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

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel *Editors*

Nutrition and Diet in Maternal Diabetes

An Evidence-Based Approach

Humana Press

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Connie W. Bales, Ph.D., R.D., Series Editors

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

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Preface

Diabetes (Type 1, Type 2 or gestational) in pregnancy can have adverse consequences for the fetus and post-natal growth. The effects of maternal diabetes can also persist into adulthood via fetal programming. Breastfeeding may also be problematic. However, these are simple concepts as maternal diabetes can also be considered as a global issue. Worldwide, gestational diabetes occurs once in every twenty-five pregnancies. In the United States the present rate of gestational diabetes lies between 5 and 9%. However, regardless of its aetiology, diagnosis or prevalence, it is important to point out that nutritional and/or dietary factors play an integral part in maternal diabetes. For example good dietary practises and advice are beneficial in maintaining adequate blood glucose control. Poor dietary practises before pregnancy, on the other hand, leads to an increase in body mass index (BMI), which in turn is a risk factor for both Type 2 and gestational diabetes. These interrelationships between diagnosis, causative factors, outcomes, diet and nutrition are complex. They involve molecular biology, cells and organs. Hitherto these associations and links have not been previously formulated into a single scientific treatise. This is however addressed in **Nutrition and Diet in Maternal Diabetes: An Evidence Based Approach**. Coverage including global and country-specific aspects, diagnosis and biomarkers, genetics and gene expression, signalling, neurology, obesity, cardiovascular disease, polycystic ovary syndrome, glucose and insulin metabolism, minerals, vitamins, fatty acids, dietary supplements, exercise and many other areas. Where appropriate, chapters have a section on either ***Recommendations*** or ***Guidelines*** and all contributions have a set of ***Key Points***.

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 **Nutrition and Diet in Maternal Diabetes: An Evidence Based Approach**.

This book is designed for nutritionists and dietitians, endocrinologists, public health scientists, medical doctors, midwives, obstetricians, paediatricians, 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

Rajkumar Rajendram
Victor R. Preedy
Vinood B. Patel

Series Editor Preface

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, inter-chapter referrals, (8) suggestions of areas for future research and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as 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.

"**Nutrition and Diet in Maternal Diabetes**", edited by Rajendram Rajkumar, 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. It is hard to imagine that it is only seven years ago that international criteria were agreed upon concerning the diagnosis of gestational diabetes during the second trimester of pregnancy. Yet, there are many nations that have not adopted these criteria and new research discussed within this volume point to the potential for earlier diagnosis, thus enhancing the potential to identify at risk women earlier and reduce associated adverse effects. This is the first volume to specifically address the nutritional aspects of maternal hyperglycemia from a global perspective. The emphasis is on identifying nutritionally related risk factors for developing gestational diabetes, for reducing the risks of Type 1 diabetes during pregnancy, for managing the nutritional components of gestational diabetes mellitus and other causes of hyperglycemia during pregnancy and postpartum. Chapters identify the key potential adverse effects of hyperglycemia during pregnancy on both the mother and offspring and outline potential nutritional strategies that can be of benefit. As one of the major risk factors for developing gestational diabetes is related to maternal weight and weight gain, it is obvious that nutrition is a key factor in all aspects of gestational diabetes and hyperglycemia in pregnancy, and this is the focus of "Nutrition and Diet in Maternal Diabetes".

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, anaesthetist and peri-operative 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 anaesthesia and intensive care in the Central School of Anesthesia, London Deanery and became a Fellow of the Royal College of Anesthetists (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 research Fellow in the Nutritional Sciences Research Division of King's College London; he has published over 50 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 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, a Fellow of the Society of Biology, the Royal College of Pathologists, the Royal Society for the Promotion of Health, the Royal Institute of Public Health, the Royal Society for Public Health and in 2012 a Fellow of 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, 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 37 chapters within this clinically important, practice-oriented volume provide the reader with a comprehensive examination of the growing global prevalence and consequences of both the effects of pre-existing diabetes as well as pregnancy-induced gestational diabetes mellitus (GDM) on maternal as well as fetal health. Data consistently show that GDM is associated with complications such as increased birth weight, macrosomia, caesarean birth and preterm birth. Women who are diagnosed with GDM have a significantly increased risk of developing Type 2 diabetes within 10 years. GDM also increases the risk of preeclampsia.

Genetic factors that affect insulin resistance, metabolomics, oxidative stress and other critical risk factors are reviewed in separate chapters. There is a broad-based review of the current definitions of gestational diabetes as well as an in-depth discussion on diagnosis and maternal co-morbidities, neonatal effects and postpartum maternal effects of gestational diabetes.

This comprehensive volume is organized into nine parts that include chapters on the clinical basis of gestational diabetes; pregnancy in women with Type 1 diabetes; relevant research from several different geographic areas; genetic factors associated with gestational diabetes and its consequences; effects of pre-existing conditions, such as bariatric surgery, on maternal health when gestational diabetes is also a critical factor; reviews of clinical data from dietary intervention studies; postpartum effects of gestational diabetes; breast feeding; dietary components and weight gain effects, and finally, a chapter devoted to providing additional resources and references on this expanding field of obstetrics.

Part I. Definitions, Characterization and Diagnosis

Part I begins with an historic overview of the evolution of the terminology used to describe maternal diabetes and Chap. 1 reviews in detail the development of diagnostic criteria for maternal gestational diabetes beginning with the criteria provided by O' Sullivan et al. in 1964 based on an oral glucose tolerance test (OGTT) at 22 weeks gestation. During the 1980s there was an attempt to use the same

criteria for Type 2 diabetes diagnosis for gestational diabetes. However, the growing knowledge of the adverse effects of higher than normal circulating glucose levels on the fetus resulted in the impetus to develop globally acceptable criteria for diagnosis. In 1980, the World Health Organization (WHO) made the recommendation to use the OGTT diagnostic criteria used to diagnose Type 2 diabetes and impaired glucose tolerance. Unfortunately, different National associations chose different blood glucose thresholds to detect abnormalities in pregnancy. The result was a variety of studies reporting different estimates and confusion for clinicians on how to define the condition.

As more women of reproductive age started to develop Type 2 diabetes, it was important to distinguish between pre-existing but undiagnosed diabetes in pregnancy from the milder form (GDM) that develops at 22 weeks and resolves postpartum. For many years, sets of risk factors were used to screen for the potential to develop gestational diabetes and it was not until 2008 that the results of the Hyperglycemia and Adverse Pregnancy Outcomes study were published and helped to clarify the serious adverse effects of high maternal glucose levels on the fetus and neonate. This landmark study enrolled over 25,000 pregnant women in an international multi-centre study and followed them through pregnancy. The results led to recommended diagnostic criteria for GDM representing the average glucose values at which the odds for birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percentage body fat >90th percentile reached 1.75 times the odds of these outcomes. The thresholds established by this study were adopted by many National and Medical Society guidelines and were also recommended by the American Diabetes Association in its 2011 position statement. We learn that in 2013 the World Health Organization proposed new criteria for the diagnosis and definition of hyperglycemia first detected in pregnancy. The definition distinguishes the more serious diabetes in pregnancy (DIP), which is more likely to persist beyond the birth and can cause serious fetal abnormalities early in pregnancy, from the relatively milder gestational diabetes. The new definition calls for an understanding of the burden of hyperglycemia in pregnancy and its relationship with the growing epidemic of Type 2 diabetes and distinguishes DIP from GDM based on the degree of hyperglycemia; a reflection that the risk of serious complications is much higher in diabetes in pregnancy than in GDM. Where studies previously reported the prevalence of GDM, under the new definition, these figures would also include the more severe hyperglycemia classified as diabetes in pregnancy under the broad title of hyperglycemia first detected in pregnancy (HFDP). Added to this definition are women with diagnosed diabetes who become pregnant; the term hyperglycemia in pregnancy (HIP) encompasses the burden of any glucose intolerance in pregnancy.

The chapter also cites the most current data on prevalence: The International Diabetes Federation (IDF) estimates that in 2015, 16.2% of live births to women between the ages of 20 and 49 years had some form of hyperglycemia in pregnancy. The vast majority of those cases were due to the milder form of gestational diabetes (85.1%) while the rest represent pre-existing diabetes only about half of which was diagnosed prior to pregnancy. This figure translates to at least 20.9 million live births affected by some form of HIP. This informative chapter also includes 8 relevant tables and figures.

The third chapter examines the potential of various diagnostic markers to identify hyperglycemia in pregnancy at the earliest time possible as the adverse consequences to maternal and fetal health are cumulative. The authors suggest that biomarkers, including the glycation of proteins such as albumin and fructosamine, represent glycemic control for the preceding 2–3 weeks be considered, as this would serve as an earlier indicator of glycemic control in a dynamic condition, such as pregnancy. These indicators are not dependent on the half-life of erythrocytes as is seen with haemoglobin A1C. It is important to have relevant choices for following pregnant women's glucose control especially if they are diagnosed with GDM.

The last chapter in this part, Chap. 4, reviews the authors' data concerning an Australian study that found an increased risk of GDM in pregnant women who showed signs of depression earlier during their pregnancy. The study followed over 3000 pregnant women and found a significant association between having an Edinburgh Perinatal Depression Scale > 13 at the first visit to pregnancy care (12–17 weeks) and the diagnosis of GDM at around 28 weeks of pregnancy even when the data were

adjusted for parity, smoking, maternal weight, age and ethnicity. As a similar association has been found in women with Type 2 diabetes, and the risk of developing Type 2 diabetes is significantly increased in women who developed GDM, greater awareness of the potential development of depression during pregnancy and afterwards in women with GDM is warranted.

Part II. The Type 1 Diabetic Mother

Chapters 5 and 6 examine the effects of Type 1 diabetes during pregnancy and the factors that further exacerbate the potential for adverse effects to both the pregnant woman and her fetus/neonate. Chapter 5 reviews the authors' findings concerning the increased, synergistic risk of adverse pregnancy outcomes associated with having Type 1 diabetes and being either overweight or obese. Their data from Sweden, which has a high rate of Type 1 diabetes that is increasing over time, indicate that compared to normal weight women with Type 1 diabetes the overweight group had a 77% higher risk for major fetal malformations, a 25% increased risk for premature delivery and a 70% increased risk of caesarean section. Chapter 6 describes the importance of frequent monitoring of glucose control during pregnancy in the Type 1 diabetic females. Hyperglycemia is detrimental to the fetus. A fivefold increase in the rate of cardiovascular malformations and a more than twofold increase in the rate of neural tube defects and urinary malformations have been documented and thus the chapter provides important practice-oriented advice to healthcare providers to emphasize the critical need for planned pregnancy and tight glucose control especially during the weeks of embryogenesis and fetal growth.

Part III. Global Findings in Gestational Diabetes

The next three chapters report on the prevalence and care of pregnant women who develop GDM in Iran, China or Italy. As we learned above, there can be wide differences in the prevalence of pregnancy-related complications and GDM rates are increasing globally. Chapter 7 provides important data on the prevalence of GDM: In Iran, there is a 4.9% estimated prevalence of GDM which varies greatly between different regions, from 0.7% in the west to 18.6% in the south near Tehran. Overweight, obesity, maternal age and lack of exercise are some of the major risk factors identified. WHO guidelines for identifying women with GDM are followed and once identified, measures to control serum glucose levels are undertaken and outlined in the chapter. The chapter concerning GDM in China, Chap. 8, highlights the data related to vitamin D status. In China, mean levels of circulating vitamin D among pregnant women were relatively low and about 60% are considered deficient. The potential causes are outlined and include Asian skin tint, older age of pregnant women, increased rate of overweight and obesity. Recent Chinese data showed that pregnant women with vitamin D deficiency at the 16th–20th gestational week had a higher prevalence of gestational diabetes and preterm delivery than those with sufficient vitamin D. This is a relatively new area of research and there are few intervention data to help healthcare providers to determine whether to either provide vitamin D supplementation or at what level of supplementation. Chapter 9 looks at the current diagnosis and screening criteria used in Italy and the chapter provides recommendations for increasing the sensitivity of screening tools. We learn that GDM occurs in about 11% of the Italian population and it is also associated with an increased rate of maternal and fetal complications compared with normal pregnancy. Maternal complications that occur with an increased frequency include: preterm delivery, polyhydramnios, macrosomia, shoulder dystocia, stillbirth and operative delivery. Fetal complications associated with an increased risk include: neonatal hypoglycemia,

jaundice, polycythemia, hypocalcemia and increased frequency of neonatal intensive care unit admission. Development of data that can identify risk factors early in pregnancy that do not depend on prior pregnancy results was a strong driver for this research team. They found that the most important variable for differentiating the risk of GDM was fasting plasma glucose (FPG). Women with a FPG value lower than 4.4 mmol/l had the lowest GDM prevalence. Patients with a FPG value higher than 5.1 mmol/l represented the subgroup of women with the highest prevalence of GDM (OR 26.5; 95% CI 14.3–49.0). In women with FPG values between 4.5 and 5.1 mmol/l, the risk of GDM was further differentiated on the basis of pre-pregnancy BMI values. Women with a pre-pregnancy BMI in the overweight range or above had a higher risk of developing GDM (OR 7.0; 95% CI 3.9–12.8) that was almost double compared with women with a normal pre-pregnancy BMI (OR 3.7; 95% CI 2.1–6.7). These data were used in Italy to derive screening criteria and the implementation is described in detail.

Part IV. Genetic and Molecular Factors Associated with Maternal Gestational Diabetes

Five chapters review the current associations between GDM and genetic as well as epigenetic findings. The first three chapters describe potential early markers of GDM that are related to maternal genetic alterations. Chapter 10 describes the epigenetic alterations in biomarkers that are associated with GDM. The chapter reviews the disease-specific metabolic imbalances indicative of low-grade inflammation and increased oxidative stress that can adversely affect the health of both the fetus and pregnant woman. Using metabolomics strategies, the authors have verified that alterations in both the level and composition of plasma lysophospholipids are the most prominent changes that correlate with the glycemic state of GDM pregnant women. Using these techniques, they hope to be able to identify GDM earlier and reduce the adverse metabolic consequences. The authors of Chap. 11 look at the data concerning a bioactive molecule, adiponectin, produced by adipose tissue that is one of the factors involved in regulating glucose metabolism. During pregnancy, the serum levels of adiponectin change to meet the needs of the growing fetus. Abnormally low levels of adiponectin have been associated with GDM that is associated with a glucose intolerance state. The authors suggest that serum adiponectin concentrations may be used as an early marker of GDM risk. Moreover, there are certain alterations in the genes affecting adiponectin synthesis that appear to increase the risk of developing insulin resistance during gestation. Chapter 12 examines the preliminary data associating single nucleotide polymorphisms in the genes encoding retinol binding protein 4 and increased risk of insulin resistance in women with GDM. As this protein is the primary carrier of the essential vitamin, vitamin A, which is critical for normal human reproduction, there appear to be several mechanisms to link genetic alterations in this carrier protein with potential adverse pregnancy outcomes. Further research is recommended by all three chapter authors.

Chapters 13 and 14 examine the increased risks associated with GDM to the mother and offspring. In women who have had GDM, the risk for developing Type 2 diabetes is increased by 7.4 fold compared to women with pregnancies unaffected by GDM. The increased risk appears to be independent of the number of pregnancies affected by GDM. With regard to increased risk of cardiovascular disease, women with GDM who had higher serum glucose when challenged either during pregnancy or postpartum demonstrated increased risk of cardiovascular disease, indicating that peak glucose levels are important predictors for future cardiovascular disease. Chapter 13 also reviews studies that have shown that women with GDM had decreased cardiac output, decreased stroke volume and increased peripheral vascular resistance postpartum, predisposing these women to cardiovascular disease. The final chapter in this part, Chap. 14, reviews data from laboratory animal studies of epigenetic alterations in the hearts of mice born to mothers with the metabolic symptoms of

human GDM. Provision of long chain polyunsaturated fatty acids to maternal diets reduced the risk of developing the cardiac abnormalities. The genetic and molecular mechanisms identified in these studies are illustrated in the seven important figures and table included in this chapter.

Part V. Pre-existing Conditions and Gestational Diabetes Risk

The three chapters in this part examine the additional burdens that are frequently seen in women who develop GDM including hypertension that can be independent of GDM or occur prior to development of GDM; polycystic ovarian syndrome, and obesity that has led to bariatric surgery. Hypertensive disorders of pregnancy (HDP), which also includes the diagnosis of preeclampsia, are often seen in women with GDM, but not always. HDP affects 5–7% of all pregnancies and 10–28% of those with GDM. Chapter 15 examines the major modifiable risk factors for HDP and GDM including glycemic control, obesity and gestational weight gain. This practice-oriented chapter's figure and tables include important recommendations for reducing the risk of HDP prior to pregnancy as well as postpartum recommendations for reduction in risk of maternal cardiovascular disease especially if the pregnancy is affected by preeclampsia.

Although polycystic ovarian syndrome (PCOS) and GDM are distinct conditions, there is a significantly increased risk of GDM in women with PCOS who become pregnant. Chapter 16 reviews the data from several studies that have found that GDM is the most predominant complication during the pregnancy in women with PCOS and the risk of GDM was found to be approximately threefold higher in women with PCOS compared to controls in the most recent study. There are also data that the prevalence of polycystic ovarian morphology is higher in women with a history of GDM. The common denominator of both is insulin resistance which is the main endocrine disruption in PCOS. The chapter includes over 100 relevant references, tables and figures.

Chapter 17 examines the plusses and minuses of bariatric surgery for obese women prior to pregnancy. Bariatric surgery has been shown to be the most effective and durable treatment for obesity and to reduce obesity-related complications during pregnancy. The chapter provides descriptions of the types of bariatric surgeries and reviews the studies that indicate that GDM was reduced in women who had the surgery and lost significant weight prior to becoming pregnant. In addition to lower risk of GDM, there were also decreases in HDP and preeclampsia that were correlated with weight loss rather than the surgery; some of the studies examined women who had pregnancies before and after bariatric surgery. This comprehensive chapter also reviews the potential adverse effects of bariatric surgery on mother and fetus/neonate and provides the reader with over 120 relevant references, tables and figures.

Part VI. Dietary Interventions and Exercise

As discussed above, there is intense research underway to identify new diagnostic tools, many of which include biomarkers related to nutrients. In addition to this research focus, there are six chapters that report on potential interventions to reduce the risk of GDM. Chapter 18 looks at the potential for a supplement of myo-inositol, a stereo-isomeric form of inositol, to reduce the risk of GDM development. Myo-inositol is physically linked to phospholipids in the membranes of all living cells. It is synthesized in the body from D-glucose and is found in various food sources. It affects insulin balance and the chapter reviews the experimental and clinical data that suggest the potential for its supplementation to reduce the occurrence of GDM. The preliminary data appear promising and further large-scale studies are needed.

The next two chapters examine the potential for low-glycemic index (GI) diets and low carbohydrate diets to reduce several of the insulin-resistant adverse effects associated with GDM. Chapter 19 reviews the data linking low-GI and low glycemic load diets with improvement in the management of body weight, glycemia and cardiovascular risks, especially in hyperinsulinemic and insulin-resistant populations. The authors assess the evidence for the treatment of GDM—a condition closely associated with hyperinsulinemia and insulin resistance—with low-glycemic diets. Both this chapter and Chap. 20 review all of the clinical studies available and acknowledge that further research is warranted to determine the optimal protocol for reducing glycemic load during pregnancies affected by GDM.

As discussed above in Chap. 10 that describes the use of metabolomics in the development of diagnostics for GDM, Chap. 21 suggests the individual evaluation of personal food metabolomics may become an important tool in the development of diet strategies. The chapter explains the processes of analysis of the food metabolome (the sum of the detectable metabolites found in the human system as a result of the ingestion and digestion of food components) for identifying dietary biomarkers of GDM, as well as elucidating the mechanisms underlying the relationship between maternal diet and GDM. There is a detailed discussion of the analytical considerations, and sampling methodology required to reproducibly analyze the food metabolome for linking the maternal diet with GDM including the analysis of blood, urine, amniotic fluid, saliva, hair, and breath. The economic considerations are also included in this topic for future research.

Chapter 22 reviews the preliminary data from survey and randomized controlled studies that have examined the potential for microbiome manipulation to prevent and/or treat GDM. There is currently little information on the microbiome composition in pregnant women who develop GDM. However, there is one study that has examined the microbiota composition in insulin-resistant women with previous GDM compared to women who had a normoglycemic pregnancy and found alterations that may affect insulin control. The chapter provides data on probiotic supplements used in studies as well as sources of prebiotics that would help to maintain beneficial probiotic bacterial populations.

The final chapter in this part, Chap. 23, examines the value of exercise for pregnant women who have GDM. The chapter discusses the studies that found that exercise can be of benefit in women with GDM and may be of help in its prevention, although further study is needed. Studies where maternal exercise appears to play an important role in the management of pregnancies complicated by GDM are tabulated. In particular, exercise has been shown to assist with maintaining blood glucose concentrations within the appropriate range. This blood glucose lowering effect of exercise in women with GDM has been demonstrated both acutely and in response to regular exercise participation.

Part VII. Postpartum Effects of Gestational Diabetes

Three chapters examine the postpartum effects of GDM on the mother that are independent of breastfeeding as this topic is discussed separately below. The fourth chapter in this part looks at one critical aspect of the neonate—neurodevelopment. Chapters 24 and 25 concern two related increased risks to women who have GDM. Clinical and epidemiological studies indicate that women who experience GDM while pregnant have a significantly increased risk of glucose intolerance, either in the form of prediabetes or overt Type 2 diabetes that may be measurable in the early postpartum period and also have up to a 60% lifetime risk for developing Type 2 diabetes. The chapter reviews many factors that are associated with the increased risk of postpartum glucose intolerance including: advanced maternal age at pregnancy, a family history of Type 2 diabetes, high pre-pregnancy weight and high pregnancy weight gain, prior GDM and insulin use during pregnancy. Control of excessive weight prior to pregnancy and excessive weight gain during pregnancy are key factors in predicting GDM as well as postpartum hyperglycemia. Two important clinical studies are reviewed: in one

cohort study of 1263 GDM-affected women, pre-pregnancy obesity and excessive pregnancy weight gain were associated with the increased risk of prediabetes or Type 2 diabetes one to five years postpartum. A randomized controlled trial from Spain (The St. Carlos Gestational study) confirmed that a high pre-pregnancy BMI and excess weight gain in early pregnancy are the major potentially modifiable risk factors for GDM. Chapter 26 reviews the mechanisms that may be responsible for the increased risk of cardiovascular disease in women who have had GDM in the past. We learn that women with GDM are at risk of developing sub-clinical inflammation as a component of GDM and the metabolic syndrome (MetS) that may be present postpartum. The chapter identifies emerging biomarkers of MetS including leptin, adiponectin, C-reactive protein, tumour necrosis factor alpha, interleukin 6, plasminogen activator inhibitor 1, fibrinogen and adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and cellular molecule (E-selectin). Future research is required to better understand the potential effects of GDM on risk factors for cardiovascular disease in women who have had GDM.

The last chapter in this part, Chap. 27, examines the preliminary data concerning the effects of GDM on the cognitive functions of offspring. In addition to GDM, there are a number of factors, such as obesity, social issues and environment that can affect neurodevelopmental and cognitive outcomes following GDM. The chapter reviews the studies describing the school age follow up of children born to mothers affected with GDM and show a pattern of lower cognitive scores, attention issues, hyperactivity and poor fine motor skills following maternal GDM. Additionally, data linkage studies reinforce concerns regarding neurodevelopmental outcome following maternal GDM and also report a link to autism spectrum disorders. Some studies report adverse neurodevelopmental outcomes following different pharmacological treatment regimens for GDM. Further research studies are proposed by the authors.

Part VIII. Breastfeeding and Maternal Hyperglycemia

The first two chapters in this part examine the effects of GDM on the ability to breastfeed and the effects on breast milk composition. Chapter 28 provides an in-depth insight into the important, long-standing assistance given to both parents in Thailand that promotes exclusive breastfeeding of the neonate for the first 4–6 months of life. Nevertheless, Thai women with GDM suffer a number of physiological changes that often result in problems with breastfeeding. The chapter outlines the three phases of lactogenesis: phase I occurs during 10–22 weeks gestation. Phase II lactogenesis develops after giving birth and 3 days postpartum. Phase III lactogenesis begins after the third day postpartum. Maternal health associated with diabetes, obesity, insulin resistance and nutrition status has effects on all phases of lactogenesis, however, phase II involves the production of prolactin and oxytocin that control early milk production and secretion. GDM is associated with delayed lactogenesis that is linked to insulin resistance and hypothyroid function that decreases production of prolactin and oxytocin. These factors often result in obese women experience breastfeeding problems due to insufficient milk supply. In addition, one-third of postpartum women with GDM reported delayed milk production by the third day postpartum. Other critical issues involve the type of delivery, size and age of the infant at birth, potential hypoglycemia of the infant and maternal hyperglycemia.

Chapter 29 details the peptides found in human breast milk, their functions and the potential effects of GDM on maternal synthesis of these peptides as well as the effects on the infant exposed to breast milk from mothers affected by GDM. The peptides normally found in breast milk are important for the regulation of neonatal metabolic pathways, modulation of appetite, regulation of fluid intake, contribution to bone formation, nutrition, regulation of sleep, blood pressure, intestinal motility, neuropsychiatric events, fat metabolism, stimulation of learning and antimicrobial activities. The

functions of the major peptides are reviewed and the importance of determining the effects of GDM on the concentrations of these bioactive peptides is emphasized.

As discussed above, pregnant women who have Type 1 diabetes are at increased risk of adverse pregnancy outcomes associated with hyperglycemia. Chapter 30 addresses the needs of these women from preconception to postpartum breastfeeding. The chapter reviews the data linking long-term breastfeeding with prevention of future obesity and may protect against development of Type 1 diabetes and Type 2 diabetes in the offspring. Early breastfeeding initiated in the first 30 min of life and repeated 10–12 times/24 h may reduce the risk of neonatal hypoglycemia. In women with Type 1 diabetes, previous experience with breastfeeding, higher educational level and number of feedings in the first 24 h after delivery are positively associated with longer breastfeeding whereas higher pre-pregnancy BMI and smoking are negatively associated with breastfeeding in this population.

Part IX. Specific Dietary Components and Weight Gain

The first three chapters of this six chapter part describe risks of weight gain and the many benefits of controlling total intake as well as intake of carbohydrates pre-pregnancy in women at risk for GDM and during any pregnancy that is affected by GDM. Chapter 31 describes the adverse effects associated with excessive gestational weight gain. Currently, over 50% of women with diabetes gain excessive weight during pregnancy and interventions to modify gestational weight gain have had minimal effect on pregnancy outcomes. Women whose weight gain during pregnancy is outside the recommended ranges are at increased risk of adverse maternal and neonatal outcomes including the development of hypertensive disorders of pregnancy, increased risk of caesarean delivery, increased infant birth weight and postpartum weight retention. Moreover, the attributable risk for childhood obesity was 16.4% for mothers who had excessive gestational weight gain. The chapter reviews the studies that looked at pregnant women with GDM who gained excessive weight during pregnancy and were found to be three times more likely to have a macrosomic infant and other adverse effects. Chapters 32 and 33 review the value of healthful diet choices for the women with GDM and emphasize carbohydrates. Chapter 32 describes the importance of medical nutrition therapy (MNT). Even though there are few available randomized controlled trials investigating the use of MNT in the treatment of GDM, these studies show beneficial effects of MNT for the mother and offspring, including improved glycemic control, appropriate gestational weight gain, lower frequency of insulin therapy and fewer perinatal complications including neonatal hypoglycemia. The chapter reviews the literature and provides valuable tables on the types of foods and intake levels of carbohydrate-containing foods that are associated with fewer adverse effects of GDM. Chapter 33 also provides important tables and references that contain more details about the types of carbohydrates that can benefit women with GDM. The literature review of evidence from randomized trials in GDM suggest that a balanced intake of higher quality complex carbohydrates results in good glycemic control, improved insulin action and improved maternal glucose tolerance, improved lipemia, and vascular benefits, while low-GI diets in particular may reduce the need for insulin, and lower postprandial glycemia. Diets for GDM that can alter maternal/fetal metabolism in late pregnancy are examined, as this is the time when fetal growth accelerates.

The final three chapters in this part examine essential nutrients including fatty acids, folic acid and iron. Chapter 34 looks at the potential for reduced transfer of long chain polyunsaturated fatty acids (LC-PUFAs) from the placenta of the woman with GDM to the fetus and consequent potential for adverse effects on the neurological development of the fetus and neonate. GDM appears to be associated with a significant decrease in the placental transport of LC-PUFAs. The chapter synthesizes the literature that documents the crucial role of LC-PUFAs in the development of the visual and cognitive function in the fetus, and the effects of the decrease in placental transfer of LC-PUFAs. The

accompanying figures help the reader to understand the potential for LC-PUFA deficiency to result in the neurodevelopmental deficiencies associated with infants born to women with GDM. Folate, an essential water-soluble vitamin, also affects fetal neurodevelopment, as shown definitively in women with folate deficiency whose infants develop neural tube birth defects. Chapter 35 examines the interactions between maternal folate status, GDM and effects on the fetus. The author suggests that further research is warranted that examines maternal vitamin B12 status, folate intake levels and birth outcomes especially in women with GDM. This chapter, as with other forward thinking text, provides the foundation for further hypothesis testing. Iron status in the pregnant woman with GDM is the topic of Chap. 36. Iron status is often below recommended levels in women who become pregnant. Iron stores (as reflected in serum ferritin levels) during pregnancy are essential in preventing negative outcomes for both infants and mothers however, there is some evidence that iron supplementation above recommended intake levels may increase the risk of GDM. The chapter reviews the data showing a positive link between a high serum ferritin levels early in pregnancy and the risk of GDM. Increased ferritin levels may be considered as a risk factor for GDM, and may be useful for screening populations at high-risk of GDM.

Part X. Resources

The final chapter in this comprehensive volume, Chap. 37, contains a compilation of important resources for health professionals who are interested in learning more about GDM and the nutritional aspects and consequences of this health condition. The chapter includes lists of relevant journals, books and references as well as websites of interest.

Conclusions

The above descriptions of the 37 chapters attest to the depth of information provided by the 100 + well-recognized and respected editors and chapter authors who come from more than 25 countries around the world and provide a unique perspective on the diagnosis, maintenance and nutritional components that are most relevant to the prevention and treatment of GDM. Each chapter includes fully defined abbreviations for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include over 150 detailed tables and informative figures, an extensive, detailed index and more than 2000 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, “Nutrition and Diet in Maternal Diabetes”, 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 glucose control before, during and after pregnancy so that both mother and child increase their opportunities for enhancing their overall health. The volume serves the reader as the benchmark in this complex area of interrelationships between maternal hyperglycemia, GDM, Type 1 diabetes and genetic as well as epigenetic factors that increase their risk; overweight and obesity prior to pregnancy and during pregnancy especially if it is affected by GDM; the potential adverse pregnancy outcomes to mother, fetus and neonate as well as potential effects on childhood cognition and increased maternal risk of subsequent Type 2 diabetes and cardiovascular disease. Additionally, we learn that GDM reduces the potential for breast feeding and this can greatly impact the health of the infant as well as

the mother. The importance of diet quality including types and quantity of carbohydrates, glycemic index and glycemic load, dietary protein intakes and long chain fatty acids are reviewed in depth. The open questions concerning the diagnosis of GDM are clearly delineated 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 first and most authoritative and unique resource in the area of hyperglycemia during pregnancy and its effects on the health of the mother and her child as well as the potential to reduce the risk of diseases associated with GDM, and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN, FASN
Series Editor

About the Series Editor

Dr. Adrianne Bendich, Ph.D., 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 "**Nutrition and Diet in Maternal Diabetes**", edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel, major new editions published in 2012–2017 include:

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

12. **Branched Chain Amino Acids in Clinical Nutrition, Volume 2**, edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
13. **Branched Chain Amino Acids in Clinical Nutrition, Volume 1**, edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
14. **Fructose, High Fructose Corn Syrup, Sucrose and Health**, edited by James M. Rippe, 2014
15. **Handbook of Clinical Nutrition and Aging, Third Edition**, edited by Connie Watkins Bales, Julie L. Locher and Edward Saltzman, 2014
16. **Nutrition and Pediatric Pulmonary Disease**, edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
17. **Integrative Weight Management** edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin and Dr. Laura E. Matarese, 2014
18. **Nutrition in Kidney Disease, Second Edition** edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes and Dr. Glenn M. Chertow, 2014
19. **Handbook of Food Fortification and Health, volume I** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
20. **Handbook of Food Fortification and Health, volume II** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
21. **Diet Quality: An Evidence-Based Approach**, **volume I** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
22. **Diet Quality: An Evidence-Based Approach**, **volume II** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
23. **The Handbook of Clinical Nutrition and Stroke,** edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, M.D., FACP, FACN, FACG, 2013
24. **Nutrition in Infancy**, **volume I** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013
25. **Nutrition in Infancy**, **volume II** edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy and Dr. Sherma Zibadi, 2013
26. **Carotenoids and Human Health**, edited by Dr. Sherry A. Tanumihardjo, 2013
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29. **Nutrition in Pediatric Pulmonary Disease**, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
30. **Nutrition and Diet in Menopause**, edited by Dr. Caroline J. Hollins Martin, Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2013.
31. **Magnesium and Health**, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
32. **Alcohol, Nutrition and Health Consequences**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
33. **Nutritional Health, Strategies for Disease Prevention, Third Edition**, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
34. **Chocolate in Health and Nutrition**, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
35. **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 Physician**s" 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 in American Women.

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Dr. Rajkumar Rajendram is a clinician scientist whose focus is on peri-operative medicine, anaesthesia, intensive care. One of the many aspects of his role is 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 pre-clinical 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 anaesthesia 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 anaesthesia 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, Anaesthesia and Peri-operative 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 peri-operative 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.

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Part I
Definitions, Characterization and Diagnosis

Chapter 1
Global Estimates of Hyperglycaemia in Pregnancy: Determinants and Trends

Leonor Guariguata, Ute Linnenkamp, Lydia Elizabeth Makaroff, Katherine Ogurtsova and Stephen Colagiuri

Key Points

- Hyperglycaemia in pregnancy is a large and growing burden in global health.
- Changes in the definition of hyperglycaemia in pregnancy affect the way the burden is quantified.
- Shifting demographics towards lower fertility and longer survival will put more women at risk of hyperglycaemia in pregnancy, especially in developing countries.
- Shifting patterns in disease from infectious to non-communicable disease will increase the risk of developing hyperglycaemia in pregnancy for women.
- There are regional variations in the burden of hyperglycaemia in pregnancy but the burden is high all over the world.
- A comprehensive public health response is required to reduce the consequences and prevent new cases of hyperglycaemia in pregnancy.

Keywords Epidemiology · Hyperglycaemia in pregnancy · Developing countries · Pregnancy and diabetes · Global estimates

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Abbreviations

DIP	Diabetes in pregnancy
GDM	Gestational diabetes
HFDP	Hyperglycaemia first detected during pregnancy
HIP	Hyperglycaemia in pregnancy
IDF	International Diabetes Federation
NCD	Non-communicable disease
NDDG	National Diabetes Data Group
OGTT	Oral glucose tolerance test
TDP	Total diabetes in pregnancy
WHO	World Health Organization

Introduction

Diabetes is a serious and growing disease with implications for health and development. More than 400 million people have diabetes [1, 2]. While the majority of cases consist of type 2 diabetes, hyperglycaemia and diabetes in pregnancy and their outcomes present a serious and increasing global challenge [3]. Babies born to women with elevated blood glucose levels are at greater risk of adverse pregnancy outcomes including foetal abnormalities, macrosomia, obstructed labour, and hyperinsulinemia and hypoglycaemia at birth [4]. Even with the mildest forms of hyperglycaemia in pregnancy (HIP), both mother and child are at increased risk of later development of type 2 diabetes, carrying on the diabetes epidemic through future generations [5].

Estimating the global burden of HIP is a challenge because of the variety of methods and definitions used [6]. However, the public health importance of HIP is high and understanding the direction of the epidemic and those most vulnerable is essential to beginning the important work of turning the tide on diabetes.

Defining Hyperglycaemia in Pregnancy, Risk Factors and Outcomes

Various national and international bodies have published a range of guidelines and recommendations on screening methods and diagnostic criteria for the screening and diagnosis of HIP. The condition was first known only as gestational diabetes mellitus (GDM) and was described for mothers developing hyperglycaemia during their pregnancies. The first diagnostic criterion was provided by O'Sullivan et al. in 1964 and was based on 3-h 100 g oral glucose tolerance test (OGTT) at 22 weeks gestation [7]. The hyperglycaemia would inevitably resolve post-partum. The criterion was validated against the risk of future development of diabetes for the mothers and gained wide acceptance. At the time, developing type 2 diabetes in women of reproductive age was so rare as to be unconsidered in the development of a definition.

In 1980, the World Health Organization (WHO) made the recommendation to use a 2-h 75 g OGTT for pregnant women to harmonise the diagnostic criteria with that used to diagnose diabetes and impaired glucose tolerance [8]. Since the 2-h 75 g OGTT had been little investigated for use in pregnancy, various associations and national guideline panels stayed with the recommendations of the U.S. National Diabetes Data Group (NDDG) to use the O'Sullivan 3-h test [9]. However, the different associations chose different blood glucose thresholds to detect abnormalities in pregnancy due to

difficulties associated with converting glucose values from O'Sullivan's studies to their equivalents when glucose was analysed using modern methods in plasma. The result for epidemiology was a variety of studies reporting wildly different estimates and confusion for clinicians on how to define the condition.

There is a dose effect on the developing foetus of increases in blood glucose. Relatively mild hyperglycaemia may lead to less serious outcomes such as macrosomia while early exposure to high blood glucose can lead to birth defects and spontaneous abortion [4]. As more and more women of reproductive age started to develop type 2 diabetes, it became important to distinguish between pre-existing but undiagnosed diabetes in pregnancy from the milder form that develops at 22 weeks and resolves post-partum.

Under the first definition of GDM, a number of studies identified potential risk factors as a way of selecting women for screening, particularly in low-resource settings where universal screening is not feasible. The most important risk factors to emerge were obesity, high blood glucose prior to pregnancy, a family history of diabetes, a history of GDM in previous pregnancy, a history of large for gestational age baby in a previous pregnancy, increasing age, excessive weight gain during pregnancy, and a history of stillbirth or congenital abnormality in the infant [10, 11]. There is considerable overlap in these risk factors with those for type 2 diabetes, which may indicate that a substantial proportion of what was categorised as GDM, was in fact pre-existing diabetes. The identification of a risk profile for screening was further complicated by the fact that many women with risk factors for GDM never developed the condition and similarly many with a low-risk profile later presented with GDM [12, 13].

Experts in the field realised that the most effective way of defining GDM and distinguishing it from pre-existing diabetes in pregnancy was to focus on outcomes. In 2008, the Hyperglycaemia and Adverse Pregnancy Outcomes [4] study tested 25,505 pregnant women in an international multi-centre study using a 2-h 75 g OGTT and followed them through pregnancy. The results lead to recommended diagnostic criteria for GDM representing the average glucose values at which the odds for birth weight >90th percentile, cord C-peptide >90th percentile, and neonatal percentage body fat >90th percentile reached 1.75 times the odds of these outcomes [14]. The thresholds established by this study were adopted by many guidelines and were also recommended by the American Diabetes Association in its 2011 position statement [15].

Most recently, in 2013 the World Health Organization proposed new criteria for the diagnosis and definition of hyperglycaemia first detected in pregnancy. The definition distinguishes the more serious diabetes in pregnancy (DIP), which is more likely to persist beyond the birth and can cause serious foetal abnormalities early in pregnancy, from the milder gestational diabetes (GDM) [16]. The new definition calls for an understanding of the burden of HIP and its relationship with the growing epidemic of type 2 diabetes and distinguishes DIP from GDM based on the degree of hyperglycaemia; a reflection that the risk of serious complications is much higher in diabetes in pregnancy than in GDM. Where studies previously reported the prevalence of GDM, under the new definition, these figures would also include the more severe hyperglycaemia classified as diabetes in pregnancy under the broad title of hyperglycaemia first detected in pregnancy (HFDP) (Table 1.1). Added to this definition are women with diagnosed diabetes who become pregnant; the term HIP encompasses the burden of any glucose intolerance in pregnancy.

Estimating the Burden of HIP

With a clear definition established and risk factors outlined, tracking the burden of HIP becomes more feasible. Some of the most important contributors to the diabetes epidemic, population ageing and changes towards the so-called 'obesogenic' lifestyle, are also contributing to the growing burden of HIP.

Table 1.1 Terminology defining hyperglycaemia in pregnancy and related conditions

Term	Definition
Hyperglycaemia in pregnancy (HIP)	Includes hyperglycaemia first detected during pregnancy (HFDP), and live births in women with previously diagnosed diabetes
Total diabetes in pregnancy (TDP)	Includes live births in women with previously diagnosed diabetes and in women with diabetes in pregnancy
Hyperglycaemia first detected during pregnancy (HFDP)	Includes diabetes in pregnancy (DIP) and gestational diabetes (GDM) as per the WHO 2013 definition
Diabetes in pregnancy (DIP)	Includes: pregnancy in women with previously undiagnosed diabetes; at anytime during pregnancy a fasting plasma glucose >7.0 mmol/L (126 mg/dL); or 2-h plasma glucose >11.1 mmol/L (200 mg/dL) following a 75 g oral glucose load (OGTT); or random plasma glucose >11.1 mmol/L and diabetes symptoms
Gestational diabetes (GDM)	At anytime during pregnancy a fasting plasma glucose 5.1–6.9 mmol/L (92–125 mg/dL); or 1-h plasma glucose >10.0 mmol/L (180 mg/dL) following a 75 g oral glucose load; or 2-h plasma glucose 8.5–11.0 mmol/L (153–199 mg/dL) following a 75 g oral glucose load (OGTT)

Data source [37]

Each of these contributors is described in turn followed by a discussion of the global and regional prevalence estimates for HIP as well as especially vulnerable populations. Finally, a discussion of future trends and projections for HIP and the public health response concludes the chapter.

The Demographic Transition

In 2012, the United Nations estimated that the global population had reached 7 billion people [17]. Population growth has been on an exponential curve with rapid increases in population and shifts towards an older population average age [18]; in just the last decade, the global population has increased by one billion people [19]. The recent period of very rapid demographic change is a result of a secular process called the demographic transition [20]. This transition follows along the development process that transforms a traditional society into an industrial one. A model of the transition is presented in Fig. 1.1. Populations prior to the transition exist with high death rates due to disease and low life expectancy but also high birth and fertility rates to compensate for low survival. Fertility tends to decline as the survival of children into adulthood increases, as family planning becomes more common, and as other competing factors in lifestyle change priorities for women and families on having children. Meanwhile, mortality decreases and increases in life expectancy come with better provision of health services, declines in infectious disease and accompanying deaths in children and young people.

Once the transition begins, the process can be divided in two distinct phases. In the first phase, death rates decline and the birth or fertility rates remain high, leading to an overall growth in the population. In the second phase, fertility rates decline leading to a stabilising or decline in growth over time. Countries have experienced, or are experiencing the demographic transition at different rates and times. Most high-income, developed countries have a large older population that reflects low fertility and high survival (Fig. 1.1). This compares with developing countries for which the demographic transition is in full force.

The demographic transition in fertility and mortality has led to important changes in the global population's age composition (Fig. 1.2). Globally, the population is shifting towards older age groups. The result is an added pressure on health systems to care for the elderly and for the non-communicable diseases (NCDs) associated with age. This in turn has a flow on effect with NCDs

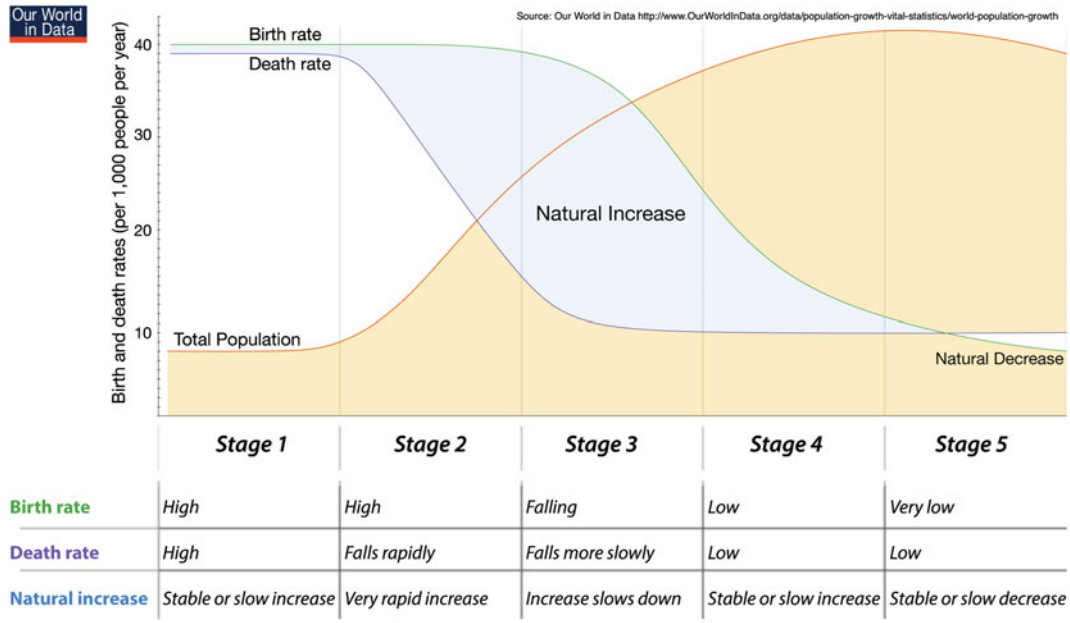

Fig. 1.1 The demographic transition in birth and death rates with effects on the total population. *Source* Our world in data http://www.OurWorldInData.org/data/population-growth-vital-statistics/world-population-growth

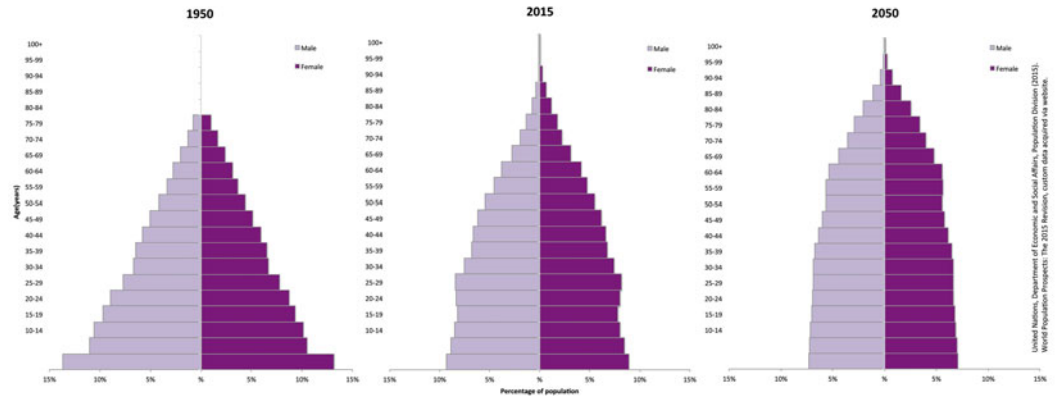

Fig. 1.2 World population distributions by age and sex for 1950, 2015, and 2050. *Data source* United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision, custom data acquired via website

emerging in younger populations and those which increase the risk to future NCDs; among these are gestational diabetes and hyperglycaemia first detected during pregnancy.

High levels of fertility are typically found in countries that also have a high infant mortality and a low use of contraceptives and family planning services [21]. In these societies, families have as many children as they are able to sustain knowing that a number of those children will not reach adulthood. The fertility and mortality rates balance each other in this scenario leading to a relatively stable population.

Further progress in birth control methods and neonatal care, as well as overall development, has shifted fertility downward with the most extreme case of two or even fewer children per woman in Western Europe with few exceptions [22]. This reproductive revolution is mainly due to two factors. First, the desired family size has declined as the cost of having children rose and child survival increased. Second, government intervention played a key role in some parts of the world. In China, for example, this took the form of the one-child policy [23], but many other countries implemented voluntary family planning programmes that provide information and access to contraceptives at subsidised prices [24].

The fertility stage when a woman can get pregnant is narrowing in relation to the total life span. Yet, the pattern of fertility occurring with development is also characterised by shifting of childbirth to older ages in a life course. Women in developed countries are having children later in life, which in turn contributes to a greater proportion of live births after 40 [25]. Changes in fertility may also lead to less children per woman in those countries since less time was left between the birth of the first child and the end of fertility.

The combination of these shifting patterns in demographics and fertility has contributed substantially to increases in HIP. Age is one of the most important risk factors for almost any type of HIP and as women of reproductive age have children at older ages, this will lead to more cases of HIP.

The Epidemiological Transition and the Obesogenic Environment

Trends in health are shifting towards NCDs and away from infectious disease. This phenomenon is known as the 'epidemiological transition' [26]. The transition is characterised by a substantial improvement in child and maternal mortality, a reduction in death and disability from infectious disease, an overall increase in survival and life expectancy, and an increase in NCDs such as cardiovascular disease, diabetes, chronic pulmonary diseases and cancer. Developing countries are experiencing this shift most rapidly and by 2020, NCDs are expected to account for 7 out of 10 deaths in these regions compared with fewer than 5 of 10 deaths today [27]. This shift in the NCD burden, which has important implications for pregnancy, is driven by a shift in the shared core group of risk factors for NCDs: poor diet, low physical activity, tobacco use, and harmful use of alcohol. Most significantly for diabetes and pregnancy, the world population is moving towards a decrease in physical activity and increases in poor diet [28]. The shift contributes to what is known as the 'obesogenic' environment which makes choices for health harder to make and unhealthy behaviours the norm. For developing countries, where the majority of women of reproductive age live, the transition is happening at greater speed [29–31].

The change is driven by a number of factors including changes to the built environment, more people using cars for transportation, and work that requires little physical activity [32]. Where countries are experiencing an epidemiological transition in disease patterns towards NCDs, changes to risk factors like physical activity are also occurring. Sedentary behaviour is considered a risk factor for type 2 diabetes and also for HIP-related conditions like gestational diabetes [33, 34]. It is also a key component of management of women with these conditions. However, it is important to consider that for many women social norms, the environment, or even safety may play a major factor in engaging in physical activity.

One of the major contributors to global increases in high blood glucose, and subsequently HIP, is changes to diet and nutrition. The so-called 'Western diet' is characterised by a high intake of processed foods, sugars, trans fats, and salt. Much of the way in which people eat is shifting away from traditional diets high in fruits and vegetables and towards the Western diet [35]. This has important implications for pregnancy where poor nutrition is a risk factor for the development of high blood glucose. For women who have already developed HIP, a healthy diet and nutrition is an

important part of management of the condition. However, where food availability is skewed towards highly processed, unhealthy food choices changing behaviour at the level of the individual is a significant challenge.

As discussed above, there is significant overlap in the type 2 diabetes epidemic and women developing or being diagnosed with HIP. The drivers of one inevitably drive the other. Where shifts in risk factors for type 2 diabetes and obesity occur and in the absence of prevention, we can expect a concomitant increase in HIP. There is a collision of risk factors as the type 2 diabetes epidemic and its determinants shifts towards younger age groups and fertility rates in women towards older age. The two combined with high birth rates in many developing countries will inevitably mean more women globally faced with high blood glucose during pregnancy.

Estimating HIP

Accurate and comparable estimates of HIP are important not just for monitoring and surveillance, but for public health planning and education of health professionals. The large variation in the definition of HIP and the terminology applied to describe associated conditions has made it difficult to estimate the burden of HIP [6]. Even with a newly adopted WHO definition of HIP [16] that marks clear boundaries in severity for gestational diabetes and hyperglycaemia first detected during pregnancy, it will take years before a unified definition is applied clinically or in epidemiological studies. Part of this may have to do with resources, but also with national standards and even the interests of the investigators.

Nonetheless, the gold standard for building an estimate of disease prevalence is the population-based study. In this study design, the researcher takes a sample of the population that is deemed to be representative of the whole and systematically tests each person within that sample for a given disease or condition. In the case of estimating type 2 diabetes, for example, such population-based studies involve investigators going door to door in the selected sampling area and testing subjects who agree to be included using a blood sample and applying the same procedure to each subject. This allows the investigators to build an estimate of the prevalence for diabetes for that sample and infer what that prevalence may be for the population within certain boundaries or confidence intervals.

Type 2 diabetes is a relatively stable disease in that once a person has developed the condition they will not spontaneously recover or go into remission without treatment. This makes it relatively straightforward to study because the timeframe used to collect data may be quite long. In the case of conditions of pregnancy, such as HIP, timing presents an added challenge. A woman is only pregnant for some months in a year. In addition, some conditions of HIP, such as gestational diabetes, will only develop after a certain point in the pregnancy so that testing is limited to an even shorter timeframe. Ideally, all pregnant women would be followed throughout their pregnancies and screened multiple times, as proscribed by the WHO recommendations: once to rule out previously undiagnosed existing type 2 diabetes early in pregnancy and thus prevent the most serious risks to the developing foetus by early treatment; and, for those who show no hyperglycaemia early in the pregnancy, an additional screening at 24–28 weeks for gestational diabetes. If this approach were universally applied, epidemiologists could simply access results from the health records of screened women to make an estimate of HIP-affected pregnancies in a year. However, universal antenatal care is far from a reality, especially in developing countries [36].

Indeed, very few population-based studies exist [6]. Most studies draw from samples in a group of hospitals or even a single hospital. These studies can hardly be considered representative for an entire country, except where near-universal antenatal care exists. A few countries have come close (e.g. Denmark, Sweden, the Netherlands and others), but for many countries, hospital data are not a

reliable source. The result is that for many parts of the world, there is simply not enough data to make a representative guess of the burden of HIP.

The estimates presented here are a combination of studies selected to be the best or most reliable and then adjusted for differences in definitions, age, and fertility patterns. These were then applied to population estimates to arrive at regional and global estimates of prevalence [3]. Where country estimates exist, studies conducted in those countries were reliable enough to be used.

Global and Regional Estimates, and Vulnerable Populations

The International Diabetes Federation (IDF) estimates that in 2015, 16.2% of live births to women between the ages of 20 and 49 years had some form of HIP (Table 1.1) [37]. The vast majority of those cases are due to the milder form gestational diabetes (85.1%), while the rest represent pre-existing diabetes only about half of which was diagnosed prior to pregnancy. This figure translates to at least 20.9 million live births affected by some form of HIP.

One of the most important risk factors for the development of HIP and especially gestational diabetes is increasing age. As seen in Fig. 1.3, the prevalence of HIP starts at around 10% for women 20–24 years old and increases rapidly to almost half of live births in women over the age of 45 (45.9%). However, as described above, fertility rates move in the opposite direction with many more total live births in younger women and fewer in the older age groups. As a result, the majority of live births affected by HIP occurred in women under the age of 30 (10.4 million). If the estimates included women and girls 15 years and older, the numbers would inevitably be higher. However, reliable data on diabetes prevalence and fertility are not available for many countries for younger age groups. (Table 1.2).

Regional Variation

There are some regional differences in the prevalence of HIP (Table 1.3, Fig. 1.4). In terms of percentage of live births affected, the South-east Asia Region that includes India and Pakistan, had the highest prevalence at 24.2% compared to 10.5% in sub-Saharan Africa (Table 1.3). When factoring in fertility rates for different regions, the numbers of live births show a similar pattern. South-east Asia also had the highest number of live births affected by HIP (6.7 million), followed by the Middle East and North Africa region (3.7 million), and the Western Pacific (3.7 million) including China, Australia and Indonesia. The Americas had the lowest numbers of live births estimated affected by HIP at just under 2 million although still close to 12% of births are affected by HIP.

HIP and Development

The vast majority (87.6%) of cases of HIP were in low- and middle-income countries (Fig. 1.5), where access to antenatal and maternal care is often limited or non-existent. Not coincidentally, middle-income countries also have the highest burden of diabetes in the world [37]. These are areas where demographic, social and epidemiological transitions are rapidly changing lifestyle patterns and fertility. The combination is an increase in life expectancy, but maintaining a high fertility rate coupled with changes in health behaviours including diet and physical activity. The result is an environment highly conducive to the development of HIP, but with a health system that is unlikely to

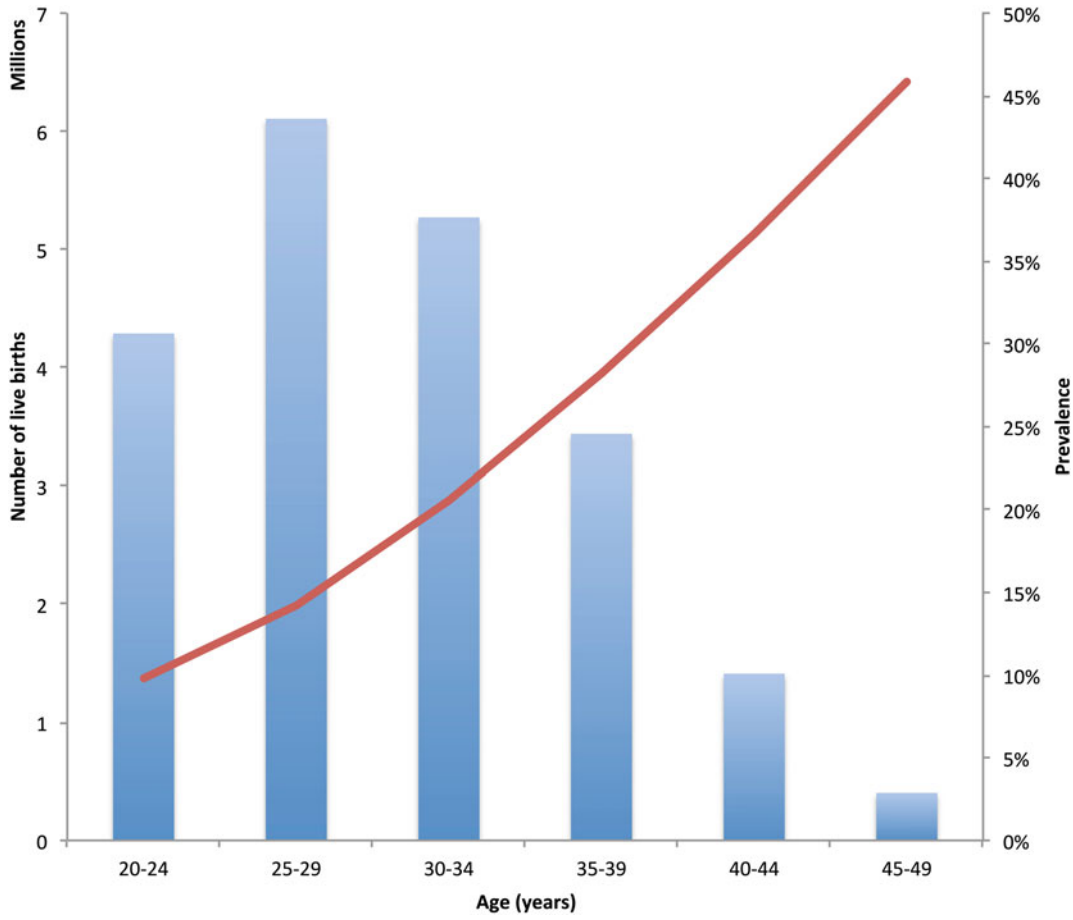

Fig. 1.3 Number of live births affected and prevalence (%) of HIP by age (years) in 2015. *Data source* [37]

Table 1.2 Global estimates of hyperglycaemia in pregnancy, 2015

Total live births to women aged 20–49 years (millions)	129.4
Hyperglycaemia in pregnancy	
Global prevalence (%) of live births	16.2
Number of live births affected (millions)	20.9
Percentage due to gestational diabetes (%)	85.1
Percentage due to diabetes first detected in pregnancy	7.4
Percentage due to previously diagnosed diabetes	7.5

Data source [37]

be able to meet this high burden. Indeed, rapid development in many parts of the world mean that population patterns and disease are shifting more rapidly than the development of health systems or prevention. The most likely scenario is that low-income countries will also follow this pattern, but that it will be many generations before the health systems of these developing countries reach a point where primary and antenatal care are sufficient to stem the burden of HIP and its outcomes.

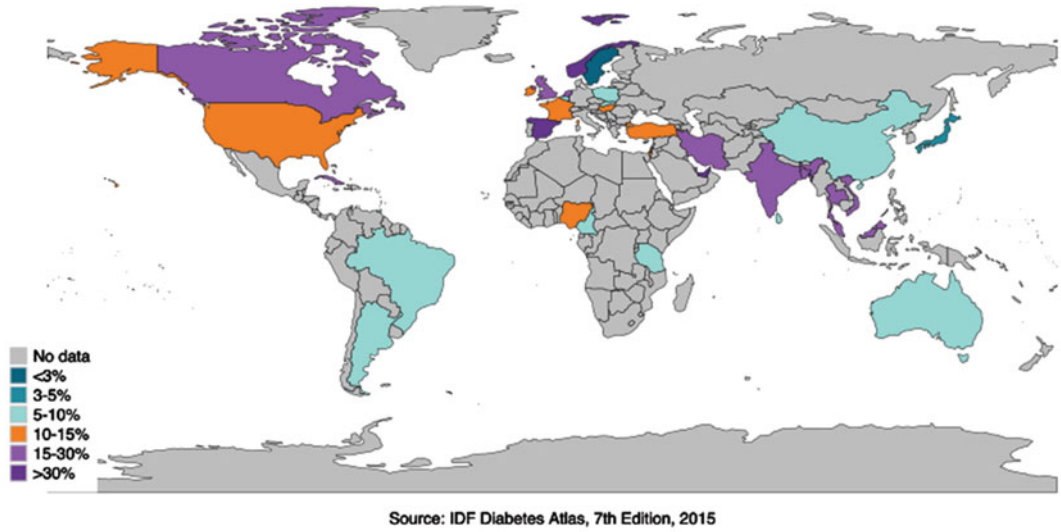

Fig. 1.4 Estimates of prevalence (%) of HIP in the world, 2015

Table 1.3 Hyperglycaemia in pregnancy in women aged 20–49 years by region, 2015

Region	Unadjusted prevalence (%)	Age-adjusted prevalence (%)	Number of live births affected (millions)
Sub-saharan Africa	10.5	9.5	3.3
Europe	15.8	13.7	1.7
Middle East and North Africa	21.8	17.7	3.7
North America and Caribbean	14.9	11.9	1.0
South and Central America	13.2	11.5	0.9
South-east Asia	24.2	26.3	6.7
Western Pacific	12.4	12.1	3.7

Data source [37]

At-Risk Populations and Indigenous Peoples

Variations in the burden of HIP also exist within country borders. Some populations and ethnic groups are developing HIP and gestational diabetes at higher rates [38, 39]. This may be due to genetic predispositions, but also to changes in lifestyle. Indigenous peoples have shown higher prevalence rates of gestational diabetes and also type 2 diabetes when compared to non-indigenous populations in the same country [40].

Many of these populations are at social disadvantage through a lack of economic and social support, education, employment, health and security. As a result, they are not only faced with higher rates of HIP but poorer outcomes associated with a lack of adequate management. Indigenous peoples shoulder a disproportionate burden of diabetes in many parts of the world and this is reflected in the burden of HIP as well.

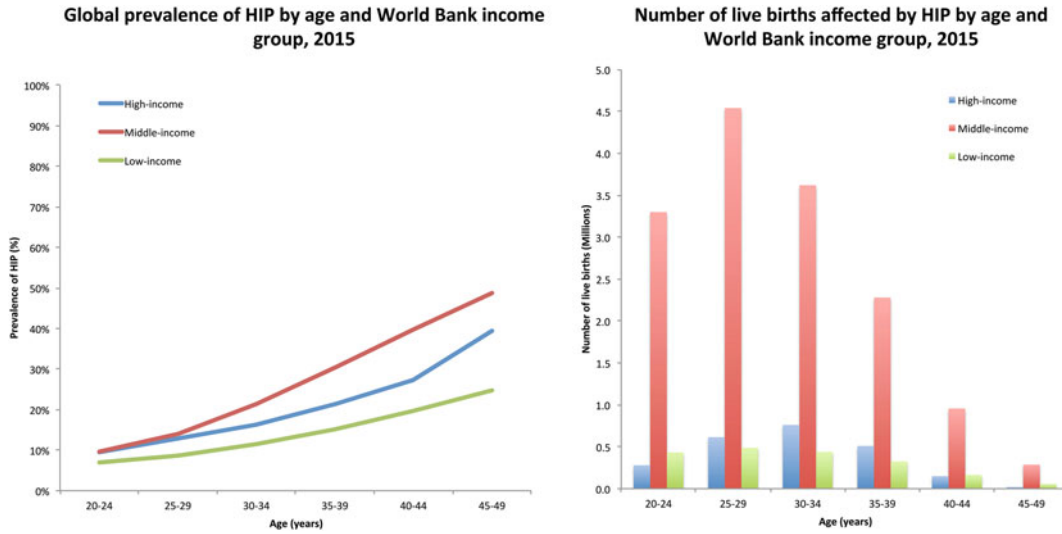

Fig. 1.5 Hyperglycaemia in pregnancy in women aged 20–49 years by income group region, 2015. *Data source* [37]

Conclusion: The Future of HIP and the Public Health Response

Quantifying the burden of HIP remains a challenge. Universal harmonisation of a definition for identification and categorisation remains to be achieved. In 2013 the WHO decided to accept the general principles behind how the IADPSG criteria were derived in the interest of moving towards a universal standard recommendation for the diagnosis of GDM. While this approach has been adopted by many national organisations, others continue to use different criteria [41].

Early identification through universal antenatal care and screening are the best chance for women and offspring to prevent the possible complications related to HIP, particularly in the most severe cases. However, a practical challenge is the reality that many developing countries and health systems around the world do not have the capacity to implement a GDM detection programme based on all or only high risk women having a 2-h OGTT and therefore options which do not involve an OGTT need to be considered [42, 43]. The other dilemma which faces health systems is maximising available country resources and prioritising and balancing resource between improving care of people with diabetes and finding and treating more people with undiagnosed diabetes, including GDM. Screening is not appropriate unless adequate care can be provided.

Trends in demographics, population growth and ageing, fertility, and diabetes are all projected to increase dramatically in the next generations. In combination with changes in lifestyle and risk factors contributing to overweight and obesity, these will lead to more and more cases of HIP. Identification, management and prevention of these cases will inevitably pose a heavy burden on the health system, particularly of developing countries where growth and change are happening at a rapid pace. For low-resource settings, priority will have to be on providing adequate antenatal care with counselling on healthy eating and physical activity. Health systems will have to be strengthened and health professionals should be educated to provide care integrated with antenatal services.