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Gestational diabetes and childhood obesity: what is the link?

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Abstract

Purpose of review—To review recently published studies examining the role of prepregnancy obesity in the relationship between gestational diabetes mellitus and childhood obesity.

Recent findings—Seven epidemiologic studies published from January 2011 to February 2012 differentiate between preexisting diabetes mellitus and gestational diabetes mellitus, and six of them examine the role of maternal obesity. In studies that account for maternal obesity as a covariate, the association between gestational diabetes mellitus and childhood obesity is attenuated significantly after adjustment for prepregnancy BMI. In the one study that does not adjust for maternal obesity, maternal glucose level during pregnancy is associated with greater offspring adiposity, independent of the child's diet and lifestyle.

Summary—This review shows a positive association between maternal gestational diabetes mellitus and offspring overweight and obesity that is attenuated significantly after adjustment for prepregnancy BMI. The relationship between maternal gestational diabetes mellitus and offspring overweight and obesity could reflect fetal programming, shared genes and/or shared environments, such as postnatal diet and physical activity. Maternal gestational hyperglycemia and subsequent fetal hyperinsulinemia may predispose offspring to increased adiposity, impaired glucose tolerance, hyperinsulinemia, and insulin resistance. Because maternal obesity is a more prevalent condition than gestational diabetes mellitus and strongly associated with offspring obesity, effective interventions addressing prepregnancy obesity need to be further explored as they may have a greater public health impact on childhood overweight and obesity than those targeting women with gestational diabetes mellitus.

Keywords

childhood obesity; gestational diabetes mellitus; prepregnancy obesity

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Conflicts of interest

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

There are no conflicts of interest.

INTRODUCTION

Four to six percent of pregnant women in the United States are diagnosed with gestational diabetes mellitus, making it one of the most common serious medical complications of pregnancy [1–5]. Children born to women who had a gestational diabetes mellitus-affected pregnancy are more likely to be overweight and obese [6–8], giving rise to the notion that gestational diabetes mellitus and fetal exposure to hyperglycemia are responsible for increased adiposity in children. However, maternal obesity likely confounds this association as it is a strong predictor of gestational diabetes mellitus and is also a risk factor for offspring overweight and obesity, likely due to shared genes and environment [9–12]. Previous studies providing support for a causal association between gestational diabetes mellitus and offspring overweight and obesity have been limited in their ability to control for maternal obesity [13] mainly because many longitudinal data sources do not have this information available. Other limitations of previous studies include combining pregestational and gestational diabetes mellitus into one exposure group, which is important because timing of hyperglycemia has been shown to have differential effects [14], and not including a nondiabetic control group [15–17]. In a recent systematic review that examined 12 articles published from January 1990 to January 2011, the effects of gestational diabetes mellitus on offspring overweight and obesity were inconclusive and associations were no longer significant after adjustment for prepregnancy BMI [13]. This review is an update of the previous systematic review, examining the most recently published studies of the relationship between gestational diabetes mellitus and childhood adiposity and discussing the role of prepregnancy obesity.

METHODS

We searched *PubMed* records for the period January 2011 to February 2012 using the following search terms: (Pregn*) AND (GDM OR gestational diabetes OR diabetes OR glucose) AND (Overweight or obes* or BMI or body mass index or weight gain or adiposity or fat) AND (child* OR adolescen* OR offspring OR long term OR fetal program* OR imprint*). From this search, we identified 323 potential articles of which 127 abstracts were reviewed. The full texts of 32 articles were retrieved for articles in which the abstracts mentioned a relationship between maternal gestational diabetes mellitus and childhood adiposity. We did not exclude studies based on the study design or on the definition of child adiposity.

EPIDEMIOLOGIC STUDIES OF GESTATIONAL DIABETES MELLITUS AND CHILDHOOD ADIPOSITY

Of the seven cohort studies published from January 2011 to February 2012, six differentiated between diabetes mellitus existing before a pregnancy (referred to hereafter as ‘preexisting diabetes mellitus’) and gestational diabetes mellitus, and all but one examined the role of maternal prepregnancy obesity [18▪–24▪]. Exposure to gestational diabetes mellitus was associated with higher childhood adiposity with crude odds ratios ranging from 1.2 to 2.8. However, maternal prepregnancy obesity consistently attenuated the association between gestational diabetes mellitus and child adiposity toward the null, although in four of

the six studies [18▪–22▪,24▪], statistically significant positive associations remained after adjustment for maternal obesity with adjusted odds ratios ranging from 1.6 to 2.3. In the one study that did not adjust for maternal obesity, maternal glucose during pregnancy had a linear association with childhood adiposity, independent of child's diet and lifestyle [23▪]. It is unclear if this association would have remained if the authors had controlled for maternal obesity. Similarly, Deierlein *et al.* [18▪] examined the role of maternal glucose during pregnancy and also found that fetal exposure to maternal glucose concentration in the high-normal range was associated with the development of overweight and obesity in the offspring at 3 years of age, independent of maternal prepregnancy BMI. In addition, Lawlor *et al.* [24▪] conducted a sibling analysis in an effort to control for shared genetics and environment and found higher BMIs in the offspring exposed to diabetes *in utero* (with no distinction between preexisting and gestational diabetes mellitus) compared with the unexposed sibling. There was no evidence that associations between maternal diabetes and offspring BMI varied by maternal BMI in early pregnancy. However, there were few obese mothers in the sample. Therefore, the role of maternal prepregnancy obesity may be a stronger risk factor than gestational diabetes mellitus in determining childhood adiposity.

THE ROLE OF PREPREGNANCY BMI

Maternal obesity is a more prevalent condition than gestational diabetes mellitus with one in five women entering pregnancy obese [12] compared with 4–6% of women developing gestational diabetes mellitus. Maternal obesity is an important risk factor for gestational diabetes mellitus; women who are obese or severely obese before pregnancy are four and eight times more likely to develop gestational diabetes mellitus, respectively, compared with normal weight women [11]. It is difficult to clearly separate the effects of maternal obesity and gestational diabetes mellitus on childhood obesity, as maternal obesity often precedes gestational diabetes mellitus. Thus, gestational diabetes mellitus may be an intermediary in the maternal and child obesity relationship. For example, in a recent study by Catalano *et al.* [25], the authors found that pre-pregnancy obesity was significantly associated with offspring being in the highest BMI tertile and for having metabolic symptoms at age 6–11 years. They also found that prepregnancy obesity was the strongest perinatal predictor of high BMI in childhood, stronger than either maternal glucose homeostasis status or weight gain during pregnancy. In another study by Pirkola *et al.* [26], the authors found that among mothers with gestational diabetes mellitus, the prevalence of overweight in offspring age 16 years was 40% among overweight mothers, compared with 8.2% among normal weight mothers. In contrast, among mothers with normal glucose tolerance, the prevalence of offspring overweight was 27.9% among overweight mothers compared with 13.5% among normal weight mothers [26]. Therefore, gestational diabetes mellitus may carry some additional risk for offspring obesity, but much of the association is explained by maternal obesity. Hence, future studies examining these associations should carefully consider the role of maternal obesity stratified by gestational diabetes mellitus status.

Decreasing the prevalence of overweight and obesity among women of reproductive age could substantially reduce the prevalence of gestational diabetes mellitus and associated delivery complications. In a recent study examining the percentage of gestational diabetes mellitus attributable to maternal overweight and obesity, the authors found that if all women

with a BMI at least 25 kg/m^2 in the state of Florida had a gestational diabetes mellitus risk equal to that of women in the normal BMI category (18.9–24.9 kg/m^2), 41.1% of gestational diabetes mellitus cases could be prevented [27]. Therefore, quality preconception care is important in addressing prepregnancy overweight and obesity. Current recommendations describe obesity as a major risk factor for adverse pregnancy outcomes and one of the indications for preconception counseling [28–30] to help women begin pregnancy at a healthy, normal weight [31]. In 2009–2010, 17.1% of adolescent girls aged 12–19 years and 31.9% of women between 20 and 39 years old were obese [32]. Thus, to achieve the Healthy People 2020 goal of increasing the percentage of women entering pregnancy at a healthy, normal weight, outreach is needed to encourage adolescent girls and young adult women to think about proper nutrition and physical activity, well before they get pregnant. Furthermore, recent guidelines for preconception care recommend that all women have their BMI calculated annually and that appropriate nutrition and weight management counseling and referrals are made [29]. Effective methods to deliver these guidelines for adolescent care should be considered. However, barriers remain in preconception care utilization, including lack of insurance coverage and a high prevalence of unintended pregnancies.

In addition to entering pregnancy at a healthy weight, women should gain an appropriate amount of weight during the pregnancy, according to their BMI category. Offspring of obese women who gain excessive weight during pregnancy are at increased risk for childhood obesity [33]. Similarly, women who gain more than the recommended amount of weight during pregnancy are more likely to retain weight in the postpartum period [34,35], which may put them at a higher BMI in their next pregnancy. Thus, programs focusing on appropriate gestational weight gain and postpartum weight loss may have a positive effect on subsequent prepregnancy BMI. A meta-analysis of gestational weight gain programs found that interventions that promote physical activity and provide dietary counseling, especially when combined with weight monitoring, are successful in reducing gestational weight gain [36,37]. Similarly, successful postpartum weight loss programs tend to be individually tailored and include both diet and exercise components [38].

A number of state-based programs focusing on childhood obesity prevention exist, components of which include increasing physical activity, access to healthy food options and breastfeeding rates, and improving healthy eating behaviors. However, with as many as 32% of women of reproductive age obese [32] and the importance of entering pregnancy at a health normal weight, there is a need to bring successful lifestyle intervention models to scale in order to reduce obesity at the population level. This includes interventions targeting both reproductive aged women and pregnant women, as previous studies among pregnant women have been small.

TREATMENT OF GESTATIONAL DIABETES MELLITUS

If treatment of gestational diabetes mellitus reduces risk of overweight or obesity in offspring, it may be difficult to consistently detect an association in observational studies. Women with gestational diabetes mellitus are instructed to monitor blood sugar and either adjust their dietary habits or take insulin to maintain normal glycemic levels that may reduce the impact of hyperglycemia on subsequent offspring adiposity. Langer *et al.* [39] found that

offspring of women with untreated gestational diabetes mellitus had a two to four times increased risk of fetal macrosomia and other metabolic complications compared with both offspring of women with treated gestational diabetes mellitus and nondiabetic women. In addition, there were no differences between the offspring of mothers with treated gestational diabetes mellitus and non-diabetic women. Furthermore, in a separate study the same authors found that overweight and obese women with poorly controlled gestational diabetes mellitus, regardless of treatment modality, had significantly higher rates of the composite outcome of metabolic complications, macrosomia, and LGA, compared with women in all weight groups with well controlled gestational diabetes mellitus [40]. Therefore, treatment with insulin and achievement of good glycemic control in obese women with gestational diabetes mellitus may have a role in preventing adverse offspring outcomes.

MECHANISMS

Obesity and pregnancy individually contribute to inflammatory changes and a state of increased insulin resistance and lipid circulation. Consequently, obese women with gestational diabetes mellitus tend to have much higher levels of insulin resistance compared with normal weight women with gestational diabetes mellitus or obese women without gestational diabetes mellitus [41]. Maternal insulin resistance and corresponding hyperglycemia can result in fetal hyperinsulinemia, which can lead to excessive fetal growth associated with macrosomia and increased adiposity [42]. Recent evidence also suggests that maternal hypertriglyceridemia resulting from the insulin resistance may also contribute to increased birth size and adiposity, even if glucose levels are well controlled [43]. Excessive adiposity at birth can affect the long-term adiposity of the offspring [44–46].

There is also evidence that increased maternal leptin levels influence the regulation of appetite and metabolic homeostasis in offspring. Leptin, a hormone secreted by adipose tissue in levels directly correlated with body fat stores, is an important regulator of metabolic homeostasis [47]. Hyperleptinemia during pregnancy may reduce leptin sensitivity in developing fetal tissues, particularly in the hypothalamus. Leptin acts on the hypothalamus to reduce food intake and increase energy expenditure; therefore, permanent alterations in leptin sensitivity could have long-term implications for energy balance in offspring, continuing the cycle of obesity [48].

FUTURE STUDIES

Currently, all published epidemiological studies have been observational and no randomized control trials exist. Most existing observational studies cannot accurately quantify the independent contribution of gestational diabetes mellitus to offspring overweight and obesity risk because of unmeasured confounding and other methodological limitations. Therefore, studies should consider these methodological limitations in designing and analyzing future findings by clearly differentiating women with gestational and preexisting diabetes mellitus, include documentation of lifestyle and other environmental factors, and consider the role of maternal obesity independent of gestational diabetes mellitus status. It is important to understand if obesity, level of glycemia, and treatment modality are independently or cumulatively responsible for fetal growth abnormalities. When possible,

randomized trials for the treatment of mild gestational diabetes mellitus should include long-term follow-up of offspring to assess the effects of maternal interventions during pregnancy on infant and child outcomes. If treatment of gestational diabetes mellitus is associated with a reduced risk of overweight or obesity in offspring, it will provide further evidence of a causal relationship and that an effective preventive intervention exists. Last, randomized trials among obese women investigating the effects of dietary and physical activity interventions during pregnancy on short-term and long-term childhood outcomes should be stratified by diabetes status.

CONCLUSION

This review of recent studies shows that although the association between gestational diabetes mellitus and offspring adiposity is attenuated after adjustment for prepregnancy obesity, a positive association remains. The previous systematic review only found two of 12 studies adjusted for maternal obesity, both of which found that with adjustment the associations were no longer significant. Therefore, further studies need to examine the role of shared genes and/or shared environments, such as postnatal diet and physical activity to better understand and separate the role of prepregnancy obesity and gestational diabetes mellitus. Animal experiments have revealed that maternal gestational hyperglycemia and subsequent fetal hyperinsulinism may predispose the offspring to overweight, impaired glucose tolerance, hyperinsulinemia, and insulin resistance, irrespective of a genetic disposition. Because maternal obesity is a more prevalent condition than gestational diabetes mellitus and is strongly associated with offspring obesity, effective interventions addressing prepregnancy obesity need to be further explored as they may have a greater public health impact on childhood overweight and obesity than interventions targeting women with gestational diabetes mellitus.

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KEY POINTS

- The positive association between maternal gestational diabetes mellitus and offspring overweight and obesity is attenuated, but generally remains statistically significant, after adjustment for maternal prepregnancy obesity.
- Prepregnancy obesity was the strongest perinatal predictor of high BMI in childhood, stronger than either maternal hyperglycemia or weight gain during pregnancy.
- Because maternal obesity is a more prevalent condition than gestational diabetes mellitus and is strongly associated with offspring obesity, effective interventions addressing prepregnancy obesity need to be further explored as they may have a greater public health impact on childhood overweight and obesity than those targeting women with gestational diabetes mellitus.