Dysglycemia in Pregnancy and Maternal/Fetal Outcomes

Corinne M. Silva, PhD,[1] Matthew E. Arnegard, PhD,[2] and Christine Maric-Bilkan, PhD[3]

Abstract

Maternal dysglycemia—including diabetes, impaired glucose tolerance, and impaired fasting glucose—affects one in six pregnancies worldwide and represents a significant health risk to the mother and the fetus. Maternal dysglycemia is an independent risk factor for perinatal mortality, major congenital anomalies, and miscarriages. Furthermore, it increases the longer-term risk of type 2 diabetes mellitus, metabolic syndrome, cardiovascular morbidity, malignancies, and ophthalmic, psychiatric, and renal diseases in the mother. The most commonly encountered form of maternal dysglycemia is gestational diabetes. Currently, international consensus does not exist for diagnostic criteria defining gestational diabetes at 24–28 weeks gestation, and potential diagnostic glucose thresholds earlier in gestation require further investigation. Likewise, recommendations regarding the timing and modality (*e.g.*, lifestyle or pharmacological) of treatment vary greatly. Because a precise diagnosis determines the appropriate treatment and outcome of the pregnancy, it is imperative that a better definition of maternal dysglycemia and its treatment be achieved. This article will address some of the controversies related to diagnosing and managing maternal dysglycemia. In addition, the article will discuss the impact of maternal dysglycemia on complications experienced by the mother and infant, both at birth and in later life.

Keywords: maternal dysglycemia, gestational diabetes, diagnostic criteria, maternal morbidity, offspring outcomes

Introduction

G LUCOSE HOMEOSTASIS DURING pregnancy is essential to the health of the mother and fetus. Maternal dysglycemia—including diabetes, impaired glucose tolerance, and impaired fasting glucose—is one of the most common complications of pregnancy. Indeed, maternal hyperglycemia currently affects approximately one in six pregnancies worldwide.[1] The Centers for Disease Control and Prevention recently estimated the national prevalence of diabetes first diagnosed during pregnancy, known as gestational diabetes mellitus (GDM), to be 6%.[2] The incidence of GDM and maternal dysglycemia more broadly is on the rise in the United States and globally.[2–5]

Along with the increasing prevalence of maternal dysglycemia, the maternal mortality rate rose dramatically in the United States from 1987 to 2014 and remains high.[6,7] In contrast, the rates of pregnancy-related deaths in high-income, peer countries of the United States decreased over the same period, as did the global average rate of maternal mortality.[8] Instances of severe maternal morbidity (*i.e.*, near misses for maternal mortality) also have become more common in the United States, affecting more than 50,000 women annually.[9–11] Dysglycemia is one risk factors for severe maternal morbidity.[12] Furthermore, maternal dysglycemia and maternal morbidity share common risk factors, such as advanced maternal age and obesity, both of which are increasing in prevalence globally.[3,5,13–16]

GDM is the most often encountered form of maternal dysglycemia and is more common than pregestational diabetes (type 1 diabetes mellitus [T1DM] or type 2 diabetes mellitus [T2DM]).[1,13,17,18] Currently, international consensus on the

¹Division of Diabetes, Endocrinology, and Metabolic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA.
²Office of Research on Women's Health, Division of Program Coordination, Planning, and Strategic Initiatives, Office of the Director, National Institutes of Health, Bethesda, Maryland, USA.
³Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland, USA.

timing of GDM screening or the criteria for its diagnosis and treatment does not exist,[19,20] and recommendations on GDM treatment targets vary.[21] This review addresses some of the controversies surrounding the screening, diagnosis, and treatment of GDM. The growing prevalence of maternal hyperglycemia, predominantly due to the increasing trends in T2DM and GDM, is an important factor in addressing the high rates of maternal morbidity and mortality in the United States, as well as poor outcomes for maternal health later in life and negative outcomes for offspring in both the short and long term.

Impacts of Maternal Dysglycemia on Maternal Outcomes

Pregnant women with any form of dysglycemia experience higher morbidity and mortality rates compared with normal pregnancies. The mortality rate in pregnant women with T1DM is twofold to threefold higher than for nonpregnant women with T1DM, and 5 to 20 times higher than the general obstetric population.[22,23] The precise causes of mortality may be difficult to determine because mortality may be due to pregnancy complications, the presence of T1DM, or causes unrelated to either pregnancy or T1DM.[22]

It has been reported that HbA_{1c} levels, albuminuria around the time of conception, and the presence of underlying conditions—such as hypertension and preeclampsia—are important determinants of maternal morbidity and mortality.[23] If the hypertensive pregnancy is associated with renal dysfunction (serum creatinine >176 μmol/L or proteinuria in the nephrotic range [>3 g/24 hour]) and/or preexisting cardiovascular disease (CVD), the risk for poor maternal outcomes increases further.[24] The prevalence rates of hypertensive disorders of pregnancy—including chronic or gestational hypertension, preeclampsia/eclampsia, and chronic hypertension with superimposed preeclampsia—are particularly high among women with diabetes.[25,26] Moreover, gestational dysglycemia increases the risk of postpartum hypertension.[27]

The rate of C-sections has been reported to be higher among pregnant women with diabetes, mostly due to macrosomia.[28] This observation is not universal, however, because some studies have reported no difference in C-section rates, at least between women with GDM and glucose-tolerant women.[29] Women with T1DM exhibit severe hypoglycemia in up to 50% of pregnancies[30] and are at increased risk for postpartum hemorrhage and infection, as well as hemolysis, elevated liver function test, and low platelet (HELLP) syndrome.[28]

In many cases, metabolic abnormalities (*e.g.*, obesity, hypertension) precede the diagnosis of GDM, and these women are at increased risk for developing T2DM and metabolic syndrome later in life.[31] The reported incidence of the development of T2DM of women with GDM varies depending on the length of follow-up after pregnancy, diagnostic criteria, and the racial and ethnic makeup of the population studied. Retrospective studies find that women with GDM have a 20% to 60% risk of developing T2DM in the 5 to 10 years after pregnancy.[32,33] One study showed that women with GDM have an almost eightfold higher risk of developing T2DM within 10 years, even after adjusting for socioeconomic status and body mass index (BMI).[34] A more recent analysis from the U.S. National Health and Nutrition Examination Survey database showed that 19.7% of women who had GDM eventually developed T2DM.[35]

Although T2DM is a known risk factor for CVD, some studies have addressed whether GDM is an independent risk factor for CVD. In a longitudinal analysis of the Coronary Artery Risk Development in Young Adults study, Gunderson et al.[36] concluded that GDM was an independent risk factor for early atherosclerosis, even beyond that related to prepregnancy obesity. Accordingly, the American College of Obstetricians and Gynecologists (ACOG) and the American Diabetes Association (ADA) stress the importance of screening women with a prior diagnosis of GDM for disorders of glucose metabolism at least once every 3 years after their pregnancies.[17,37] Not only does this screening have health implications for the mother, it also has important implications for subsequent pregnancy outcomes, including the health of her offspring.

Impacts of Maternal Dysglycemia on Offspring Outcomes

The most serious outcomes of diabetic pregnancies are neonatal mortality, stillbirths, preterm delivery (before 37 weeks of gestation), excessive fetal growth, and congenital abnormalities.[28] Despite improvements in maternal glycemic monitoring and control, perinatal mortality rates and short-term complications continue to rise.[38] The rates of perinatal mortality among women with either T1DM or T2DM are threefold to fourfold higher than among the general obstetric population.[39] Although stillbirths remain a common outcome of diabetic pregnancies, lower rates of stillbirth have been reported recently, at least in some countries,[40] which may be a result of improved preconception care and better glycemic control during pregnancy.

The mechanisms by which intrauterine exposure to maternal hyperglycemia translates to increased rates of fetal death, stillbirth, and preterm birth remain incompletely understood. It is thought that, because of the acquired dependence on maternal hyperglycemia *in utero*, babies born to mothers with GDM are at an increased risk for hypoglycemia at birth, which may lead to brain injury if left untreated.[41]

Maternal hyperglycemia leads to fetal β cell hyperplasia and increased endogenous production of insulin and insulin-like growth factor 1.[42] The resultant fetal hyperinsulinemia lowers fetal glucose levels, thus increasing the glucose concentration gradient across the placenta, driving glucose flux to the fetus.[43] This persistent fetal hyperinsulinemia has adverse effects on offspring health, both short- and long-term. Fetal hyperinsulinemia, in turn, contributes to pancreatic β cell dysfunction and insulin resistance, even prenatally.[44] Another neonatal complication of hyperglycemic pregnancy is respiratory distress syndrome. In particular, GDM is an independent risk factor for neonatal respiratory distress syndrome after 34 weeks of gestation.[45] Although preterm delivery and asphyxia may be the cause of the increased incidence of respiratory distress syndrome in the infants of diabetic mothers, it also is thought that metabolic derangement, *per se*, may contribute to the inadequate production of pulmonary surfactant.[46]

Uncontrolled maternal hyperglycemia leading to fetal hyperinsulinemia is associated with fetal growth acceleration and macrosomia (defined as a birth weight of >4–4.5 kg and/or >90th percentile weight for gestational age).[28,47] Macrosomia in offspring exposed to maternal hyperglycemia is associated with defects in many organs—including heart, kidney, liver, and pancreas.[48] For example, hyperglycemia has been shown to alter the development and maturation of

fetal cardiomyocytes at genetic, structural, and functional levels, leading to fetal cardiomyopathy.[49] Maternal hyperglycemia results in reduced nephron endowment in the fetal kidney, thus increasing the risk for hypertension and chronic kidney disease later in life.[50]

Although birth defects resulting from diabetic pregnancy have been significantly reduced over the past two decades[51]—in part because of improved glycemic control—the risk of congenital malformations in the offspring of mothers with diabetes remains twofold to fivefold higher than in normal pregnancies.[40,52] Maternal hyperglycemia is associated with congenital heart, kidney and urinary tract, neural tube, and gut defects.[53,54] The Type 2 Diabetes in Adolescents and Youth (TODAY) study, a recent randomized controlled trial designed to compare three treatment options for youth with T2DM, highlighted the severe effects of uncontrolled T2DM during pregnancy.[55] Despite consent and extensive counseling to use contraception during the study to avoid pregnancy, 10% of the 452 girls enrolled became pregnant. Of these pregnancies, 26.4% resulted in miscarriage or stillbirth, and 20.5% of the live births had major congenital abnormalities.

Animal studies have shed some light on mechanisms of teratogenesis due to maternal diabetes. Reported mechanisms include ''fuel-mediated teratogenesis'' (*i.e.*, increased delivery of fuels—including glucose and ketones—leading to biochemical disturbances in the fetus); insufficient apoptosis inhibition; and altered expression of developmental control genes (e.g., *Pax3*, *Akt*, *JNK1/2*, and *Pkrc*) as a result of oxidative stress.[53,56,57] Animal studies have shown that this transgenerational transmission of hyperglycemia is associated with epigenetic modifications in germ cells, such as a dysregulation of *Igf2/H19* methylation in the pancreatic islet cells of offspring.[58]

Studies in humans and experimental models have shown that an offspring exposed to maternal dysglycemia (due to GDM, T1DM, or T2DM) has a higher risk for CVD, obesity, GDM, T2DM, and associated metabolic diseases later in life, even after adjusting for confounders.[59,60] Children of mothers with GDM, for example, are twice as likely to develop childhood obesity compared with offspring from normal pregnancies, even after adjusting for such confounders as maternal BMI.[61] The fact that children of mothers with dysglycemia due to either T1DM or T2DM are at increased risk of developing this condition in their own pregnancies highlights the vicious intergenerational cycle of maternal dysglycemia.[62,63]

Insufficient insulin production is one proposed mechanism behind the long-term metabolic consequences of intrauterine hyperglycemia for offspring. A study of 104 adult children of Pima Indians found decreased insulin response to glucose infusion (even in the absence of impaired glucose tolerance) only in offspring exposed to a diabetic environment *in utero*.[64] This finding might explain the effect of maternal hyperglycemia on β cell programming in the fetus and its long-term consequences. Epigenetic alterations also have been suggested as a vehicle for transmitting maternal hyperglycemia to the offspring and affecting their long-term health.[65]

Studies in animals show that adverse offspring outcomes of maternal hyperglycemia are largely preventable by normalized maternal blood glucose levels.[66] The extents to which tighter control of maternal hyperglycemia in humans can prevent long-term consequences of maternal dysglycemia for offspring remain to be elucidated. Long-term follow-up studies have been lacking in this regard. Basic research aimed at better understanding the mechanisms underlying the long-term consequences of maternal hyperglycemia for offspring also are needed.

Diagnosis and Management of Maternal Dysglycemia

Because of the risks that maternal dysglycemia poses for both mother and offspring, it is important to know how to define GDM, as well as how and when blood glucose levels and glucose tolerance should be measured. Furthermore, if GDM is diagnosed, it is critical to know how it should be treated, while considering both the immediate effects during pregnancy and long-term outcomes for mothers and their offspring. Clarifying these issues is not straightforward, and current recommendations vary across countries and even among U.S. medical centers.[67]

GDM, as defined by the Fifth International Workshop Conference on Gestational Diabetes Mellitus, is glucose intolerance with onset or first recognition during pregnancy.[68] Current practice guidelines recommend testing for GDM at 24–28 weeks of pregnancy (just before or during the third trimester). The ACOG recommends a two-step process.[17] The first step (screening) involves giving the pregnant woman a 50-g glucose load in a nonfasting state. If, after 1 hour, the plasma glucose level is above a threshold (ranging from 130 to 140 mg/dL, depending on guidelines where the screening is being performed), the second step is followed. The second step (an oral glucose tolerance test) involves administering a 100-g glucose load after an overnight fast. Plasma glucose is measured before the glucose load and again after 1, 2, and 3 hours. If two of these four values exceed certain levels, GDM is diagnosed: fasting (>95 mg/dL), 1 hour (>180 mg/dL), 2 hours (>155 mg/dL), and 3 hours (>140 mg/dL). Most U.S. medical centers and hospitals adhere to this two-step process.

In contrast, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) and World Health Organization (WHO) recommend a one-step test.[69,70] The plasma glucose level is measured after an overnight fast and then again at 1 and 2 hours after a 75-g glucose load. If only one of these plasma glucose measures is higher than the predefined levels (fasting, 92 mg/dL; 1 hour, 180 mg/dL; 2 hours, 153 mg/dL), then a diagnosis of GDM is made. According to these international criteria, 18% of pregnant women in the United States would be diagnosed with GDM.[71]

The differences in screening procedures described above resulted from the international Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).[26] The HAPO study was designed to clarify the risks of adverse outcomes associated with degrees of maternal glucose intolerance less severe than those found with overt diabetes during pregnancy. An ethnically diverse group of 25,505 women was recruited from across 15 centers and 9 countries. Women were given a 75-g oral glucose tolerance test at 24–32 weeks of pregnancy (levels measured at fasting, 1 hour, and 2 hours) and another random glucose measurement at 34–37 weeks. The results from 2.9% of the women analyzed reached

glucose levels either diagnostic of overt diabetes or above predetermined safety levels and thus were not included in further analysis. Primary outcomes for those remaining in the study were as follows: birth weight >90th percentile, primary cesarean section delivery, clinically defined neonatal hypoglycemia, and cord C-peptide >90th percentile. Secondary outcomes were preeclampsia, preterm delivery, shoulder dystocia or birth injury, hyperbilirubinemia, and intensive neonatal care.[26]

The results of the HAPO study showed that glucose levels below those that currently were used to diagnose GDM demonstrated a linear association with increased risks for both mother and baby, including the need for cesarean section, high birth weight, and low neonatal blood glucose level at birth. There also were significant associations with secondary outcomes, although they were somewhat weaker.[26] Furthermore, at ~11 years after delivery, mothers (and children) from the HAPO study were followed up for metabolic analysis. Of the 4,697 mothers who took part in the HAPO follow-up study, 14% would have been diagnosed with GDM during their pregnancy under the stricter IADPSG criteria. In fact, more than half of these women had developed either T2DM or prediabetes.[72] Along with the other factors that also were measured—including age, BMI, and family history—this HAPO follow-up study showed that increased glucose levels during pregnancy were an independent risk factor for the development of diabetes in the mother 11 years after pregnancy. Furthermore, the children of these mothers (average age, 11 years) had increased measures of adiposity compared with those whose mothers did not have GDM during their pregnancy.[73,74]

With the increasing incidence of obesity and maternal age, the prevalence of both GDM and overt diabetes first detected during pregnancy are increasing.[75–79] Many of these high-risk women are being screened for overt diabetes or GDM early in pregnancy.[37] However, no consensus yet exists regarding when to measure and how to treat GDM. A 2014 U.S. Preventive Services Task Force (USPSTF) review concluded that evidence was insufficient to recommend either for or against GDM screening before 24 weeks of pregnancy, given the lack of consistent evidence for a treatment effect on either maternal or infant outcomes.[80]

Insulin resistance and, therefore, plasma glucose levels are known to increase throughout pregnancy.[81,82] The natural change in glucose metabolism during pregnancy complicates the diagnosis of GDM. In July 2018, the ADA published a Special Article Collection in *Diabetes Care* titled "Reconsidering Pregnancy with Diabetes," highlighting the importance of addressing diagnostic criteria, outcomes for both mother and baby, and comparison of treatment paradigms, both lifestyle based and pharmacological (*e.g.*, metformin, glyburide, insulin).[83–88]

In 2017, NIDDK sponsored a workshop to identify research gaps in GDM diagnosis and treatment. Like the USPSTF in 2014, the workshop proceedings' concluded evidence was insufficient to either support or rule out screening for GDM before 24 weeks of gestation.[89,90] The workshop highlighted the need for further studies, not only to define diagnostic criteria but to identify alternative markers (beyond glucose measurements) and, ultimately, to determine the effects of early GDM diagnosis and treatment on maternal and birth outcomes.[89,90]

Following the recommendations of this workshop, an NIDDK-funded study will investigate the use of continuous glucose-monitoring devices to better understand how glucose levels change during pregnancy and whether glucose levels early in pregnancy reflect those measured at 24–28 weeks. Results from this study should help define the parameters for future studies to assess the potential benefits of treatment strategies during pregnancy that may lead to better outcomes for mothers, for babies at birth, and for long-term maternal and offspring health.

Conclusion

Although tremendous progress has been made in understanding the adverse outcomes of maternal dysglycemia for mothers and their offspring, important knowledge gaps remain in terms of the mechanisms underlying these effects. It is also essential to achieve a better understanding of the course of maternal dysglycemia and its diagnosis. Only when there is a precise diagnosis of this condition will the most appropriate treatment be determined. This knowledge is critical to improving maternal glucose homeostasis and, in turn, the course and outcome of pregnancy.

ACOG and WHO recognize that improving the health of mothers and newborns depends on the continuity of pre-pregnancy, antenatal, and postpartum care.[91,92] The effects of maternal dysglycemia on mothers later in life and the trans-generational cycle of metabolic disease risk rooted in maternal dysglycemia illustrate the added importance of broadening this continuum to the entire course of a woman's life and even across generations. Research in the context of an integrative life-course framework will help advance the diagnosis, prevention, and treatment of maternal dysglycemia to the benefit of mothers, offspring, and future generations.

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Address correspondence to:
Christine Maric-Bilkan, PhD
Division of Kidney, Urologic, and Hematologic Diseases
National Institute of Diabetes
and Digestive and Kidney Diseases
National Institutes of Health
6707 Democracy Boulevard
Bethesda, MD 20892
USA

E-mail: christine.maric-bilkan@nih.gov