Impact of Maternal Obesity on Fetal Health

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Key Words

Obesity · Fetal programming · Pregnancy complications · Congenital anomalies · Macrosomia · Childhood obesity

Abstract

The obesity epidemic is a problem of global importance with a profound impact on maternal-fetal health. Maternal overweight and obesity causes pregnancy complications such as gestational diabetes, hypertension and preeclampsia and affects fetal growth. Maternal obesity offers an altered genetic, hormonal and biochemical environment for the developing fetus/embryo and influences fetal growth and organ development. Offspring of obese mothers are subject to an increased risk of fetal demise, congenital anomalies and disrupted growth patterns, causing an increase in perinatal mortality. The impact of maternal obesity extends beyond intrauterine and neonatal life to childhood, adolescence and adulthood.

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The obesity epidemic is a problem of global importance with a profound impact on maternal-fetal health. It has reached a point at which 50% of women of childbearing age are either overweight (BMI 25–29.9) or obese (BMI >30) [1]. Furthermore, 15–20% of women starting pregnancy are obese [2, 3], and 20–40% of pregnant women suffer from excessive weight gain during pregnancy [4].

Maternal obesity is an obstetric risk factor because of its potential consequences for mother and offspring. Maternal overweight and obesity causes pregnancy complications such as gestational diabetes, hypertension and preeclampsia and affects fetal growth. As a result of increased complication rate, more than 50% of mortality cases during pregnancy, childbirth or the puerperium are of women who are either obese or overweight [4].

Obesity is also associated with a marked increase in fetal/neonatal complications including stillbirths [5], neonatal deaths, neonatal intensive care unit admission, preterm births, and congenital abnormalities [6]. Offspring of obese mothers are also subject to disrupted growth patterns (both growth restriction and overgrowth). Increased fetal weight and adiposity at birth increases macrosomia and difficulties associated with delivery of large-for-gestational-age infants. It has also long-term effects on neonatal, childhood and adult health.

Mechanism of Action of Obesity on Fetal Growth

Maternal obesity impacts the growing fetus/embryo by way of several pathways: genetic, environmental and the diverse network of interactions between them. The exact mechanism in which obesity mediates poor health outcomes for both mother and fetus, are far from clear. Pieces of the puzzle are placed together incorporating knowl-

edge gathered from epidemiological studies, experiments on animals and placenta models.

The embryo inherits a given set of genes from both parents. It draws upon this genetic milieu for its continued development and growth. Genome-wide association studies have identified several common genetic variants associated with high adiposity and obesity, each with weak effects [7]. Some of the candidate genes mentioned are those of insulin, insulin-like growth factor and their receptors because these hormones are known to influence fetal growth and body composition [8]. The genetic influence of maternal obesity on the developing child cannot be explained by Mendelian-model inheritance of a given set of genes alone. Children of obese mothers are more at risk of overweight or obesity than those of obese fathers [9]. This illustrates the pivotal role of intrauterine conditions on susceptibility to obesity, type 2 diabetes, and cardiovascular disease in the offspring. Epigenetic processes have a crucial role in determining fetal, neonatal and adult health.

The developing fetus depends upon a complex feto-maternal interaction. This intricate interaction relies on several components: maternal nutritional intake, placental transfer mechanisms and uterine blood supply, which depend on maternal metabolic and cardiovascular condition.

Glucose was considered the main metabolite that transmits the effect of obesity to the developing fetus. The obese population suffers from elevated blood glucose levels, insulin resistance and high rates of overt diabetes. Obese women are characterized by a significantly higher postprandial glucose peak value, increased 1- and 2-hour postprandial glucose levels, increased time interval for glucose peak, and significantly lower mean blood glucose during the night [10]. Maternal hyperglycemia during pregnancy was thought to be one of the most important predictive factors of pregnancy complications in the obese population. It is now recognized that other maternal parameters associated with obesity and/or overnutrition during pregnancy are also involved including hyperglycemia and hypertriglyceridemia. The altered endocrine milieu associated with obesity (increased levels of insulin, androgens, and leptin) [11] is also associated with a number of maternal metabolic disturbances such as insulin resistance, diabetes and increased blood pressure [12] all of which influence fetal well-being.

Obesity is associated with a chronic state of inflammation [13, 14] and alternation in the homeostasis of cytokines and adipokines. Adipose tissue is an active endocrine organ and a source of proinflammatory cytokines (adipokines) such as adiponectin. Adiponectin is deemed important in promoting insulin sensitivity and stimulat-

ing glucose uptake in skeletal muscle. In pregnancy, it influences placental transfer of nutrients and placental insulin-stimulated amino acid uptake. Pregnant women suffering from obesity demonstrate low circulating levels of adiponectin. Low levels of adiponectin are associated with increased fetal growth [15]. Furthermore, in animal models, adiponectin administration causes downregulation of activity and expression of key placental nutrient transporters. Adiponectin also binds to the adiponectin receptor-2 on the trophoblast cell and activates p38 MAPK and PPAR- α , which inhibits the insulin/IGF-1 signaling pathway. Therefore, it is not surprising that maternal serum adiponectin is inversely correlated to fetal growth throughout the full range of birth weights.

Individuals inflicted by obesity demonstrate high plasma levels of glucose and free fatty acids. The 'accelerated starvation' of pregnancy (meaning the increase in ketosis observed in pregnant women) is responsible for the decrease in insulin's ability to suppress lipolysis in pregnant women. This causes a further two- to threefold increase in the blood levels of cholesterol and free fatty acids with advancing gestation [16]. Maternal high levels of triglycerides (which are not readily transferred across the placenta) alternate placental lipases activity and increase placental transfer of metabolites which are stored as fetal fat deposits [17]. Oxidized lipids can be cytotoxic and influence gene expression by acting as ligands for nuclear receptors [18]. They may also affect antenatal organ development and impact postnatal response to environmental stimuli. Furthermore, intrauterine exposure to high lipid levels, which act as both transcriptional activators and signaling molecules, may cause epigenetic changes in lipid sensing and metabolism genes [19]. This may mediate epigenetic changes in the offspring of obese mothers that induce obesity in the offspring.

Obesity has also been associated with tissue-specific changes in mitochondrial function and elevated production of reactive oxygen species leading to increased oxidative stress [20]. The combination of excess fatty acids and oxidative stress leads to the production of oxidized lipids. Oxidized lipids can inhibit trophoblast invasion and influence placental development, lipid metabolism and lipid transport [18] – which may explain some of the adverse pregnancy outcomes related to obesity such as pre-eclampsia.

Other changes associated with maternal obesity may also lead to alterations in placental development or function. For example, maternal obesity is associated with a reduction in placental villous proliferation and apoptosis which may increase susceptibility to adverse pregnancy

outcomes [21]. Animal models suggest that a lifelong high-fat diet results in altered placental vascularization which causes an increase in placental hypoxia and oxidative stress. In this model, the consequences of such placental changes were an increase in stillbirths, and a decrease of birth weight and in neonatal survival [22]. Epidemiologic studies also demonstrated a correlation between maternal metabolic syndrome and placental dysfunction [23].

Serum concentrations of leptin are positively associated with body fat stores [24]. Maternal obesity is accompanied by maternal hyperleptinemia and placental leptin resistance contributing to alternations in placental function and amino acid transfer [25]. Amino acids also stimulate insulin secretion so an increase in amino acid trans-placental transfer contributes to fetal hyperinsulinemic state. IGF-1:IGFBP3 ratio and leptin levels are higher in cord blood of large-for-date fetuses. Higher IGF-1:IGFBP3 ratio may indicate a greater amount of unbound IGF-1 causing increased fetal growth [26]. These are some examples for processes which act in league to cause a net increase in available energy and 'building blocks' to the fetus and this combined with the hyperinsulinemic state may explain the increase in large-for-gestational-age infants seen in obese women. There is some evidence to suggest that maternal obesity also influences the in utero environment by altering the regulation of appetite, satiety, and adipocyte maturation in the fetus [27]. Offspring of rats that were fed high-fat diets during pregnancy exhibit postnatal hyperphagia [28]. These offspring also continued to consume more and maintain higher body weights than controls, thus maintaining their 'obese phenotype'.

Thus, the malevolent effect of obesity on embryonic/fetal growth and development is profound and apparent throughout pregnancy.

Early Pregnancy

Metwally et al. [29], in a meta-analysis including 12 studies, found that women with BMI ≥ 30 were at increased risk of miscarriage compared to women with normal BMI [odds ratio (OR), 1.89; 95% confidence interval (CI), 1.14–3.13]. This excess risk of miscarriage in the overweight and obese population is not explained by an increase of embryonic aneuploidy [30]. Obesity may increase early pregnancy-loss rate in a mechanism that is not dependent upon oocyte or ovarian function but rather endometrial or placental. Bellver et al. [31] demonstrated that obese and overweight women receiving oocyte dona-

tion did not differ from non-obese women in implantation and pregnancy rates, but showed a decrease in ongoing-pregnancy rate related to BMI. An unfavorable hormonal environment characteristic of maternal obesity combined with the chronic inflammatory state associated with excess adipose tissue may be the underlying mechanism. Observational data [32] suggest that weight reduction may reduce miscarriage rate in obese population.

Maternal obesity is also associated with an increased risk of dizygotic twinning. Reddy et al. [33] conducted an analysis of 51,783 pregnancies (561 twin) in the Collaborative Perinatal Project. They found that the incidence of dizygotic twins in women with BMI ≥ 30 was 1.1% compared to 0.5% in women whose BMI was <25 . Others [34] also found an increased incidence of dizygotic, but not monozygotic, twin gestation in the obese population. There is very little data specifically concerning twin pregnancy outcome in the obese population. It is beyond the scope of this review to discuss the full complexity and challenge in following twin pregnancies in general and in the obese population in particular. It is sufficient to mention the excess risk of pregnancy complication associated with twin pregnancy including preterm birth, preeclampsia, diabetes and fetal growth disturbances. It is also of importance to briefly mention that in obese gravidae, the estimation of fetal weight, especially for the second twin, has been shown to be decreased in accuracy, which may mislead clinical judgment when considering timing and mode of delivery [35].

Congenital Anomalies

Good ultrasound imaging of the fetus is more difficult in obese gravidae compared to normal-weight women [36–38]. As a result, the antenatal detection rate for congenital anomalies is lower in obese women, resulting in fewer antepartum diagnoses and more affected liveborns and stillborns among births to obese mothers. For example, the analysis of data collected in the FaSTER study indicates that the performance of second-trimester genetic sonography is influenced by obesity, with a significantly higher missed diagnosis rate for multiple minor markers and lower likelihood for detecting common anomalies in the obese population [38].

Furthermore, some congenital anomalies are more prevalent in the offspring of obese mothers. The increase in the absolute rate of specific congenital anomalies is increased with increasing maternal weight. Stothard et al. [39] reviewed 39 observational studies and 18 meta-analyses. They calculated pooled ORs for specific anomalies

in the obese population. Compared with mothers of normal BMI, obese mothers were at increased odds of pregnancies affected by neural tube defects (NTD) (OR, 1.87; 95% CI, 1.62–2.15), spina bifida (OR, 2.24; 95% CI, 1.86–2.69), cardiovascular anomalies (OR, 1.30; 95% CI, 1.12–1.51), septal anomalies (OR, 1.20; 95% CI, 1.09–1.31), cleft palate (OR, 1.23; 95% CI, 1.03–1.47), cleft lip and palate (OR, 1.20; 95% CI, 1.03–1.40), anorectal atresia (OR, 1.48; 95% CI, 1.12–1.97), hydrocephaly (OR, 1.68; 95% CI, 1.19–2.36), and limb reduction anomalies (OR, 1.34; 95% CI, 1.03–1.73). The risk of gastroschisis among obese mothers was significantly reduced (OR, 0.17; 95% CI, 0.10–0.30).

Another meta-analysis reviewed the risk for NTDs in pregnancies of obese mothers [40]. The OR for NTD was 1.22 (95% CI, 0.99–1.49) for overweight mothers, 1.70 (95% CI, 1.34–2.15) for obese women, and 3.11 (95% CI, 1.75–5.46) among severely obese women, compared with normal-weight women. This risk of NTDs increases with increasing pre-pregnancy weight and may not be ameliorated by increase in folate intake [41].

Maternal obesity adversely affects trans-abdominal ultrasound imaging of fetal anatomy during the second trimester. There is little to be done to technically improve the image obtained. Delaying, repeating, or increasing the duration of the examination may only partially, if at all, mitigate the technical limitations that obesity imposes on visualization [42]. In the general population, several studies have demonstrated the efficacy of late first- or early second-trimester anatomy scans [43, 44]. In the obese population early fetal anatomic assessment by trans-vaginal ultrasound may provide an alternative and more satisfactory window for better evaluating fetal anatomy [45].

Labor and Delivery

Onset of Delivery

Obesity is not inherently associated with an increased risk of spontaneous preterm birth. A meta-analysis [46] including 39 studies found that after adjustment for confounders, the risk for spontaneous preterm birth (sPTB) in the obese and overweight population was actually reduced (adjusted OR, 0.87; 95% CI, 0.74–1.04). Others [47] also found a reduced risk of sPTB in pregnancies complicated by obesity and even found that obese/overweight women exhibit less uterine activity than normal/underweight women [48]. Although the risk for spontaneous preterm birth is not increased in obese women, the

overall rate of preterm delivery may be increased. The increase in preterm deliveries in the obese population is not related to an innate part of pregnancy course but rather a measure of obesity-related medical and antenatal complications and is increased as BMI rises [46, 49]. Furthermore, maternal obesity is related to prolongation of pregnancy (i.e. postterm pregnancy). The explanation for this is yet to be puzzled out. Stotland et al. [50] found that higher pre-pregnancy BMI was associated with higher risk of progressing past 40 weeks (adjusted OR, 1.69; 95% CI, 1.23–2.31 for reaching 42 weeks' gestation). There is an inverse relationship between BMI and the likelihood of spontaneous onset of labor at term, and higher rates of postdate pregnancy in women who were already obese during first trimester or had excess weight gain during pregnancy [51].

Macrosomia and Birth Trauma

The relationship between maternal weight, weight gain during pregnancy and fetal/neonatal birth weight is well documented [52–55]. Studies investigating the relationship between maternal obesity and fetal growth have shown that obese women have an 18–26% increased chance of delivering large-for-date infants, even after controlling for maternal diabetes [56].

The metabolic (environmentally induced) macrosomia, as opposed to constitutional macrosomia, is characterized by excessive fat accumulation and fetal hyperinsulinemia during fetal life which results in growth of a fetus beyond its genetic potential. Infants above the 97th birth weight percentile have a 2–3-fold higher risk of unexplained intrauterine fetal death [57]. Excessive fetal growth carries significant perinatal morbidities although an exact estimation of their prevalence in the obese population is lacking. Macrosomic infants of obese mothers have an increased likelihood of operative delivery, shoulder dystocia, and brachial plexus injury [58, 59]. Larger fetuses also run a higher risk of fetal hypoxemia and shoulder dystocia especially for those above 4,500 g [60]. Lewis et al. [61] tried to prospectively evaluate risk factors for shoulder dystocia. They found that 32% of cases occurred to obese (>90 kg) women and 25% of women experiencing shoulder dystocia had excessive maternal weight gain (>20 kg). Others [62] found that 5% of extremely obese (over 250 pounds) women were found to have experienced shoulder dystocia. For obese non-diabetic women carrying fetuses whose weights were estimated to be within normal limits, there was no increased risk of shoulder dystocia [63]. The issue is further complicated by the decreased ability to accurately estimate fe-

tal weight at the upper extremes of the growth curve, with errors exceeding 10% of the birth weight, in particular on the basis of suboptimal visualization [64, 35]. This compromises the clinicians' ability to counsel obese patients about labor-related issues such as the preferred mode of delivery.

Neonates born to obese women have a higher rate of low Apgar score than those of normal-weight women [47, 65, 66]. In view of the aforementioned higher rate of labor-related complications, it is not surprising that, after delivery, newborns of obese mothers show an increase in neonatal admissions to neonatal intensive care units with complications such as neonatal trauma and incubator requirement [67]. Maternal obesity is associated with increased overall risk of infant death, mainly neonatal deaths related to pregnancy complications or preterm birth [68].

A meta-analysis including 9 studies by Chu et al. [69], described an increased risk of stillbirth in the obese population. OR for stillbirth was 1.47 (95% CI, 1.08–1.94) for overweight women and 2.07 (95% CI, 1.59–2.74) for obese pregnant women, compared with normal-weight pregnant women. The increase in stillbirth rate in obese women is presumed to occur due to the accelerated fetal growth induced by the fetal hyperinsulinemia and excess nutrient 'influx', in combination with uteroplacental insufficiency, which may lead to fetal hypoxia and death.

Maternal overweight and obesity are the most important potentially modifiable risk factors for stillbirth in high-income country settings. The number of stillbirths attributed to obesity across high-income countries is in the vicinity of 8,064 each year [70]. Implementation of preconception care, routine weighing at first antenatal visit, individualized pregnancy care plan, including dietitian counseling (exercise and diet), could potentially reduce these risk factors [71].

Life-Long Impact

Later in life, there is an inverse relationship between birth weight and health at both ends of the birth weight curve. Excessive maternal body weight or weight gain during pregnancy disrupts intrauterine environment and brings about permanent changes in the hypothalamus, pancreatic islet cells, adipose tissue and other body weight-regulating mechanisms of the offspring. Maternal pre-pregnancy overweight has been found to be an independent risk factor for infant and adolescence overweight and abdominal obesity [72]. Whitaker et al. [73]

described a retrospective cohort study of 8,400 children, who were born to obese mothers (based on BMI in the first trimester). These children had a double rate of obesity at age 2 years. The prevalence of childhood obesity (BMI >95th percentile) in children of women with BMI >30, at ages 2, 3, and 4 years was 15.1, 20.6, and 24.1%, respectively. The infants who were overweight at 3–5 years of age were 4.1–7.9 times more likely to be obese in young adulthood. Hence, fetal overnutrition during pregnancy carries an increased risk of various ailments later in life such as obesity, hypertension, diabetes, etc. [74]. Several studies have found that infants born at the highest end of the distribution curve for weight were at a higher risk of being obese in childhood, adolescence and adulthood when compared with normal-sized infants [75, 76].

Some studies also suggest that children exposed to pregnancies complicated by metabolic conditions, such as diabetes, hypertension, and obesity, showed an increased risk of neurodevelopmental disorders, autism spectrum disorders and developmental delay [77], although interpretation of data is limited by lack of information on potential confounders.

Maternal overnutrition and/or obesity during pregnancy afflict upon the developing child a fate of later-life overweight, thus creating a vicious cycle of epidemic scale. However, this mechanism is not a 'perpetuum mobile'. Obese women and health care providers have it within their power to reverse the tide on the obesity epidemic. Dietary restriction and weight loss prior to pregnancy are proven strategies to improve infant health outcome. Pregnancies after bariatric surgery are less likely to be complicated by gestational diabetes mellitus, hypertension, preeclampsia, and macrosomia than are pregnancies of obese women who have not undergone such surgery [78–80]. Bariatric surgery prior to a planned pregnancy is the best strategy for reducing obesity-related complication for mother and child. In unplanned pregnancies, controlled or minimal weight gain during pregnancy may also mitigate the impact of obesity and produce a dramatic positive impact on pregnancy outcome. Pregnancy also provides a 'window of opportunity' in which obese women are more susceptible for lifestyle interventions such as diet and exercise counseling, thus allowing health care givers to intervene.

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