Review Article

Maternal obesity and pregnancy outcome

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Summary

The increasing prevalence of maternal obesity worldwide provides a major challenge to obstetric practice from preconception to postpartum. Maternal obesity can result in unfavorable outcomes for the woman and fetus. Maternal risks during pregnancy include gestational diabetes and chronic hypertension leading to preeclampsia. The fetus is at risk for stillbirth and congenital anomalies. Intrapartum care, normal and operative deliveries, anesthetic and operative interventions in the obese demand extra care. Obesity in pregnancy can also affect health later in life for both mother and child. For women, these risks include heart disease and hypertension. Children have a risk of future obesity and heart disease. Women and their offspring are at increased risk for diabetes. Obstetrician-gynecologists should be well informed to prevent and treat this epidemic. Interventions directed at weight loss and prevention of excessive weight gain during pregnancy must begin in the preconception period.

Key words: Obesity; Infertility; Birth defects; Preterm labor; Gestational diabetes mellitus; Macrosomia; Hypertension; Stillbirth.

Introduction

Obesity has become a worldwide epidemic. The latest report of the WHO indicates that in 2005, approximately 1.6 billion adults were overweight and at least 400 million were obese. WHO also projects that by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese [1].

Obesity in women of reproductive age is increasing at a unprecedented rate in our society. Between 2004 and 2005, one in five women who delivered in the United States were obese. Black women had a prevalence about 70% higher than Whites and Hispanics. (Black 29.1; White 17.4; Hispanic 17.4) [2]. Obesity in pregnancy is considered as a high risk state because it is associated with an unequivocal increase in maternal and fetal complications [3]. Obesity is bad for everyone, but it is particularly bad for pregnant women.

Obese women have a higher prevalence of infertility, higher chances of early miscarriage and intrauterine death. It may be an independent risk factor for birth defects, fetal mortality and preterm delivery. It adversely impacts pregnancy outcome primarily through increased rates of hypertensive disease (chronic hypertension), diabetes (pre gestational and gestational) [4]. Maternal obesity also increases the risk of delivery of a macrosomic neonate, who is in turn at an increased risk of subsequent childhood obesity and is associated morbidity. As such maternal weight may influence the prevalence and severity of obesity in future generations [5].

Delivery in an obese patient is complicated by higher rates of instrumental delivery, cesarean section, increased risk of anesthesia, postoperative complications like wound infection, distruption, delay in wound healing, respiratory complications and venous thromboembolism.

Much attention is also paid to higher risk of anesthesia complications like difficulties in intubation, requirement of high dosages of anesthetic medications, and problems with regional anesthesia. Hence, avoidance of obesity and excess weight gain during pregnancy may benefit the health of both mother and fetus.

This review focuses on pregnancy complications associated with maternal obesity and interventions directed towards weight loss and prevention of excessive weight gain.

Obesity and infertility

The association between obesity and infertility is partially related to oligoovulation or anovulation but also contributes to infertility in women who ovulate normally. It is not clear how obesity affects fertility in women who ovulate normally. According to van der Steeg, distruptions in the Ntirmohe leptin, which regulates appetite and energy expenditure, may prevent successful fertilization [6].

van der Steeg, of Amsterdam's Academic Medical Center, found that obesity was an additional risk factor for infertility in women who had regular menstrual cycles [6]. Reproductive endocrinologist William Dodson claimed that the role of obesity in reproduction is more complex than what was once thought [6].

Herzog and collegues at the Garvan institute of medical research in Sydney have shown that one of the neuropeptide Y receptors, Y4, directly affects fertility. The level of some of the hormones involved in ovulation are partially controlled by Y4 receptor signalling. Obese people were found to have elevated levels of brain-signalling molecules called neuropeptide Y leading to difficulty in conceiving [7].

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High estradial levels from increased peripheral aromatization of androgen also have a direct negative effect on the hypothalamus, modifying GnRH pulsatality and reducing gonadotrophins at the pituitary leading to anovulation [6, 8, 9].

Truncal obesity associated with insulin resistance and increase in free testosterone and dihydro testosterone. Insulin binds with low affinity to the LH receptors in the theca cells and hyperinsulinemia may stimulate compensatory ovarian steroidogenesis and androgen production via the saturation of the receptors which may inhibit normal ovulation via premature follicular atresia and premature luteinization [10, 11].

In addition, leptin, a surrogate marker for a fatty mass, can directly modulate granulosa, theca and intestitial cells with inhibition of steroidogenesis and oocyte maturation thereby providing an additional potential mechanism for ovulation [12].

Although some controversy still exists regarding the effect of obesity in patients who have IVF, three large population-based retrospective studies have shown lower pregnancy rates in obese women**.** Linsten and colleagues reported the results of 8,457 IVF patients showing a significantly lower birth rate in women with a BMI greater than or equal to 27 (odds ratio (OR) 0.67; 95% confidence interval (CI) 0.48-0.94) [13].

Fedorcsak and colleagues reviewed 5,019 IVF patients and found lower cumulative live birth rates in obese women 41.4% versus 50.3% in normal weight women (95% 32.1-50.7) [14].

Wang and colleagues reported the results of 3,586 patients and established a significant linear reduction in fecundity from moderately obese patients to a very obese group ($p < .001$) [15]. In this study, in severely obese women 43% were less likely to achieve pregnancy than normal-weight women or women who were considered overweight. All studies suggest that infertility treatment should be preceeded by weight reduction.

Body fat distribution in women of reproductive age seems to have more impact on fertility than age or obesity itself; a 0.1-unit increase in waist-hip ratio led to a 30% decrease in probability of conception per cycle (hazard ratio 0.7; 95% CI 0.5-0.8) [16].

Ultrasound in obese pose unique challenges

As BMI increases, the ability to complete the survey decreases and requires a greater number of ultrasounds to get the information. There was a significant inverse association between increasing BMI and ultrasound (US) completion rates of trisomy screening. As a result, obese women may be underscreened for aneuploidy compared with normal weight women [17].

Because of the technical challenges of scanning, US screening may be incomplete or require extra scans in obese pregnant women. Many would suggest considering delaying a scan until 20 weeks of gestation in patients with BMI over 35 in order to reduce the number of scans.

Everyone performing such diagnostic examinations, from sonographers to medical sonologists and fetal medicine experts, is fully aware of the frustration and the difficulties experienced when performing a 20-week anomaly scan or a fetal echocardiogram in an obese pregnant woman. However, fetal medicine experts and fetal medicine doctors, have a duty to draw the attention of healthcare professionals, patients, lawyers, insurers and health-policy makers to yet another negative and costly effect of the irreversible and mounting wave of obesity: a significant reduction in the detection rate of congenital anomalies at the mid-trimester screening US examination [18].

Repeated US examination for suboptimal US visualization (SUV) of the fetal heart at a later gestational age dramatically reduces SUV. However, obese patients continue to have much higher rates of persistent SUV. The rate of SUV was associated with the obesity class (1.5% for non obese, 12% for obesity I, 17% for obesity II, and 20% for morbid obesity; $p < .0001$) [19]. This information should be included when counseling obese patients about anomaly screening and also the limitations of sonography in obese patients.

Obesity and birth defects

Maternal obesity has a significant detrimental impact on fetal development, probably secondary to glucose intolerance and gestational diabetes mellitus (GDM) with an increased risk for isolated and multiple fetal abnormalities. It is unclear whether obesity alone is a risk factor for fetal anomalies however, there seems to be a 7% increase in risk for fetal anomalies for each 1 u increment in BMI above 25 kg/m^2 [20].

Researchers carefully reviewed 39 observational studies and they found a significant association between maternal obesity and a raft of different fetal abnormalities [21].

In 1994, Waller and colleagues [22] first suggested that offspring of obese women were at increased risk of neural tube defects (OR 1.8; 95% CI 1.1-3.0), especially spina bifida (OR 2.6; 95% CI 1.5-4.5). These results have been confirmed by subsequent studies and also have shown increased risk of heart defects (OR 1.18; 95% CI 1.09-1.27) and omphalocele (OR 3.3; 95% CI 1.0-10.3) [23].

A possible dose-response relationship between maternal BMI and risk for birth defects OR per incremental unit increase in BMI for women of average weight or heavier was 1.08 (95% CI: 1.03-1.10, $p = 0.0001$) [24]. According to Cedergan *et al*., there is positive association between obesity and orofacial clefts in the offspring. The possible explanation being nutritional deficits in obese women, e.g., improper nutrition [25].

A case control study by clinical geneticists reviewed all of the cases of congenital birth defects. Mothers of offspring with spina bifida, heart defects, anorectal atresia, diaphragmatic hernia, hypospadias, limb reduction defects and omphalocele were significantly more likely to be obese women with ORs ranging between 1.33 and 2.10. Mothers of offspring with gastrochisis were significantly less likely to be obese than mothers of a control group [26].

Stillbirth and fetal death

Stillbirth remains at a frequency of two to five per 1,000 births, and constitutes more than half of perinatal deaths. In a large British register-based study, overweight and obesity were only modestly related to intrauterine death (OR 1.1; CI 0.9-1.2 and OR 1.4; CI 1.1-1.7, respectively) after adjustment for obesity-related disease in pregnancy [27].

Prepregnancy BMI and fetal death were examined in the Danish National Birth Cohort study among 24,505 pregnant women. Maternal obesity was associated with a more than doubled risk of stillbirth (OR 2.8; CI 1.5-0.53) compared with women of normal weight. No statistically significantly increased risk of stillbirth and neonatal death was found among underweight or overweight women [28].

In a large Swedish population-based cohort of 167,750 women, the odd ratios for late fetal death were increased among nulliparous women who were overweight and obese (OR 3.2; CI 1.6-6.2 and OR 4.3; CI 2.0-9.3, respectively) [29].

Moreover, Salihu and colleagues reported in a large cohort of 134,527 obese women, that about 40% were more likely to experience stillbirth than non obese women (adjusted hazard ratio (HR) 1.4; CI 1.3-1.5). The risk of stillbirth increased in a dose-dependent fashion with increasing BMI: class 1, HR 1.3; CI 1.2-1.4; class 2 HR 1.4; CI 1.3-1.6; class 3 HR1.9 CI 1.6-2.1 [30].

Maternal risk of gestational diabetes mellitus (GDM)

Approximately 3%-15% of women develop GDM during pregnancy. Although many factors are related to this risk, including ethnicity, previous occurrence of GDM, age, parity, and family history of diabetes, obesity is an independent risk for developing GDM, with a risk of about 20% [31, 32].

Sebire and colleagues found a two-fold increase in the rate of GDM (OR 1.68; 95% CI 1.53-1.84), Sebire *et al*. and Kumari, comparing obese and non obese patients, found a rate of GDM of 24.5% and 2.2%, respectively [28, 33]. Bianco *et al*. reported a three-fold increase in GDM for obese patients. Weight gains of more than 25 pounds were associated strongly with birth of a large-for-gestational age (LGA) neonate ($p < 0.01$); however, poor weight gain did not appear to increase the risk of delivery of a low birthweight neonate. Gestational weight gain was not associated with adverse perinatal outcomes, but it did influence neonatal outcome. To reduce the risk of delivery of an LGA newborn, the optimal gestational weight gain for morbidly obese women should not exceed 25 pounds [34].

It has been shown that a minor degree of carbohydrate intolerance is related to obesity and pregnancy outcome [35]. A population-based cohort study of 96,801 singleton births found that not only obese women but also overweight women had a markedly increased risk for GDM (OR 5.0 and 2.4, respectively) [20].

The risk of developing GDM is about 2-4.8 times higher among overweight, obese and severely obese women, respectively compared to normal weight pregnant women. The public health implications are significant because of the high prevalence of obesity, increasing prevalence of GDM, and the potential adverse consequences associated with obesity and GDM, including higher risk of adverse infant outcomes, higher risk of diabetes for the mother later in life, and a higher risk of diabetes and overweight for the offspring [36, 37].

The challenges of obesity and obstetric anesthesia

Obesity is a risk factor for anesthesia-related maternal mortality. Obese women are not only at risk of airway complications, cardiopulmonary dysfunction, perioperative morbidity and mortality but also pose technical challenges. Once in labor, an early anesthesia consultation is highly recommended irrespective of delivery mode.

A more liberalized use of regional techniques may be a means of further reducing the anesthesia-related maternal mortality [38]. Maternal obesity is associated with increased difficulty in performing neuraxial aesthesia, but not with increased failure rate. No differences between obese and non obese parturients were found in rate of cesarean deliveries, co-morbidities, indications for delivery or anesthesia complications [39].

Obesity as an independent risk factor for cesarean section

Studies report a nearly two-fold increased risk of cesarean delivery in women who are obese even after controlling for other factors. Why obesity increases the risks for cesarean section needs further study, probably due to macrosomic babies and difficulty in intrapartum monitoring. The increased risk in obese women is an issue of great concern. Apart from the immediate operative risk, there is an increased risk of postoperative complications like wound infection/breakdown, excessive blood loss, deep vein thrombosis and endometritis.

In a large retrospective study of 26,682 nulliparous women with singleton term deliveries, the incidence of cesarean delivery increased with increased prepregnancy BMI from 14.3% for lean women to 42.6% obese women [40]. Similar results were reported by Vahratian *et al*. and Holger and colleagues [41, 42].

Interestingly, Brost and colleagues [43] found that for each one unit increase in prepregnancy BMI, there was a parallel increase in the odds of cesarean delivery. Obesity is also associated with increased risk of vaginal operative delivery: 33% in the obese and 47.4% in the very obese group versus 20.7% in controls [44].

Risk of post-dated pregnancy

Higher maternal BMI in the first trimester and a greater change in BMI during pregnancy were associated with longer gestation and increased risk of post-dated pregnancy. Decreased likelihood of spontaneous onset of labor at term and increased risks of complications were also associated [45].

Obesity and intrapartum care

Morbidly obese women are at a significantly increased risk of complications during the intrapartum period and require more intervention leading to increased morbidity and cost.

They are more prone to invasive fetal monitoring (27% vs 0%), difficult uterine contraction monitoring (30% vs 0%), more medical personal involvement (22% vs 2%), multiple epidural attempts (28% vs 0%) complications in labor (32% vs 6%) and pediatric involvement (26% vs 3%) [46].

Preterm delivery

Current evidence suggests that obesity may be associated with induced preterm delivery and non spontaneous preterm birth. Smith and colleagues reported that among nulliparous women, the risk of spontaneous preterm birth decreased with increasing BMI, whereas the risk of requiring elective preterm delivery increased due to associated risk factors [47]. Obese nulliparous women were at increased risk of all causes of preterm delivery.

Bhattacharya and colleagues [48] also reported that the frequency of induced labor increased with increasing BMI. In a large retrospective cohort study including 62,167 women within the Danish National Birth Cohort, the crude risks of preterm premature rupture of membranes and of induced preterm deliveries were higher in obese as compared with normal women, especially before 34 weeks of gestation (HR 1.5; CI 1.2-1.9 and HR 1.2; CI 1.0-1.6, respectively).

Maternal obesity is associated with an increased risk of elective preterm delivery. The association is stronger among nulliparous women, probably as a result of their increased risk of preeclampsia, and here it led to an overall association between obesity and preterm birth in this group. Obese nulliparous women are at increased risk of the serious negative consequences associated with preterm births [49].

Obesity and thromboembolic complications

Pregnancy itself is a prothrombic state with increases in the plasma concentration of coagulation factors 1, VII, VIII and X , a decrease in protein S, and inhibition of fibrinolysis resulting in a five-fold increased risk of venous thrombosis [50].

Abdollahi and colleagues [51] evaluated the risk of thrombosis in a case-controlled study because of overweight and obesity after a first episode of objectively diagnosed thrombosis. Obesity, BMI >/30 increased the risk of thrombosis two-fold. Obese individuals have higher levels of factor VIII and IX but not of fibrinogen. In addition the combined effect of obesity and oral contraceptive pills among women aged 15 to 45 revealed that pill users had a ten-fold increased risk for thrombosis when BMI was greater than 25.

Obesity and fetal overgrowth

From the review of many studies, it appears that obesity and overweight have independent risk factors for macrosomia large-for-gestational age (LGA) infants and this risk is proportional to the level of obesity. The mechanism by which obesity affects neonatal birthweight is unclear. Possible explanations include obesity-related insulin resistance and genetic factors. The co-presence of undetected type 2 or gestational diabetes, both of which have been shown to be associated with obesity, is another possible explanation [52].

Ehrenberg and colleagues reviewed the results of 12,950 pregnancies and found that obesity and pregestational diabetes are both independently associated with increased risk of macrosomia. In a study by Jensen and colleagues, all women with GDM were excluded. They evaluated pregnancy outcome and BMI in glucose-tolerant non diabetic Danish women and concluded that macrosomia was significantly increased in both overweight and obese women [35, 53].

The magnitude of effect of obesity on the risk of macrosomia in normal (non diabetic) pregnancies varies considerably between different studies and has been reported to range from 1.4-18-fold. Several studies have shown a continuous relationship between maternal obesity and risk for fetal macrosomia/LGA infants, so that the higher the BMI, the higher the risk. According to Baeten *et al*., the prevalence and frequency of over-weight and obesity is nearly ten times that of GDM (45% vs 4.5%), and abnormal maternal body habitus is likely to have the strongest attributable risk on the prevalence of macrosomia [36, 54].

Apart from pre-gravid maternal obesity, excessive weight gain during pregnancy has also been reported to be an independent risk factor for macrosomia. Ray and colleagues calculated that for each 5 kg increase in weight during pregnancy, the risk for LGA infants is increased by 30%. Weight gains of more than 25 pounds were associated strongly with birth of a LGA neonate ($p < 0.01$); however, low weight gain did not appear to increase the risk of delivery of a low birthweight neonate. Gestational weight gain was not associated with adverse perinatal outcome, but it did influence neonatal outcome. To reduce the risk of delivery of an LGA newborn, the optimal gestational weight gain for morbidly obese women should not exceed 25 pounds [34, 55].

Obesity and hypertensive disorders

Arterial blood pressure, hemoconcentration and cardiac functions are all altered by the hemodynamic changes brought about by obesity. Some investigators have suggested a ten-fold higher rate of chronic hypertension in obese women [29].

Sattar *et al*. reported the results of the risk of hypertensive complications of pregnancy in association with a waist circumference of > 80 cm in data from 1,142 pregnant women. The risk of pregnancy-induced hypertensions was two-fold greater and preeclampsia three-fold

greater in association with visceral obesity. Waist circumference was demonstrated to be a more sensitive risk marker than BMI [56].

In a study of 287,213 pregnancies, Sebire and colleagues [28] included 176,923 (61.6%) normal weight, 79,014 (27.5%) overweight and 31,276 (10.9%) obese women. Obese women were two to three times more likely to develop proteinuric preeclampsia.

A BMI greater than 40 was associated with hypertensive disorder of pregnancy in 28.8%, compared with 2.9% in the non obese group. A meta analysis showed that the risk of preeclampsia doubled with each 5 kg/m^2 to 7 kg/m^2 increase in pre-pregnancy BMI. This relation persisted in studies that excluded women with chronic hypertension, diabetes mellitus or multiple gestations and other confounders [57].

Studies suggest a two to three-fold increased of preeclampsia with a BMI higher than 30 [57].

Preeclampsia risk rose strikingly from a BMI of 15 to 30 kg/m^2. Compared with women with a BMI of 21, the adjusted risk of preeclampsia doubled at a BMI of 26 (odds ratio 2.1 [95% CI, 1.4, 3.4]), and nearly tripled at a BMI of 30 (2.9 [1.6, 5.3]). Women with a BMI of 17 had a 57% reduction in preeclampsia risk compared with women with a BMI of 21 (0.43 [0.25, 0.76]), and a BMI of 19 was associated with a 33% reduction in risk (0.66 [0.50, 0.87]) [58].

Obesity associated with other pregnancy complications

Research by the University of Edinburgh found that obese mothers were nearly ten times more likely to suffer from chest infections, twice from headache and heartburn and three times from carpel tunnel syndrome and a threefold increased risk of symphysis pubis dysfunction compared with normal weight women. The costs of treating these minor complications were estimated to be more than three times that of treating women with a healthy body weight [59].

Conclusions

Obesity is a complex, costly and debilitating condition. The health implications of obesity are vast and the cost of treating this condition is a burden on the NHS in terms of finances and resources. Obesity needs to be given due attention if these trends are to be reversed and the health of the nation is to be improved. Estimates put the cost of treating obesity and its associated complications at over 1 billion pounds/year in the UK, and this figure is predicted to rise to 45 billion by the year 2050 (Wintour 2007) [60].

Obesity as described earlier causes significant complications for the mother and fetus. Interventions directed towards weight loss and prevention of excessive weight gain must begin in the pre-conceptional period. The most important measure is to address the issue of weight prior to pregnancy. Women should ideally be counselled by obstetrical care providers pre-conceptionally about the increased risks and complications conferred by obesity and the importance of weight loss and be encouraged to lose weight actively, and some may be candidates for bariatric surgery.

Obstetric units should institute appropriate guidelines for the management of pregnancy in this "high-risk" group of women. A multidisciplinary approach is useful including a family physician, dietician, physical director and obstetrician. Maternal and fetal surveillance may need to be heightened during pregnancy. The knowledge about various negative reproductive effects of prepregnancy obesity could perhaps contribute to behavioral changes concerning nutrition and physical exercise among women of fertile age.

The primary objective in the management of obesity during pregnancy is prevention. Prevention rather than treatment may offer the best hope of breaking the vicious cycle of obesity during pregnancy. Treatment options during pregnancy using pharmacological or surgical means are contraindicated. However, increased physical activity and healthy food choices may result in a better pregnancy outcome for both mother and child.

The worldwide epidemic of adolescence and adult obesity may not only be a result of our lifestyle of inadequate activity and poor diet, it may also be propagated and enhanced at a much earlier stage in life because of abnormal metabolic milieu in utero during gestation.The link between maternal lifestyle and fetal environment reinforces the idea that the best solution for obesity prevention may begin with the promotion of a healthy lifestyle before and during pregnancy.

Starting pregnancy at a healthy weight and gaining the right amount during pregnancy is critical to giving a baby a healthy start in life, according to the March of Dimes in response to new guidelines from the Institute of Medicine (IOM). Thus it is imperative to prevent excessive weight gain and to promote a healthy lifestyle during prenatal life and the postpartum period, especially for those women who are overweight and obese.

Progressive weight loss between pregnancies with a multidisciplinary approach may help decrease the risk of GDM and hypertension in subsequent pregnancies.

Dieting and exercise together are more effective than dieting alone in reducing weight retention after childbirth. Compliance may be improved by incorporating childcare and children into the exercise routine. Postpartum women should seek approval from their healthcare provider before beginning a moderately structured exercise program, which should begin slowly at three times per week, and increased to four or five times per week.

In general, a 10% loss within six months can be reached in those with BMIs from 27-35 with a daily 300-500 kcal intake reduction. In those with higher BMIs, a similar loss can be achieved following 500-1000 kcal reduction.

In conclusion, optimal management includes preconceptional counselling, pre-gravid weight-loss programs, monitoring of gestational weight gain, repeated screening for pregnancy complications and long-term follow-up to minimize the social and economic consequences of pregnancy in obese women.

Future studies should include information on functional biological pathways and gene variants associated with severe obesity.

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