Review

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Maternal Obesity, Gestational Diabetes, and Fetal Macrosomia: An Incidental or a Mechanistic Relationship?

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Abstract

Gestational diabetes mellitus (GDM) is a well-established risk factor for fetal macrosomia. A significant number of patients with GDM also suffer from obesity, a factor associated with fetal macrosomia. An important question is whether GDM is independently associated with fetal macrosomia, or whether this relationship is merely the result of maternal obesity acting as a confounder. In this review of the literature, we attempt to further elucidate the relationship between GDM, maternal obesity, and fetal macrosomia.

Keywords: Fetal macrosomia; Gestational diabetes; Maternal obesity; Maternal weight gain; Pre-pregnancy weight

Introduction

Gestational diabetes mellitus (GDM) affects around 10% of all pregnancies and is defined as hyperglycemia or any degree of glucose intolerance that begins, or is first recognized, during pregnancy, excluding pregestational diabetes that is first discovered in pregnancy.[1] The incidence of GDM varies with patients' racial background and by region or country. For example, the United States Centers for Disease Control and Prevention estimates that GDM affects 2%–10% of pregnancies in the US.[2] On the other hand, a study by Bashir *et al.*[3] found that it complicates 24% of pregnancies in Qatar. GDM screening recommendations and guidelines differ from one country to another and estimating the cost-benefit analysis of such screening therefore also varies across countries. The International Federation of Gynecology and Obstetrics recommends that all pregnant women undergo testing for hyperglycemia during pregnancy using a one-step procedure. Likewise, the American College of Obstetricians and Gynecologists recommend that all pregnant women undergo a laboratory-based screening test at 24–28 weeks of gestation.[5] On the other hand, the UK's National Institute for Health and Care Excellence recommend screening pregnant women using risk-stratification involving factors such as body mass index (BMI), prior history of GDM, and family history of diabetes.[6] The diagnostic criteria for GDM also vary amongst the different guidelines.

GDM is associated with several fetal and maternal complications. Maternal complications include increased risk of pre-eclampsia, gestational hypertension, operative vaginal and cesarean delivery, genital tract trauma, postpartum hemorrhage, progression to type 2 diabetes mellitus after pregnancy, and an eight-fold risk of developing metabolic syndrome later in life.[7] Fetal and neonatal complications include congenital malformations, fetal macrosomia defined as birth weight >90th percentile for gestational age, birth trauma including shoulder dystocia, transient hypoglycemia, polycythemia, hyper-bilirubinemia, and stillbirth.[8,9] The aims of this review were to explore the interconnected relationship between gestational diabetes, maternal obesity, and fetal macro-somia.

Maternal obesity and gestational diabetes

Globally, the incidence of GDM is increasing in parallel with that of maternal obesity.[10] It is now widely recognized that maternal obesity (defined as BMI ≥30 kg/m^2) is a strong risk factor for the development of GDM.[11] There are several studies demonstrating a significant association between maternal obesity and GDM (Supplemental Table 1, http://links.lww.com/MFM/A12). This strong relationship was apparent in a Pregnancy Risk Assessment Monitoring System database meta-analysis, which showed that obese women had increased odds ratios (*OR*) of gestational diabetes (adjusted *OR*: 2.78, 95% confidence interval (*CI*): 2.6–2.96) independently of weight gain during pregnancy.[12] A study by Agudelo-Espitia *et al.*[13] found a significant difference in the rates of GDM amongst women with increased pre-pregnancy weight (31.5%) compared to women with normal pre-pregnancy weight (1.5%). This finding was also reported in women with multiple gestations. The *OR* for developing GDM was increased among overweight (*OR*: 3.3, *95% CI*: 1.52–7.3) and obese (*OR:* 3.2, *95% CI*: 1.41–7.1) women with twin pregnancies relative to normal-weight women.[14] This risk was found to be greater with increasing obesity. Chu *et al.*[15] found that the *OR* for developing GDM was 8.56 times greater in severely obese compared to normal-weight pregnant women

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in a meta-analysis involving twenty studies. The *OR* was 2.14 and 3.56 for overweight and obese women respectively, relative to normal-weight pregnant women.

Maternal obesity and fetal macrosomia

In addition to its association with GDM, maternal obesity is established as a risk factor for the development of fetal macrosomia in many studies (Supplemental Table 2, http://links.lww.com/MFM/A12). A 5-year cohort study based on an Iranian population demonstrated an increased incidence of fetal macrosomia in women with a high BMI compared to normal-weight women, while a Canada-based cohort study showed that women who were either overweight or obese before pregnancy were 60% and 90% more likely to deliver macrosomic neonates, respective-ly.[16,17] A large Turkish population study showed that women with elevated pre-pregnancy BMI and higher gestational weight gain were significantly more likely to deliver macrosomic neonates in the absence of gestational diabetes.[18] This finding was supported by a 2017 meta-analysis which showed that pre-pregnancy maternal obesity was associated with fetal macrosomia with an adjusted *OR* of 1.93 (*95% CI*: 1.65–2.27).[19] A similar meta-analysis by Gaudet *et al.*[20] showed that maternal obesity alone was significantly associated with fetal macrosomia.

Fleten *et al.*[21] proposed that birth weight increased by 20.3 g foreveryone-unitincreaseinmaternal BMI(1 kg/m^2). The aforementioned articles support a causal relationship between maternal obesity and fetal macrosomia. Since maternal obesity independently increases the risk of both GDM and fetal macrosomia, it would be reasonable to suggest that the association between GDM and fetal macrosomia is likely to be indirect. If this is the case, then what role does maternal obesity play in the relationship between GDM and fetal macrosomia?

Maternal obesity, gestational diabetes, and fetal macrosomia

To explore the interaction between all three factors, we reviewed studies presenting a relationship between GDM and fetal macrosomia, especially when the authors made an adjustment for maternal obesity (Supplemental Table 3, http://links.lww.com/MFM/A12).

In a meta-analysis of thirty relevant articles, Tabrizi *et al.*[22] found that the rate of fetal macrosomia in GDM mothers was 13.3%, compared to just 2.9% in non-GDM mothers. However, the authors did not adjust for different obesity rates in the two groups, thus creating a limitation in dismissing a potential major confounder of fetal macrosomia. Therefore, clinicians must exercise caution when interpreting such conclusions.

In contrast, many studies explored the association between GDM and fetal macrosomia while adjusting for maternal obesity. In doing so, they showed the true nature of the relationship between these two factors without including the cofounder of maternal obesity. For example, Wang *et al.*[23] concluded that obese women were 4.17 times more likely to give birth to macrosomic fetuses, and that GDM was not a risk factor after adjusting for confounders including maternal obesity. Although this study showed that GDM is not an independent risk factor for macrosomia, others did indeed demonstrate this link after adjusting for maternal obesity. In a study by Agudelo-Espitia *et al.*,[13] for example, GDM was shown to be an independent risk factor for fetal macrosomia (*OR*: 2.04, 95% *CI*:1.51–2.76). A retrospective chart review by Yang *et al.*[24] found that the rate of fetal macrosomia in newborns of GDM mothers was 16.4%, compared to 11.2% in controls. In this study, the *OR* for maternal GDM in macrocosmic neonates was 1.55 (*95% CI*: 1.5–1.6). The elevated ratio, though still significant, dropped to 1.25 (*95% CI:* 1.21–1.29) after adjusting for BMI and taking several other maternal factors into consideration. This demonstrates that, although an independent relationship between the two exists, the risk could be overestimated if maternal obesity is not adjusted for. The effect of maternal obesity on fetal macrosomia in GDM was estimated by Pereda *et al.*,[25] who calculated that the *OR* for fetal macrosomia in the GDM cohort was 1.60 but decreased to 1.39 after adjusting for confounders including maternal obesity. Catalano *et al.*[26] found that the risk of macrosomia was significantly increased in women with GDM (*OR*: 2.19, 95% *CI*: 1.93–2.47) and in women with obesity (*OR*: 1.73, 95% *CI*: 1.50–2.00). Importantly, this work showed that the presence of GDM and maternal obesity together increased the risk of fetal macrosomia to a greater degree than the presence of one risk factor alone (*OR*: 3.62, 95% *CI*: 3.04–4.32).[26]

Furthermore, a study on 23,000 women found the risk of fetal macrosomia in obese women to be two-fold greater than in normal-weight women regardless of whether the pregnancy was complicated by GDM or not.[27–29] The risk of fetal macrosomia was 1.5 times greater in GDM mothers compared to non-GDM mothers in both obese and non-obese women. Another important aspect of this study was that 26% of macrosomic neonates were born to non-obese mothers with GDM, while 41% of macrosomic neonates were born to obese mothers without GDM. These findings offer an important perspective — that GDM is an independent risk factor for macrosomia, and that maternal obesity constitutes a much bigger, often underestimated, risk factor. We may conclude that maternal obesity is a stronger risk factor for fetal macrosomia, but that more cases of macrosomia can be attributed to obesity rather than to GDM.

Other studies, however, had a contradictory conclusion with regards to this relationship: GDM may not be an independent risk factor by itself, but rather a factor that strengthens a preexisting relationship between obesity and macrosomia. In attempting to separate the specific contributions of maternal obesity and GDM to the development of macrosomia, Ricart *et al.*[30] found that maternal obesity had a greater impact on macrosomia compared to GDM. In this cohort, normal-weight women with GDM did not a have a significantly higher risk of delivering a macrosomic neonate (*OR*: 1.32, 95% *CI*: 0.83–2.01), while women who were overweight had a significantly higher risk (*OR*: 1.82, 95% *Cl*: 1.47–2.25), but especially so when they were overweight and diabetic (*OR*: 2.16, 95% *CI*: 1.43–3.26). This study supports the hypothesis that GDM potentiates a pre-existing relationship between maternal obesity and fetal macrosomia but does not act as an independent risk factor for the macrosomia. Ijäs *et al.*[31] similarly analyzed data from nearly 25,000 patients and demonstrated that the risk of macrosomia in normal-weight women with GDM was not significantly increased relative to normal weight women without GDM (*OR*: 1.17, 95% *Cl*: 0.85–1.62). Obese women without GDM had an increased risk of fetal macrosomia compared to normal-weight women without GDM (*OR*: 1.50, 95% *CI*: 1.19–1.88).[31]

These different studies offer varying conclusions about GDM: GDM may or may not be an independent risk factor, GDM may be compounded by maternal obesity, and GDM may amplify the preexisting relationship between maternal obesity and fetal macrosomia. Simply put some uncertainty remains in the literature with regards to the relationship between GDM, maternal obesity and fetal macrosomia.

A potential relationship defined on pathophysiological basis

A question worth asking here is: Does pathophysiology underlie the association between obesity and gestational diabetes? It has been shown that adipose tissue and the adipokines it produces play a role in increasing resistance to insulin. Such adipokines include the adipocytokines leptin, adiponectin, tumor necrosis factor-a, and interleu-kin-6. These add to a natural resistance to insulin that occurs in normal pregnancy.[32] Furthermore, local hypoxia in adipose tissue of obese patients increases adipocyte death and production of pro-inflammatory cytokines which also contribute to insulin resistance and thus a tendency towards hyperglycemia.[33] These changes can explain, at least partially, the increased risk of gestational diabetes in obese women.

The complex interplay between gestational diabetes, maternal obesity, and fetal macrosomia can be examined by taking a closer look at some of the mechanisms that underlie this relationship. Some theories propose a direct relationship between GDM and fetal macrosomia while others support different conclusions. For example, maternal hyperglycemia, the hallmark of GDM, leads to increase in-utero transport of glucose and a subsequent anabolic state that predisposes to fetal macrosomia. Similarly, adiponectin seems to support a more direct role in the relationship between gestational diabetes and fetal macro-somia. Adiponectin impairs transport of amino acids across the placenta, limiting fetal growth and reducing the risk of fetal macrosomia. The production of this adipokine is reduced in mothers with gestational diabetes through gene methylation. This reduction more strongly correlates with insulin resistance than with measures of adiposity.[34] This demonstrates a perspective that favors a direct correlation between gestational diabetes and fetal macro-somia. Furthermore, a microarray analysis study that compared placentas of GDM and non-GDM women found that microRNA changes in GDM may contribute to fetal macrosomia through enhancing epidermal growth factor receptor signaling which promotes fetal growth.[35]

At the same time, changes in leptin could reinforce the role of maternal obesity in macrosomia, more so than GDM. Augmented production of leptin leads to enhanced transport of amino acids across the placenta, contributing to fetal macrosomia.[36] Interestingly, maternal obesity may be the main determinant of leptin levels ($P < 0.0001$) rather than gestational diabetes ($P = 0.34$),[37] supporting the proposition that perhaps maternal obesity is a greater risk factor for fetal macrosomia than gestational diabetes is.

The multifaceted impact of maternal obesity and GDM on fetal macrosomia makes it difficult to characterize the true relationship. For clinicians, the optimal management approach for these two (usually coexisting) risks factors is still fraught with difficulties. A commonly used approach is to directly address maternal obesity as a way of reducing risk of GDM. In fact, studies have shown that lifestyle changes reduce the risk of GDM in obese women. For example, a randomized control study by Koivusalo *et al.*[38] found that individualized counseling on diet, physical activity, and weight control reduced GDM rates in obese women from 21.6% in the control group to 13.9% in the treatment group. Another randomized controlled study by Wang *et al.*[39] found that exercising three times per week for at least 30 minutes per session reduced the risk of GDM in obese women (GDM incidence rate of 22.0% *vs.* 40.6%, $P < 0.001$). Although preventing GDM is associated with overall improved outcomes, strategies implemented in the study did not correlate with a significant risk reduction in macrosomia (6.3% *vs.* 9.6%; *OR*: 0.624, 95% *CI*: 0.233–1.673, $P = 0.3$).[39] On the other hand, a meta-analysis by Horvath *et al.*[40] showed that treating gestational diabetes (with diet or insulin) was associated with a lower risk of macrosomia. These conclusions must be considered when attempting to target the risk of macrosomia with lifestyle modifications.

Conclusions

All in all, GDM is becoming an increasingly prevalent complication of pregnancy due to the worldwide surge in maternal obesity. Given its association with fetal macro-somia and several other maternal and neonatal comorbidities, it would be helpful to understand the respective contribution of GDM and maternal obesity. Several studies have shown GDM to be an independent risk factor for fetal macrosomia, while many others found it to be a potentiating factor that functions only to magnify the effect of maternal obesity. Both relationships are supported by specific pathophysiological explanations with alteration in adiponectin levels and microRNA expression supporting the role of GDM, while changes in leptin levels supporting the effect of obesity.

In conclusion this review unfortunately failed to find conclusive evidence that neither maternal obesity nor GDM individually are the predominant factor that is associated with fetal macrosomia. What is certain is that the combination has a multiplier effect most likely mechanistically. There is the need for more well-designed studies to further unravel these complex relationships.

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Conflicts of Interest

None.

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