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Obesity in pregnancy and gestational diabetes

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Abstract

Obesity is widely regarded as a major global pandemic that has extensive complications. Obesity rates have increased dramatically which can significantly lead to both maternal and fetal health complications during pregnancy. Obese women are predisposed to pregnancy complications such as gestational diabetes mellitus (GDM). Both share common metabolic characteristics. Obesity and gestational diabetes are both related to serious problems during pregnancy, but also to long term maternal – fetal consequences. Children of obese women with GDM are more likely to have propensity for obesity and be insulin resistant, leading to a the vicious cycle of metabolic disorders into the next generation Therefore evaluating the combined association of these problems with pregnancy outcomes is an important issue. In this article, we review the relationship of maternal obesity and GDM and the complications they are associated to.

Key words: Obesity, gestational diabetes, pregnancy, pregnancy outcomes

Introduction

Obesity is a condition of abnormal or excessive fat accumulation in adipose tissue. For adults, WHO defines overweight as a BMI greater than or equal to 25 and obesity as a BMI greater than or equal to 30.

Obesity is a growing global health problem. Over the past few decades the prevalence of overweight and obesity has increased significantly. Worldwide obesity has nearly tripled since 1975¹. In 1997, the World Health Organization (WHO) formally recognized obesity as a global epidemic. In order to understand the

magnitude of this problem, it must be noted that the prevalence of obesity among U.S. women adults aged 20–39 is 35.7%².

Considering those rates it is not surprising that obesity is a major problem during pregnancy and increases the risks of maternal and perinatal complications.

Evidences suggest that maternal obesity in pregnancy increases the risk of miscarriage, fetal congenital anomaly, gestational diabetes, thromboembolism, pre-eclampsia, stillbirth, dysfunctional labour, post-partum

hemorrhage and neonatal death. Moreover obesity may be a risk factor for maternal death.

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy⁵. There is a strong association between maternal diabetes and obesity, especially during pregnancy result of white fat accumulation during first trimester adaptation which increases the risk of glucose intolerance. It has been calculated that the risk of developing GDM is about two times higher among overweight, four times higher among obese, and eight times higher among severely obese, compared with normal-weight pregnant women⁴.

With increasing frequency of maternal obesity, it is likely that adverse obstetric and perinatal outcomes associated with obesity will also increase the frequency of gestational diabetes. It is well known that gestational diabetes mellitus (GDM) and obesity are independently associated with adverse maternal and neonatal outcomes. The combination of two, however, has a greater impact than either one alone. Moreover, it must be mentioned that there are findings that indicate that particularly central obesity, increases the risk of gestational diabetes³.

Complications

1. Congenital malformations

Pregestational diabetes mellitus (PGDM) is known to be associated with an increased risk for congenital anomalies among offsprings⁷. Even though the exact association of diabetes and congenital anomalies has not been clarified, there is a strong link with hyperglycemia⁸. Recently a large number of studies have investigated the possible association between GDM and congenital anomalies. Moreover obesity that is correlated with diabetes has been reported to be associated with some of these anomalies and especially with renal and urinary track anomalies⁹.

Additionally, spina bifida and holoprosencephaly,

present increased prevalence to obese complicated with gestational diabetes women compared to normal weight women without gestational diabetes¹⁰.

Evidence indicate that both hyperglycemic intrauterine environment in combination with obesity are correlated with cardiac malformations¹¹, mostly presented as tetralogy Fallot or left ventricular out-flow tract defects¹².

It is obvious that there is a significant association between gestational diabetes and congenital anomalies, among offspring of women with pre-pregnancy obesity¹³.

2. Macrosomia

Among the issues that are related to obesity and diabetes, is also macrosomia. Although macrosomia can be effected by both genetic and environmental factors, both obesity and diabetes are risk factors.

It is reported that maternal pre-pregnancy obesity was associated with a 2-fold higher risk of delivering large for gestational age infants comparing to women with normal pre-pregnancy weight¹⁶.

Additionally obese women with GDM have an increased risk of delivering infants with macrosomia (37%)^{9,17} and is related to poor glycemic control during pregnancy¹⁸.

Recent studies indicate that in order to adequately evaluate the risk of excessive fetal growth, both the maternal obesity and diabetes should be carefully assessed¹⁹.

3. Preeclampsia

Approximately 10% of pregnancies are complicated by hypertensive disorders with preeclampsia to be a significant contributor to maternal and perinatal morbidity and mortality.

Obesity is a well-known risk factor for developing preeclampsia^{20,21} and increases 2- to 3-fold the overall risk of preeclampsia²².

It has been indicated, that not only the presence

but also the degree of obesity is related to the risk for preeclampsia and as maternal BMI is increasing, it is associated with late-onset preeclampsia²⁷.

There is an independent and significant association between GDM and preeclampsia. Insulin resistance has been hypothesized to contribute to the pathophysiology of preeclampsia. Insulin resistance is estimated to be present in two-thirds of obese individuals²⁶.

There are evidence that insulin resistance and mild inflammation are contributing to the pathophysiology of preeclampsia^{27,35}.

Several studies indicate that obesity in correlation to gestational diabetes are associated with a greater risk of preeclampsia than either factor alone²⁸.

Researchers work to identify clinical and biochemical risk factors for preeclampsia in women with obesity and interaction with gestational diabetes. However, the mechanisms mediating the pathogenesis of this maternal disorder and its rising prevalence are far from clear.

Giving the fact that obesity is a state of chronic inflammation, obese pregnant women are primed to have elevated inflammatory responses to placental ischemia²³.

Another factor that seems to play a critical role in the hypertension associated with obesity is leptin levels, which are found to be higher in obese with preeclampsia women²⁴.

Regarding the increased prevalence of this disease, there are several studies that are trying to correlate preeclampsia in pregnancies with obesity and gestational diabetes, with biomarkers like adiponectin, interleukin-6 (IL-6), high sensitivity C Reactive Protein (hs-CRP) and placental growth factor (PlGF)²⁵.

4. Childhood Health Consequences

Considering that obesity has become a major

health problem for children and adolescents there is a great interest in the origin of this disease. Multiple studies are evaluating whether the propensity for obesity start in-utero. There are several data that correlate maternal pre-pregnancy obesity and excessive gestational weight to an increased risk of obesity throughout childhood^{36,37}. Obese children are on increased risk of developing major morbidities including type 2 diabetes or impaired glucose tolerance, dyslipidemia, and hypertension, and both maternal pre-pregnancy obesity and excessive gestational weight gain are associated with cardiovascular and metabolic risk factors³⁸.

Therefore, children of obese mothers have a 3-fold higher risk of an adverse childhood cardiometabolic risk profile such as high abdominal fat mass, high blood pressure, high insulin and triglycerides levels and low HDL-cholesterol level³⁹.

Childhood obesity is an important risk factor for the development of insulin resistance^{40,41}. Moreover increased glucose levels during the third trimester are strongly associated with the risk of type 2 diabetes in the children⁴².

Of great interest is that offspring large for gestational age of obese or GDM mothers, are associated to an increased risk of metabolic syndrome⁴³.

In certain studies maternal obesity during pregnancy is associated to a 31% increased risk of asthma⁴⁴ and a small number of studies reported that obesity and diabetes during pregnancy were correlated to an increased risk of kidney disease in adulthood¹⁴.

It is obvious that the health status in utero environment has a major impact on the descendants.

5. Stillbirth

It is well established that increased pre-pregnancy weight is related to unexplained fetal death⁵¹. Obese women have higher incidence of fetal distress and neonatal deaths⁵², while it has been reported

that overweight and obese mothers have over 40% risk of stillbirth⁵³. Moreover recent studies indicate that 20% of stillbirths are associated with maternal obesity⁵⁴.

Giving the fact that overweight and obese women may have more than one risk factor for stillbirth it is highly likely that the cause is multifactorial.

Gestational diabetes is a major risk factor for stillbirth and the risk of developing gestational diabetes appears to increase with increasing BMI. However studies indicate that obesity is also an independent risk factor for stillbirth, as obese women without diabetes or hypertensive disorders are three times more likely to have a stillbirth compared to normal-weight women⁵. Regarding obesity it is essential that obese and extremely obese women should be treated as high-risk obstetric patients.

6. Autism

Autism spectrum disorder (ASD) is a neurological and developmental disorder that begins early in childhood and lasts throughout a person's life. Considering the fact that the prevalence of ASD has increased dramatically the last decades, pushed researchers to investigate the connection between obesity, gestational diabetes and ASD.

Many evidence link obesity in combination with gestational diabetes, with an increased risk of offspring ASD and intellectual disabilities.¹⁵

7. Maternal complications

Not only for offspring but also for mothers, long-term health risks are associated to gestational dia-

betes and obesity. Metabolic status during pregnancy is a likely contributor to long-term maternal health.

Several studies indicate that gestational diabetic women are at increased risk of hypertension, hyperlipidemia, electrocardiogram abnormalities and death⁴⁵.

Moreover, gestational diabetes is related to an increased risk of metabolic syndrome and diabetes type 2^{43,46}. Excessive gestational weight gain has also been linked to the development of diabetes type 2⁴⁷.

On the other hand high pre pregnancy weight and excessive weight gain during pregnancy are related to weight retention after pregnancy and higher BMI later in life^{48,49}.

Keeping an excessive weight results to higher risks for cardiovascular disease, type II diabetes, atherosclerosis, and metabolic syndrome.

Thus, it is really important consult women for the long-term complications of gestational diabetes and obesity to prevent their future health⁵⁰.

Management

There are several opinions managing obesity in pregnancy that focus on dietary and lifestyle interventions. The correlation between obesity and adverse outcomes during pregnancy made necessary to determine guidelines to promote appropriate weight gain⁶. (Table 1)

Calorie restriction

Calorie restriction is a controversial method of managing the unfavorable pregnancy outcomes of

Table 1 New Recommendations for Total and Rate of Weight Gain during Pregnancy, by Prepregnancy BMI

Prepregnancy BMI	Total Weight Gain	Rates of Weight Gain* 2nd and 3rd Trimester
Mean (range) in kg/week		
Underweight (< 18.5 kg/m ²)	12.5–18	0.51 (0.44–0.58)
Normal weight (18.5–24.9 kg/m ²)	11.5–16	0.42 (0.35–0.50)
Overweight (25.0–29.9 kg/m ²)	7–11.5	0.28 (0.23–0.33)
Obese (≥ 30.0 kg/m ²)	5–9	0.22 (0.17–0.27)

obesity. Severe calorie restriction ($\geq 50\%$) has been found to increase ketonuria and ketonemia in pregnant obese gestational diabetic women. This condition is correlated to mental development issues of the fetus³².

Exercise

Despite old belief that physical activity during pregnancy is contraindicated, recent data consider it necessary. Physical exercise is essential in order to decrease the risk for excessive fat gain during pregnancy^{33,34}.

However, interventions like diet and physical activity in women with obesity during pregnancy is not adequate to prevent gestational diabetes, or to reduce the incidence of large-for-gestational-age infants³¹.

Although any improvement in outcomes might be modest, consulting women who are overweight or obese during pregnancy focusing on a healthy diet and maintaining physical activity is a prudent approach. Initially the best approach, is consulting before conception about the increased pregnancy risks associated with obesity, and encouraging them to lose weight.

Metformin

Metformin is the first-line medication for the treatment of type 2 diabetes. It reduces insulin resistance and glucose blood levels, inflammation and angiogenesis. It is a therapeutic agent that is also used to treat pre-diabetes, gestational diabetes and polycystic ovarian disease.

There are several trials studying the efficacy of metformin in gestational diabetes and future effects in mother and offspring. It has been proven that obese pregnant women are significantly more insulin resistant and hyperglycaemic than pregnant women with normal weight and give birth more frequently to macrosomic offsprings. However there is

no proven efficacy in reducing the risk of gestational diabetes³⁰. Also, metformin has no effect on birthweight²⁹ in obese and severely obese pregnant women without diabetes.

On the other hand data indicate that metformin may be beneficial in long term risk of obesity and metabolic syndrome regarding offsprings. Despite the initially results there are no sufficient evidence to support the use of metformin and more trials are required in order to further evaluate the efficacy in perinatal outcome^{29,30}.

Conclusion

Overweight and obesity constitute an increasing global problem that may lead to serious sequelae. Understanding the interplay between gestational diabetes and obesity is essential for both health care providers and obese women. More epidemiological studies on obesity and gestational diabetes are needed to explore the interaction between prepregnancy BMI on the development of diabetes. Effective interventions, avoidance and reduction of obesity is likely to be the clue to reduce obesity-related adverse pregnancy outcomes.

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