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Obesity and Diabetes in Mothers and Their Children: Can We Stop the Intergenerational Cycle?

Sharon J. Herring and

Center for Obesity Research and Education, Temple University School of Medicine, 3223 North Broad Street, Suite 175, Philadelphia, PA 19140, USA

Emily Oken

Obesity Prevention Program, Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA

Sharon J. Herring: Sharon.Herring@temple.edu

Abstract

Obesity prevalence in the United States has reached an alarming level. Consequently, more young women are entering pregnancy with body mass indices of at least 30 kg/m². While higher maternal weight entering pregnancy is related to several adverse pregnancy outcomes, some of the strongest and most compelling data to date have linked prepregnancy obesity to gestational diabetes mellitus (GDM). The mechanisms by which excess maternal weight influences metabolic dysfunction in pregnancy are similar to those in obese nonpregnant women; adipocytes are metabolically active and release a number of hormones implicated in insulin resistance. Heavier mothers are also more likely to have higher glucose levels that do not exceed the cutoff for GDM, but nevertheless predict poor perinatal outcomes. Longer-term complications of GDM include increased risk of maternal type 2 diabetes and offspring obesity. Promising intervention studies to decrease the intergenerational cycle of obesity and diabetes are currently underway.

Keywords

Gestational diabetes mellitus; Obesity; Pregnancy; Postpartum; Maternal health; Child health; Glucose metabolism; Fetal growth; Insulin resistance; Gestational weight gain; Adiposity; Type 2 diabetes mellitus

Introduction

The prevalence of obesity (defined as a body mass index [BMI] of at least 30 kg/m²) is alarmingly high, having reached 33.8% among US adults in 2008 [1]. With respect to morbidity, mortality, and economics, the burden of obesity is enormous [2]. Risks of cardiovascular disease, some cancers, and type 2 diabetes increase with rising BMI [2]. The unfavorable effects of obesity may be more severe for women than for men [3]; for example, obese middle-aged women have a twofold higher risk of stroke than BMI-matched men [4]. Further, obesity rates are higher among women (35.5%) than men (32.2%), with the highest rates among minority women. Nearly 50% of black women are obese and non-Hispanic

black women are more than twice as likely to be obese, compared with non-Hispanic white women [1].

Consequently, young women are increasingly likely to enter pregnancy obese. Using data from 26 states and New York City ($n=75,403$ women) participating in the 2004 to 2005 Pregnancy Risk Assessment Monitoring System (PRAMS), Chu et al. [5] found that 1 in 5 women were obese when they became pregnant; the prevalence was as high as one-third in some geographic and racial/ethnic subgroups. Higher maternal weight entering pregnancy is associated with a number of adverse pregnancy outcomes, including increased rates of cesarean section, fetal macrosomia, and prolonged or complicated vaginal delivery [6], along with higher postpartum weight retention in the mother [3]. Additionally, children born to heavier mothers are at higher risk for being overweight themselves in later life [7]. Thus, maternal obesity has become one of the most common preventable risk factors for a complicated pregnancy in the United States.

In parallel with the rise in maternal obesity, the number of women with gestational diabetes mellitus (GDM) has increased [8]. Several recent systematic reviews and meta-analyses have confirmed a strong, independent association between obesity and diabetes in pregnancy; compared with normal weight women, obese mothers have more than a threefold increased risk of developing GDM [9, 10]. Regardless of a woman's prepregnancy weight, weight gain both during and between pregnancies additionally predisposes to increased GDM risk [11, 12]. Heavier mothers are also more likely to have higher glucose levels that do not exceed the cutoff for GDM, but nevertheless confer elevated risks similar to those associated with frank GDM [13•].

Like obesity, GDM is associated with complications both during and after pregnancy. Women with GDM have a greater risk of developing hypertensive disorders of pregnancy such as preeclampsia [14], and approximately 50% of women with a history of GDM develop type 2 diabetes mellitus within 5 to 10 years after delivery [15]. Children of mothers with GDM are not only more likely to be macrosomic and have higher body fat at birth, but they are also at elevated risk in later life of becoming overweight and developing related complications such as higher blood pressure and type 2 diabetes [14]. Thus, maternal obesity begets glucose intolerance in pregnancy, which begets additional cases of obesity and diabetes [16]. Interrupting this intergenerational cycle could have long-lasting benefits for maternal and child health.

In this article, we review causes and sequelae of hyperglycemia in pregnancy. We start with a brief review of the usual physiology of glucose metabolism in pregnancy, and then turn to mechanisms by which excess adiposity results in GDM. We present recent evidence about how higher gestational weight gains and obesity risk behaviors in pregnancy (ie, maternal physical inactivity, poor diet quality) may confer additional diabetes risk. We review data linking GDM with offspring weight and cardiometabolic risk. We also address current controversies around timing of GDM screening and diabetes classification, particularly among mothers with pregravid obesity. Finally, we focus on strategies to help obese mothers lose prepregnancy and postpartum weight to decrease the risk of diabetes development in both mothers and their children.

Glucose Metabolism in Pregnancy

Normal pregnancy is associated with marked changes in insulin resistance and glucose metabolism that are needed to provide substrate for the growing fetus. Among lean women (pregnancy BMI <25 kg/m²) insulin secretion increases in early pregnancy, whereas insulin sensitivity is unchanged, or even slightly improved [17]. Maternal lipogenesis

results, as preparation for the rise in energy needs to support rapid fetal growth in the second half of pregnancy [18].

As pregnancy progresses, maternal insulin secretion from pancreatic β cells further increases, yet hepatic glucose production, which is normally suppressed by insulin, also increases by severalfold [17]. Why? Peripheral insulin sensitivity declines from 33% to 78% by late pregnancy, approaching rates observed in individuals with established type 2 diabetes [17]. Thus, insulin is unable to suppress lipolysis, free fatty acid concentrations rise, and more energy to drive gluconeogenesis is available [19]. This metabolic pattern is a consequence of continuous withdrawal by the fetus of nutrients from maternal blood coupled with maternal hormonal and metabolic factors secreted by adipose tissue (leptin and triglycerides), the growth hormone axis (insulin-like growth factor binding proteins), and the placenta (human placental lactogen and tumor necrosis factor- α) [20, 21].

Gestational Hyperglycemia

Mothers with GDM, defined as carbohydrate intolerance first diagnosed in pregnancy, experience an additional decrease in whole-body insulin sensitivity by late pregnancy [17]. Decreased hepatic insulin sensitivity is more pronounced in women with GDM compared with weight-matched controls [22], leading to more hepatic glucose production and hyperglycemia. Insulin secretion increases, but less so than the increase seen among normoglycemic pregnant women, because of inadequate β -cell function in mothers with GDM [23]. Additional defects in insulin signaling on a background of chronic insulin resistance are thought to lead to the development of GDM [17, 23]; however, the underlying mechanisms (particularly the genetics) of maternal GDM have yet to be fully elucidated.

The Metabolic Milieu in Obese Pregnant Women

Obesity has a significant effect on glucose metabolism in pregnancy. Unlike lean mothers, obese mothers' peripheral insulin sensitivity declines in early pregnancy and little or no increased fat is accrued, perhaps because of a lesser need for additional caloric reserves [24, 25]. Even in the first trimester, peripheral and hepatic insulin resistance increase, which persists and intensifies as pregnancy progresses [23]. Not surprisingly, obese women have more than a threefold higher risk of developing GDM compared with lean women [9, 10]. The mechanisms are similar to those driving carbohydrate intolerance in obese nonpregnant women. The enlarged adipose tissue mass eventually results in greater release of inflammatory markers and free fatty acids [26]. Free fatty acids not only increase insulin resistance, but also inhibit insulin's antilipolytic action, leading to even greater free fatty acid release. Thus, obese women begin pregnancy already relatively insulin resistant; it is this background of chronic insulin resistance to which the insulin resistance of pregnancy is partially additive [23]. Once β -cell dysfunction develops, GDM ensues.

Obesity-Related Risk Factors for GDM

While the traditional, and most cited, risk factors for GDM are higher maternal prepregnancy BMI, age, and parity, along with a family history of type 2 diabetes and the previous birth of a macrosomic baby [27], behaviors associated with obesity, including physical inactivity and poor diet quality, have themselves been implicated in the pathogenesis of hyperglycemia in pregnancy.

Skeletal muscle contraction triggers glucose uptake and promotes insulin sensitivity, and more intense exercise has a stronger hypoglycemic effect [28]. Not surprisingly, pregnant women enrolled in the Nurses' Health Study who had the highest quintile of physical activity were 20% less likely to develop GDM than inactive women (relative risk [RR], 0.81; 95% CI, 0.68–1.01 for total activity; and RR, 0.77; 95% CI, 0.69–0.94 for vigorous

activity) [29]. Similarly, we found that women enrolled in the Project Viva cohort who engaged in vigorous physical activity before pregnancy and light-to-moderate or vigorous activity during pregnancy experienced a reduced risk for developing GDM and abnormal glucose tolerance [30]. However, when we stratified by BMI, vigorous activity during pregnancy was protective against the development of abnormal glucose tolerance only among women with BMI of 25.0 kg/m² or less (adjusted odds ratio [OR], 0.56; 95% CI, 0.36–0.88). Although a recent study by Retnakaran et al. [31] also found that the relationship between pregravid vigorous/sport activity and hyperglycemia in pregnancy was stronger in lean women, no effect modification by BMI was noted in two other papers [29, 32]. Several ongoing prevention studies designed to test whether increasing physical activity will reduce the risk of developing GDM should help to provide greater clarity about the protective effects of physical activity before and during pregnancy, and whether BMI modifies this effect [33–35].

The relationship between diet quality and GDM is more uncertain. In 2008, Tieu et al. [36] published a meta-analysis that showed little consistent association between nutritional factors and gestational glucose intolerance. The authors noted that low glycemic index diets appear promising, however, and larger trials of low glycemic index diets are underway. It may be that prepregnancy diet has a greater influence on GDM risk than diet during pregnancy. This hypothesis has been supported by two large Nurses' Health Study II publications, which revealed higher prepregnancy intakes of sugar-sweetened soda and processed meats were associated with an increased risk of GDM [37, 38]. Studies examining dietary factors in pregnancy, conversely, have not reported associations with GDM [39].

Fat Deposition During Pregnancy: Do Excess Gestational Weight Gains Predict GDM?

Approximately 30% of weight gained in pregnancy is made up of maternal fat stores, thought to be important as a caloric reserve for late pregnancy and lactation [40]. Given that adipocytes are metabolically active and release a number of substances implicated in insulin resistance, it seems plausible that greater gestational weight gains, and thus larger adipocyte cell mass, would increase the risk of GDM. Most early studies examining associations of gestational weight gain with risk for GDM were limited in that they assessed gestational weight gain through the total duration of the pregnancy [41]. Diagnosis of GDM, typically between 24 to 28 weeks gestation, may have influenced subsequent weight gain. A few recent studies have examined associations of weight gain prior to glycemic screening with risk for abnormal glucose tolerance. In a study of women enrolled in the Pregnancy, Infancy, and Nutrition cohort, Saldana et al. [42] found a twofold increased risk of impaired glucose tolerance (a moderate state of abnormal glucose tolerance in pregnancy) among overweight women who gained weight at a rate higher than recommended by the US Institute of Medicine (IOM) prior to glycemic screening. However, this measure of gestational weight gain was not associated with any increase in risk of GDM, and no associations were evident in normal weight or obese mothers. We found similar results among women in the Project Viva cohort, although we did not observe an interaction with prepregnancy BMI [43]. We did find a trend toward a greater risk of GDM among mothers with higher rates of weight gain that was isolated to early pregnancy (OR, 1.70; 95% CI, 0.98–2.94), results that were replicated by Hedderson et al. in 2010 [12]. While available data suggest a direct relationship between gestational weight gain during the first two trimesters of pregnancy and abnormal glucose tolerance at glycemic screening, it is possible that weight gain in pregnancy primarily influences more moderate degrees of glucose intolerance.

Evidence that the association of higher gestational weight gain with glucose intolerance may be causal comes from a recent clinical trial. Wolff et al. [44] recently reported that 50 obese

Danish women enrolled in a dietary counseling intervention in early pregnancy had lower weight gain throughout pregnancy, a 20% reduction in serum insulin levels at 27 weeks gestation, and an 8% reduction in fasting blood glucose at 36 weeks gestation compared with women who did not receive the intervention. However, the intervention women did not experience a reduction in risk of GDM, which may be partly explained by the small sample size (no intervention mothers developed GDM compared with three women in the nonintervention group). In addition, this protocol was not a randomized controlled trial, as the non-intervention mothers were from an unenrolled comparison group. More data are needed to convincingly show that lower weight gains are causally associated with lower risk for developing GDM.

How much weight gain is healthy in pregnancy, particularly for obese mothers? Although it appears that the less gain the better for maternal health, either too much or too little weight gain in pregnancy can adversely impact the health of children. Greater gestational weight gain is associated with maternal prenatal hyperglycemia, hypertensive disorders of pregnancy, delivery complications, and obesity in mother and child, whereas very low gains are associated with small-for-gestational age neonates and perhaps increased risk for preterm delivery [45]. Both under- and over-gain may also increase risks for infant death [45]. In an attempt to optimize both maternal and child outcomes, in 2009 the IOM revised gestational weight gain guidelines for the first time since 1990 (Table 1) [46]. These guidelines recommend smaller gains for women with higher prepregnancy BMIs, particularly for women entering pregnancy with a BMI of at least 30 kg/m². Although the 2009 IOM guidelines recommend less weight gain for obese mothers compared with 1990 guidelines, even smaller gains, or no weight gain at all, may be associated with the best outcomes among mothers with BMIs over 35 kg/m² [47]. The optimal weight gain in pregnancy among mothers with class II pregravid obesity (BMI 35–39.9 kg/m²) and class III pregravid obesity (BMI ≥40 kg/m²) remains unknown, largely because few studies have included sufficient numbers of these heaviest women.

Postpartum Sequelae of GDM

Type 2 Diabetes in the Mother

For most women, the postpartum period is accompanied by a restoration of insulin sensitivity. However, mothers with a history of GDM are at substantially increased risk for future development of type 2 diabetes, with incidence rates of 17% to 63% within 5 to 16 years of the index pregnancy [15]. In a cohort of nearly 7,000 Australian women with a history of GDM, the mean annual diabetes risk was 1.7% and the cumulative 5-year risk was 8.1%. In contrast, the cumulative 5-year diabetes risk was 0% in the nearly 800 women without GDM [48]. Factors associated with progression to type 2 diabetes include prepregnancy obesity, severity of GDM (number of abnormal values on the 100-g diagnostic oral glucose tolerance test), and low C-peptide/glucose score during pregnancy (indicative of limited β -cell capacity) [49]. Several possibilities exist for the prevention of type 2 diabetes in women with a history of GDM, including implementation of a healthy lifestyle/weight loss, breastfeeding, and pharmacotherapy [50]; however, efficacy studies remain sparse (more details described in the “weight loss and diabetes prevention” section below).

Obesity and Diabetes in the Offspring of GDM Mothers

Infants born to mothers with maternal hyperglycemia are more likely to be large or macrosomic, which places them at increased risk for short-term complications, such as shoulder dystocia at delivery, and longer-term complications including obesity and diabetes into adulthood [14]. Some of the first studies to show associations of GDM with offspring diabetes and obesity were among the Pima Indian population from the early 1980s; maternal

diabetes in utero was identified as the strongest risk factor for diabetes in Pima Indian children, independent of maternal obesity and infant birth weight [51]. Data from ethnically diverse samples since then have revealed a doubling of obesity risk among children and adults born to mothers with GDM, compared with children born to glucose tolerant mothers [52].

However, solely treating GDM and not obesity, as recently observed in a follow-up study of Australian mothers with mild GDM, reduced infant macrosomia but not obesity in preschool-aged children [53]. Additionally, as Pirkola et al. [54] recently reported, 16-year-old adolescents exposed to both maternal prepregnancy overweight and GDM in utero had an increased risk of overweight (OR, 4.05; 95% CI, 1.90, 8.62) and abdominal obesity (OR, 3.82; 95% CI, 1.66, 8.82) at age 16 years, whereas no statistically significant risks for overweight and abdominal adiposity were found among offspring of normal-weight women with GDM. These observations raise the possibility that non-glucose abnormalities of obesity, including alterations in fatty acid metabolism and abundant circulating inflammatory markers, may play a critical role in “programming” offspring obesity and metabolic syndrome [55]. Or as Yajnik [55] suggested in a recent editorial related to the clinical trial described above [53], “did intensive treatment [among GDM mothers] introduce an element of intrauterine growth restriction that promoted a childhood catch up [and thus, no changes in obesity rates]?” Further study is warranted.

What mechanisms might explain the relationships of maternal hyperglycemia with persistent offspring obesity and diabetes? Increasing circulating blood glucose levels among GDM mothers result in fetal hyperglycemia, hyperinsulinemia, and elevated leptin synthesis, which influences appetite regulation in the brain, even prenatally [56]. Maternal prenatal hyperglycemia may also influence the fetal epigenome, thereby influencing expression of genes that direct the accumulation of body fat or related metabolism. Recently, Bouchard et al. [57•] found maternal hyperglycemia to be moderately correlated with placental leptin gene DNA methylation levels (fetal side: $r=-0.44$, $P\leq 0.05$; maternal side: $r=0.53$, $P\leq 0.01$). Whether epigenetic variability at the leptin gene locus has functional consequences for the fetus, leading to obesity development, is still unknown. Although more research is needed, these results provide initial evidence for unfavorable molecular adaptations from maternal hyperglycemia in pregnancy.

Is the Diagnosis GDM or Overt Diabetes? New Controversy Exists for Obese Mothers

Whether obese mothers develop new-onset glucose intolerance during pregnancy or had pre-existing diabetes that was not diagnosed before pregnancy is currently up for debate. The distinction between the two conditions may be important; unlike most unborn babies of women who develop glucose intolerance in pregnancy, those of women with pre-existing diabetes are typically exposed to hyperglycemia in the first trimester of pregnancy resulting in an increased risk of cardiovascular and other congenital abnormalities [27]. Further, mothers with overt diabetes need close follow-up postpartum and frequently require more intensive treatment than their GDM counterparts.

Because of the evidence described above, the Consensus Panel of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recently recommended that high-risk women (ie, those with prepregnancy obesity) should be screened for diabetes at their initial prenatal visit. Those who screen positive should be diagnosed as having overt diabetes rather than GDM [58•]. If overt diabetes is not diagnosed in the first trimester, and for all other women, the panel recommended that a fasting 2-hour, 75-g oral glucose tolerance test should be performed between 24 to 28 weeks gestation. Thresholds for the

diagnosis of diabetes from both tests were lowered by the IADPSG, based on results from the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) study, which identified strong continuous associations of maternal glucose levels below those currently diagnostic of diabetes with several perinatal outcomes [13•]. If these new screening guidelines are adopted, more mothers with both overt diabetes and GDM will likely be diagnosed. Thus, targeted interventions to treat pregravid obesity and other modifiable behaviors associated with diabetes have never been more urgent.

Weight Loss and Diabetes Prevention

Preventing Type 2 Diabetes

Strong evidence demonstrates that small changes in body weight and physical activity among nonpregnant individuals lead to large reductions in diabetes risk [59, 60]. Data from the DPP (Diabetes Prevention Program) revealed that intensive lifestyle modification substantially reduced the incidence of type 2 diabetes in individuals with obesity and impaired glucose tolerance [59]. Despite only a modest mean weight loss of 5.6 kg (7% of initial body weight), participants in the lifestyle modification group had a 58% RR reduction in the incidence of type 2 diabetes compared with the placebo group ($P<0.001$). A subset of the DPP population—women with a self-reported history of GDM—lost less weight than the general DPP population but still experienced a 55% reduction in the development of type 2 diabetes with the lifestyle intervention, compared with women in the placebo group [59]. Although several studies have shown that postpartum weight retention can be altered through a healthy lifestyle intervention [61], none has specifically assessed changes in metabolic parameters among women with GDM. Adding breastfeeding and/or medications may augment diabetes prevention efforts among mothers with a history of GDM [50]; however, further evaluation of multicomponent intervention programs is needed.

Preventing Incident GDM

Even among obese women, preventing incident GDM is possible. Newer pregnancy data among gastric banding patients have been encouraging, with significant incidence rate decreases for GDM compared with matched controls [62•]. Similarly, limiting gestational weight gain in obese women through dietary counseling has been associated with reductions in serum insulin, leptin, and glucose levels [44]. However, systematic reviews and meta-analyses are mixed about the success of lifestyle interventions for achieving healthy weight gain in pregnancy. Although two recent reviews found inconclusive results about the success or failure of gestational weight gain trials [63, 64], a meta-analysis based solely on intervention trials focusing on physical activity and diet showed a significantly lower average gestational weight gain in the intervention groups compared with controls (average reduction of 1.2 kg) [65]. The small sample sizes and different health care settings of many of the studies have limited widespread adoption of these pregnancy weight gain intervention strategies to date. Additionally, only one published trial focused on metabolic outcomes in addition to weight gain [44]. Several studies are currently underway and should provide better evidence for the effect of lifestyle modification in preventing GDM, particularly with regard to physical activity [33–35].

Conclusions

As the epidemic of obesity persists among childbearing women, a need exists to better understand the relationships among excess maternal weight, GDM, and offspring adiposity. Over the past two decades, data suggest that adipocytes are not just storage depots for excess calories, rather these cells are metabolically active and release a number of substances implicated in insulin resistance. Greater insulin resistance in pregnancy leads to greater

circulating levels of glucose and other nutrients that predispose to neonatal macrosomia and later childhood obesity. While several studies provide promise toward diabetes prevention among obese women both during and after pregnancy, weight loss and maintenance for most individuals remains challenging. Public health campaigns focused on obesity prevention in young women are therefore critical to improve the health of mothers and their children.

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Table 1

Total weight gains and rates of weight gain recommended for women with singleton pregnancies in the 2009 US Institute of Medicine guidelines

Pregnancy weight status (body mass index category)	Recommended total weight gain ranges		Recommended rates of weight gain in the 2nd and 3rd trimester ^a
	Pounds	Kilograms	
Underweight (< 18.5 kg/m ²)	28–40	12.5–18	1 (1–1.3)
Normal (18.5–24.9 kg/m ²)	25–35	11.5–16	1 (0.8–1)
Overweight (25–29.9 kg/m ²)	15–25	7–11.5	0.6 (0.5–0.7)
Obese (≥ 30 kg/m ²)	11–20	5–9	0.5 (0.4–0.6)

^aCalculations assume a 0.5-kg to 2-kg (1.1-lb to 4.4-lb) weight gain in the first trimester

(Adapted from Institute of Medicine [46])