Obesity and Risk of Preeclampsia

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INTRODUCTION

The global epidemic of obesity is unfolding, resulting in new challenges for all health-care professionals. Obesity is often associated with insulin resistance, dyslipidemia, and hypertension, which has led to the concept of metabolic syndrome [1,2]. Recent evidence has suggested that the prevention of obesity may begin before conception [3,4].

The rapid shift in populations towards a more obese phenotype in a relatively short period of time, less than half a century, has led to a marked increase in the incidence of overweight and obese women of childbearing age, which has raised specific issues for the management of pregnancy in obese women. Maternal obesity is a well-known risk factor for the development of preeclampsia. Several large population studies have shown that obese women are two to three times more likely to develop preeclampsia than their leaner counterparts. This association between maternal obesity and an increased incidence of preeclampsia is an important factor that deteriorates perinatal mortality and morbidity in obese mothers. In this review, we described the epidemiology, possible mechanistic background, transgenerational effect, and lifestyle interventions concerning the association between maternal obesity and risk of preeclampsia.

Abstract

The incidence of obesity in women of childbearing age has consistently increased in the last half-century. Maternal obesity is a strong risk factor that deteriorates the perinatal outcome of both mothers and neonates, and this has raised specific issues related to the management of pregnancy in obese women. Maternal obesity is a well-known risk factor for the development of preeclampsia. Several large population studies have shown that obese women are two to three times more likely to develop preeclampsia than their leaner counterparts. This association between maternal obesity and an increased incidence of preeclampsia is an important factor that deteriorates perinatal mortality and morbidity in obese mothers. In this review, we described the epidemiology, possible mechanistic background, transgenerational effect, and lifestyle interventions concerning the association between maternal obesity and risk of preeclampsia.

Preeclampsia

Preeclampsia is a pregnancy-specific syndrome that complicates approximately 3-6% of pregnancies, and is associated with a high risk of preterm delivery, intrauterine growth restriction, placental abruption, and perinatal mortality [17-20]. The WHO reported that that 784 of 2,538 cases of maternal near miss or maternal deaths in 29 countries cases (25.9%) had eclampsia or preeclampsia [21] and that haemorrhage and hypertensive disorders were major contributors to maternal deaths in developing countries [22]. Reducing the number of maternal deaths is a high priority for the international community, especially in view of the increased attention on Millennium Development Goals [22]. Previous studies have suggested that preeclampsia may serve as a sentinel marker for women at risk of cardiovascular, cerebrovascular, and/or other chronic diseases later in life [23-26]. The central dogma of the pathophysiology of preeclampsia is that a reduction in organ perfusion develops secondary to vasospasm and activation of the coagulation cascade; however, the exact cause as well as pathophysiology of preeclampsia remains elusive despite extensive research [27-29].

Obesity in pregnancy

Obesity in pregnancy was recognized to increase the risk of gestational diabetes mellitus, hypertension, preeclampsia, cesarean delivery, postpartum weight retention, preterm delivery, still birth, congenital anomalies including neural tube defects, spontaneous abortion, recurrent miscarriage, macrosomia, birth injury, difficulties related to anesthesia management, and emergency cesarean section, more than 50 years ago [7,30-48]. Therefore, a recent marked increase in the incidence of overweight and obese women of child bearing age has raised specific issues related to their management in pregnancy.

Obesity in pregnancy and preeclampsia

Maternal obesity is a well-known risk factor for the...
development of preeclampsia [12,49-51]. Several large population studies have shown that obese women are two to three times more likely to develop preeclampsia than their leaner counterparts [35,36,42,51]. A population-based study of 159,072 singleton births in U.S.A. revealed that not only obese women (prepregnancy body mass index [BMI]≥30.0), but also overweight women (prepregnancy BMI=25.0–29.9) were at a significantly higher risk for preeclampsia (Odds ratio 2.0 and 3.3, respectively) than women with a prepregnancy BMI of less than 20.0 [35]. A British population-based study of 287,213 births reported that the incidence of preeclampsia was significantly higher in obese women (prepregnancy BMI≥30.0; Odd ratio 2.14) as well as overweight women (prepregnancy BMI=25.0–29.9; Odd ratio 1.44) than in women with a prepregnancy BMI of 20.0-24.9 [36]. A population-based study of 972,806 births in Sweden revealed that obese women (prepregnancy BMI 29.1-30.0, prepregnancy BMI 35.1-40.0, prepregnancy BMI >40) were at a significantly higher risk of preeclampsia (Odds ratio 2.62, 3.90 and 4.82, respectively) than women with a prepregnancy BMI of 19.8-26.0 [42]. Kumari et al., reported that 57 cases of preeclampsia (28.7%) among 188 extremely obese women with BMI=40 [52], Lisonkova et al., also reported a strong association between maternal obesity and the risk of early-onset preeclampsia [53].

Risk of preeclampsia and prepregnancy metabolic disorders due to obesity

An overlapping spectrum of disorders is commonly observed in obese women [36,54,55] and obesity is hypothesized to play a central role in the concept of “metabolic syndrome” [56]. Chronic hypertension, insulin resistance and/or hypertriglyceridemia may be present prior to conception in obese women. Insulin resistance as well as hypertriglyceridemia are risk factors for preeclampsia [57-59], and are also important cofactors in the development of endothelial dysfunction [60-62]. Since endothelial dysfunction is hypothesized to play a central role in the pathogenesis of preeclampsia [63], it is plausible that the prepregnancy presence of endothelial dysfunction by insulin resistance and/or hypertriglyceridemia may be causatively associated with the high incidence of preeclampsia in obese pregnant women [49]. Therefore, the association between maternal obesity and preeclampsia is sometimes confused by the presence of metabolic syndrome due to obesity. However, Jensen et al., studied 2,459 women with normal glucose tolerance and found that the incidence of preeclampsia was still significantly higher in obese women (prepregnancy BMI≥30.0; Odd ratio 5.6) and overweight women (prepregnancy BMI=25.0–29.9; Odd ratio 1.7) than in women with a prepregnancy BMI of 18.5-24.9 [64]. O’Brien et al., carried out a systematic review of 13 studies, which included nearly 1.4 million women, and reported that the risk of preeclampsia rose with increases in BMI, even after adjustments for other clinical and metabolic confounding factors [50].

Prevalence of preeclampsia and obesity

Preeclampsia has increased in both the youngest and oldest women of the reproductive generation [65,66]. The incidence of preeclampsia has increased from 2.5% in 1987 to 3.2% in 2004 in the United States [67]. This increase may have been influenced by a variety of factors, including age groups, period effect, changes in diagnostic criteria, and the earlier identification of symptoms during pregnancy. Women born in the “older” cohorts may have different lifestyle factors, such as smoking or illicit drug use, than women born in more recent cohorts. Among these numerous factors, an increase in obesity among women of reproductive age is expected to be one of the strongest risk factors underlying the increasing prevalence of preeclampsia [65,68,69]. Population level variations in obesity have been shown to differ according to both age and time period [70] and higher rates of preeclampsia in populations with higher proportions of obese women are expected; therefore, a birth cohort effect explaining trends over time may occur. Previous studies have reported the presence of cohort effects in obesity rates over time, which suggests that such effects may then extend to cohort effects in preeclampsia [71,72]. Ananth et al. investigated 120 million women and concluded that changes in the population prevalence of obesity were associated with the period and cohort trends in preeclampsia, but did not fully explain these trends [65].

Transgenerational risk of preeclampsia and possible association with maternal obesity

Boyd et al., demonstrated that preeclampsia in a woman’s family, but not in a man’s family, was associated with a 24%-163% increase in the risk of developing preeclampsia [73]; however, controversy surrounds the involvement of a man’s family [74]. Genetic studies have failed to identify associations between common genetic variants and the risk of preeclampsia [75-77]. The mechanism underlying the transgenerational and/or familial risk of preeclampsia has not yet been fully clarified, although some studies have suggested the possible involvement of large numbers of rare mutations [78,79].

On the other hand, maternal obesity, a well-established risk factor of preeclampsia [12,49-51], elevates the risk of large-for-gestational-age infants [37,41,42,46] who are predisposed to obesity during childhood and adolescent period [36,80,81]. Maternal obesity in pregnancy was shown to be tightly connected to the developmental origins of obesity in the offspring [82-84]. An increasing amount of evidence has pointed to a possible association between environmental aggression in utero and the emergence of chronic diseases, such as obesity, throughout life, leading to a new link between causality and the possibilities of the early establishment of metabolic adjustments that determine morbidity throughout life. This represents a new branch of scientific knowledge known as the ‘developmental origins of health and disease (DOHaD)’ [85,86]. Therefore, it is speculated that maternal obesity may increase the risk of preeclampsia in female offspring due to a predisposition for obesity being involved, at least partly, in the development of a transgenerational risk of preeclampsia among obese pregnant women. More intensive investigations are needed.

Lifestyle interventions for obese pregnant women

The current prevalence of obesity in the childbearing generation poses a challenge to the management of pregnancy as it is associated with adverse maternal and perinatal outcomes. Lifestyle interventions, such as exercise and dietary interventions, for general obesity are effective in some individuals, but unsuccessful in the entire protestation against the increasing
prevalence of obesity in developing as well as developed countries [87]. Evidence for lifestyle interventions resulting in improved pregnancy outcomes in obese pregnant women is conflicting [88]. Oteng-Ntim performed a systemic review and meta-analysis and concluded that antenatal lifestyle interventions for obese women before pregnancy were only effective in reducing gestational diabetes, but not other complications [88]. Thangaratnam et al. carried out systemic reviews and meta-analysis and reported that weight management interventions or dietary interventions in obese pregnant women resulted in a significant reduction in the incidence of preeclampsia [89]. The American College of Obstetricians and Gynecologists (ACOG) recommended that nutrition and exercise counseling should continue not only antepartum, but also postpartum until attempting another pregnancy for obese pregnant women [31]. A recent Cochrane database showed that no randomized control trials demonstrated the effectiveness of reducing maternal weight in obese pregnant women and also that there can be no practical recommendation for obese pregnant women to intentionally lose weight during the pregnancy period [90]. To the best of our knowledge, no studies have scientifically proven the effectiveness of antepartum exercise to reduce the incidence of preeclampsia in obese mothers, although Sui et al., proposed the possibility that exercise during pregnancy may provide obese mothers with positive psychological feelings and family influences, and advice from health professionals [91].

CONCLUSIONS

Large population studies have shown that obese women are two to three times more likely to develop preeclampsia than their leaner counterparts. Therefore, the recent marked increase in obesity in women of childbearing age has raised specific concerns regarding the risk management of preeclampsia. Since maternal obesity appears to shift their offspring toward a predisposition to obesity, this cycle may continuously increase not only the incidence of preeclampsia, but also numerous risk factors associated with pregnancy during the next half century. Lifestyle interventions before conception as well as postpartum until attempting another pregnancy is the most effective strategy to reduce the risks associated with pregnancy in obese women; however, this has not been very successful. Since global preventive medical care programs have been unsuccessful in protecting against the overwhelming prevalence of the "Obesity Tsunami" in developed as well as developing countries [92], new medical care strategies, such as preemptive medicine (http://www.nih.gov/strategicvision.htm), are needed.

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REFERENCES


