol to reach the fetus [10]. Accordingly, research on maternal prenatal stress physiology and fetal programming has broadened to incorporate factors that regulate this barrier enzyme. The extent to which 11βHSD2 is affected by diet and nutrition, in broad terms, is not yet evident, but one interesting example is liquorice which contains glycyrrhizin, an inhibitor of 11βHSD2. There is now evidence suggesting that liquorice consumption in pregnancy is associated with poorer cognitive development and elevated cortisol levels in the child [11] – the same outcomes that have been linked with prenatal maternal stress and will be discussed in this chapter. Although liquorice consumption may have limited relevance for the diet and nutrition of most women, this example illustrates parallels and confounds between research on prenatal maternal stress and prenatal diet and nutrition. In addition to placental mechanisms, the blood-brain barrier (BBB) of the fetus is also a reasonable target for research on prenatal maternal stress, as well as diet and nutrition. The BBB is not fully developed in the fetus and may be particularly susceptible to maternal insults including stress and inflammation [12].

Even if the mechanisms are not yet resolved, what is abundantly clear from hundreds of studies in animal models and humans is that prenatal stress can have an impact on the development of nearly every body system in the fetus. For this reason, it is impossible to comprehensively review the large body of research on stress and infant development in a single chapter. Therefore in this chapter we have selected four particular aspects of infant physiology that may have particular relevance for our aim of identifying overlap and congruence in research on prenatal maternal stress and diet and nutrition: stress physiology, growth and metabolism, immune function, and neurodevelopment.

We offer an important caveat in interpreting the research on maternal stress and child outcomes. Integrating and interpreting research on "stress" in pregnancy is complicated by the number of different (but related) terms and concepts have been used (Table 1.1). It is helpful that evidence of a prenatal

Table 1.1 Some common ways to assess psychosocial stress and related constructs during pregnancy

Construct	Description	Sample publication
Anxiety	Excessive and uncontrolled intense worry or concern	O'Donnell et al. (2012)
Life events stress	Major events such as illness, job loss, death or illness to friend or family member, or divorce that affects subjective well-being during pregnancy	Barrett et al. (2013)
Natural disasters	Acute environmental stressor (e.g., flood, ice storm) in subject's immediate environment during pregnancy	Liu et al. (2016)
Trauma	Ongoing mental or emotional response to extreme adverse events, often occurring much earlier	Moog et al. (2016)
Pregnancy-related distress	Symptoms of anxiety related to the pregnancy itself (e.g. worry about pain during labor, fears about health of fetus)	DiPietro et al. (2006)

"stress" effect on child outcomes is not confined to one measure or type of measure – and it is unlikely that these different but moderately overlapping measures differentially reflect maternal stress-related biology (neuroendocrine, immune, hormonal systems) that may alter fetal and child development. Therefore in this review, "stress" is used as a generic term, recognizing that there are multiple distinct, but over-lapping constructs that are likely to influence fetal physiology in similar ways and through similar mechanisms.

Prenatal Maternal Stress and Infant Stress Physiology

A basic tenet of and one of the most extensively tested hypotheses in this field proposes that prenatal maternal stress alters or "programs" infant stress physiology, represented most commonly by the HPA axis, including corticotropin releasing hormone [CRH] and cortisol (Fig. 1.2). These HPA axis alterations are then hypothesized to drive changes in infant behavior and biology that underlie a range of health outcomes. Animal models overwhelmingly support this hypothesis [13, 14] and such a mechanism could account for the widespread behavioral and biological effects that have been linked to prenatal maternal psychosocial stress across studies in numerous species. The basic physiological model proposes that prenatal maternal stress activates the mother's HPA axis, leading to elevated maternal cortisol levels. As discussed, maternal cortisol can crosses the placenta (in a limited manner) [15] and may also modify 11βHSD2 production, making the placenta more permeable to glucocorticoids and increasing fetal exposure to cortisol [10]. This elevated fetal exposure to cortisol is then hypothesized to program subsequent developmental trajectories, leading to a wide range of generally averse outcomes. Although well-articulated and substantiated by extensive animal data, the model is only partly confirmed by data from human studies. There is evidence that prenatal stress is associated with altered maternal cortisol profiles [16] and placental 11βHSD2 activity, with the net effect being greater prenatal exposure of the fetus to glucocorticoids [10] and altered HPA axis function in the offspring. At birth, placental expression of mitochondrial genes involved in the stress response is predicted from maternal prenatal stress levels [17]. These alterations in HPA axis activity may persist long-term. In fact, studies have found that following maternal prenatal stress, HPA axis activity is altered among offspring not only during the neonatal period and infancy [18], but even up to 15 years of age [19], suggesting the downstream sequelae of prenatal stress may be "programmed" .

Notably, there is not yet strong direct evidence that alterations in HPA axis function mediate the relationship between maternal distress during pregnancy and subsequent behavioral and biological outcomes in the child. The implication is that there may be an over-emphasis on HPA axis-mediated pathways and too little attention to alternative explanations including immune systems changes and inflammation. In addition, until recently, genetic and epigenetic changes were also under-studied. It is in this context that we reiterate an organizing theme of this chapter, that is, the current lack of integration

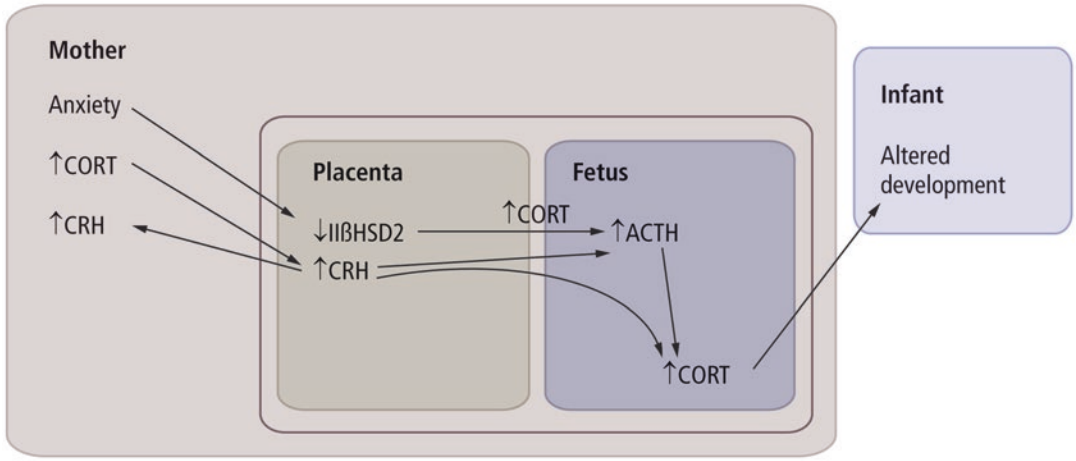

Fig. 1.2 A schematic model for understanding maternal stress, HPA axis activity, and infant development

between research on prenatal maternal stress and diet and nutrition and related factors, such as exercise. The need for integrative research is especially underscored when discussing glucocorticoids, which have, by design, a fundamental connection to stress response and diet and metabolism. Although we discuss glucocorticoids in the context of stress in this chapter, their important role in glucose metabolism and more generally, energetics should not be forgotten.

Prenatal Maternal Stress and Infant Growth and Metabolism

The hypothesis that maternal prenatal diet and nutrition can have significant and potentially lasting effects on infant growth and metabolism is strongly supported [20] and the clinical applications of this research are well-developed. Many kinds of controlled trials that manipulate prenatal diet have demonstrated that there can be beneficial effects on subsequent child outcomes; prenatal zinc is just one example [21]. What may be less familiar is the growing evidence base indicating that prenatal stress can also predict physical growth and metabolism in the baby, with potentially lasting effects and in a manner consistent with the programming hypothesis that underlies the Developmental Origins of Health and Disease (DOHaD) model. A starting point for this literature is the number of studies linking prenatal maternal stress with birth weight, gestational age, and the likelihood of being born small for dates [22, 23]. Several mechanisms have been explored. Placental concentration of CRH in late pregnancy is associated with infant birthweight (adjusting for gestational age) as well as patterns of weight gain in infancy [24]. Additionally, prenatal anxiety is associated with altered methylation of genes involved in fetal growth (IGF2 and H19), particularly in female fetuses [25].

The association between prenatal stress and fetal growth has obvious public health significance given the wealth of data linking low birth weight to endocrine and metabolic dysfunction – and ultimately cardiovascular disease and diabetes – in adulthood [26, 27]. One plausible pathway linking size at birth to adult metabolic disease is that the postnatal "catch-up growth" typical of low birth weight babies leads to the increased subsequent metabolic risk. Indeed, change in infant fat mass from birth to 6 months is among the strongest predictors of childhood obesity [28]. More recently, several studies have directly implicated maternal stress in pregnancy as a potential causal factor underlying growth patterns and body composition later in childhood; for example, neuroendocrine correlates of maternal prenatal distress such as cortisol and CRH have been associated with child adiposity and obesity [29], as well as levels of adiponectin (a protein involved in glucose regulation) at age 3 [30].

Understanding how prenatal maternal stress and nutrition may interact to alter offspring development requires manipulation or control over both of these exposures. That is not possible in human research, but there is a substantial animal literature that may offer some guidance. One valuable take-home message from these studies – with potential application to human development – is that prenatal maternal stress and prenatal dietary manipulations may both predict metabolic outcomes in the offspring, such as obesity [31]. The implication that prenatal stress may mimic the effects of prenatal nutritional deprivation or a high fat diet (or perhaps other forms of suboptimal diet in pregnancy) underscores the theme of this chapter that stress and diet are parallel and confounding influences that require integration in subsequent research.

Whereas animal studies have the benefit of experimental research designs, human studies have relied on observational studies, which offer less leverage for causal inference. Nonetheless, some intriguing findings are emerging. One interesting example is a recent report suggesting that higher polyunsaturated fatty acid intake (operationalized as the n3:n6 ratio) attenuated the effects of prenatal stress on infant temperament in an African-American sample [32]. There is a need for greater insight into how prenatal stress and prenatal nutrition are confounded that moves beyond the covariation between stress and obesity, for example, and which stress-related constructs may modify or be modified by specific nutrients in predicting infant growth and metabolism.

Prenatal Maternal Stress and Immune Function

There are many reasons for considering the maternal and infant immune systems mechanisms in the context of prenatal maternal stress. For example, the immune system is a stress-responsive system and pregnancy is itself a significant immunological stressor characterized by sizable changes in levels of pro- and anti-inflammatory cytokines [33]. In humans, the infant immune system develops prenatally and may therefore be influenced by in utero exposures, including maternal stress. In mid-gestation (approximately 20–24 weeks), the fetal immune system begins to develop in response to in utero and exogenous antigens, such as maternal antibodies and inflammatory cytokines [34]. Following this immunoregulatory response, the maternal system establishes an active immunological tolerance against placental antigens released by the fetus. The fetal and maternal tissue are not in direct contact, but the placenta functions as an important intermediary for maternal-fetal immune system communication [35]. This bi-directional communication is critical to a healthy pregnancy, and leaves the fetal immune system vulnerable to environmental disruptions and exposures in the maternal system [36]. Psychosocial stress during pregnancy can lead to immune dysregulation in the maternal environment, which in turn may alter brain development and immune function in the child [12, 37].

Research on the impact of prenatal maternal stress on maternal and child immune function, and the potentially complicating role of diet and nutrition, is just beginning. This line of research has the important disadvantage that there is a less well-developed animal model, and the animal data reported may be a less than adequate guide. That is, although there are many studies of prenatal stress and the immune system in the mouse, [38], humans and rodents are born at different points in ontogeny and at differing points in immune development [39]. Non-human primates provide a more suitable model system with findings likely to be more relevant to human health, but that research base is more limited. Nonetheless, studies have shown that, for example, pregnant rhesus macaques who are stressed during the second or third trimester have offspring who displayed blunted immune responses to antigens. Compared to controls, these prenatally stressed infants demonstrated a blunted IL-6 and TNF-alpha response following lipopolysaccharide stimulation [40], as well as reduced T-cell response to antigens [41].

In women, stress during pregnancy is associated with elevated levels of pro-inflammatory cytokines [42]. Alterations in maternal cytokine levels have, in turn, been associated with higher risk of allergies in infants [43]. Prenatal anxiety and stress have also been linked to illness and antibiotic use

in infancy [44]. It is also worth considering that some of the other infant outcomes linked to maternal stress, such as somatic illnesses [45], and higher BMI and obesity prevalence [46], may well be immune-mediated rather than strictly HPA axis mediated, as is often assumed. The potential effects of maternal stress on the child's immune system may continue throughout adulthood. A recent study found that that young women whose mothers experienced major negative life events during their pregnancy demonstrated over-production of IL-4, IL-6 and IL-10, a cytokine profile consistent with asthma and autoimmune disorders [47]. Furthermore, these women were also found to have higher BMIs, percentage body fat, and primary insulin resistance [48]. In a recent, large-scale Danish cohort study, young men whose mothers had experienced a major life stressor (death of a close relative) during pregnancy were more likely to be overweight and obese in adulthood [49]. Collectively, these findings suggest reliable associations between – and confounds among – prenatal maternal stress physiology, immunology, and diet and nutrition that may predict child health outcomes.

Prenatal Maternal Stress and Child Neurodevelopment

One of the most commonly studied areas of research related to prenatal diet and nutrition is child cognitive and neurodevelopment. There is an equally well-developed literature examining prenatal maternal stress as the exposure of interest. Dozens of studies in various animal models have linked prenatal stressors to neurodevelopmental outcomes spanning many domains, including memory, cognition, and social behavior. That the offspring of stressed dams show concomitant anatomical and cellular changes in key brain regions offers further support for a programming model [50]. Not surprisingly, studying these phenomena in humans once again presents a challenge for many reasons. One major complications is the potential for confounding by socioeconomic factors and parenting behaviors as well as postnatal maternal stress and depression.

Nevertheless, even after adjusting for these confounding factors, there is robust evidence that maternal stress is associated with neurodevelopmental changes in children that are evident at birth. Maternal anxiety during pregnancy is associated with changes in orientation, self-regulation, and reactivity among neonates [51]. Temperamental changes have been reported later in infancy. Prenatal stress and anxiety have been linked to a "difficult" infant temperament (according to maternal report), and heightened fearfulness in a structured experimental setting [52, 53]. Furthermore, motor and mental development may be delayed in such infants [52, 54].

Biological evidence further supports this behavioral and observational data and mirrors results from animal models. Ultrasound and heart rate data during pregnancy suggest relative developmental immaturity among fetuses carried by stressed mothers, with particularly acute delays among female fetuses [55]. Postnally, children of mothers who exhibited depressed symptoms during pregnancy also have different patterns of brain activity as measured by electroencephalogram starting as early as 1 week of age and extending into later infancy [56]. Finally, functional magnetic resonance imaging shows further changes in the brains of prenatally stressed children, including changes in functional connectivity (particularly in the amygdala) and brain volumes of key regions such as the hippocampus [57, 58].

To further underscore the impact of maternal prenatal stress on resulting child development, it is worth noting that like many other aspects of fetal programming, effects may be long-lasting. Stress-related neurodevelopmental changes in the brain and neuroendocrine systems may be still apparent in behavior and cognition in mid-to-late childhood. For example, anxiety during pregnancy predicts poorer executive function (including working memory, inhibitory control, and externalizing problems) at age 6–9 [59, 60]. As teenagers, the offspring of women who suffered from perinatal anxiety and/or depression are at increased risk of themselves developing anxiety disorders and more likely to have academic problems [61, 62].

It will again be evident that the above findings connecting prenatal maternal stress and child neurodevelopment resemble what has been reported for prenatal nutrition and child outcomes. There is, for example, a sizable literature linking prenatal obesity and child neurodevelopment [63, 64]. A focus on child neurodevelopment therefore provides a further illustration of the confounded and parallel literatures on prenatal stress and prenatal nutrition for child health and development.

Conclusions

In summary, although they are typically studied individually, prenatal stress and dietary factors often covary, may act upon the same developing body systems, and predict parallel and overlapping child outcomes. Adopting a multidisciplinary model, incorporating both exposures in relation to infant outcomes, is needed before deriving clear conclusions about the effects of either type of exposure. Of course that would not resolve the matter completely because of the myriad concurrent other exposures that may be relevant for child health and development also including, but not limited to: physical activity, environmental exposures, and medication use. Nevertheless, by integrating concurrent assessments of diet and stress (through standardized questionnaires or biospecimens) into study designs, we can improve our current understanding of how these exposures affect infant development. This approach will allow us to move away from overly simplified "main effects" models to interaction models that may more accurately approximate the complex and confounded patterns of prenatal exposures relevant for child health.

Future Directions

There remain a number of unanswered questions regarding prenatal stress and infant development. Additional directions that warrant future research include: (1) further elucidating the biological and molecular mechanisms by which maternal stress is transmitted to the fetus, including the role of the placenta and immune pathways; (2) examining the extent to which male and female fetuses respond differently to maternal stress, as has been suggested by several lines of research in this field; (3) identifying critical windows of exposure during pregnancy; (4) exploring whether developmental changes in the offspring of stressed mothers may sometimes represent adaptations to prepare for a harsh postnatal environment, rather than pathologies; and (5) developing interventions to reduce prenatal stress in order to improve infant health and developmental trajectories, particularly in at-risk populations.

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