Section A -Research paper

Effect of Obesity on Maternal Complications in Pregnancy: Review Article

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Abstract:

The increasing rate of maternal obesity provides a major challenge to obstetric practice. Maternal obesity can result in negative outcomes for both women and fetuses. The maternal risks during pregnancy include gestational diabetes and preeclampsia. The fetus is at risk for stillbirth and congenital anomalies. 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 are well positioned to prevent and treat this epidemic.

Keywords: Obesity, Pregnancy, Complications.

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Introduction:

Maternal obesity increases the risk of a number of pregnancy complications (Table 1) and, as such, requires adjustment to routine prenatal care (summarized in Table 2). Maternal obesity is a risk factor for spontaneous abortion (for both spontaneous conceptions and conceptions achieved through assisted reproductive technology), as well as for unexplained stillbirth (intrauterine fetal demise).

A recent meta-analysis of 9 studies revealed that obese pregnant women have an estimated risk of stillbirth that is twice that of normal weight pregnant women. Several mechanisms have been proposed for this relationship, including the increased risks of hypertensive disorders and gestational diabetes that are associated with maternal obesity during pregnancy**.(1)**

Table (1): Obstetric Complications in Obese Pregnant Women (2)

Complication	OR (95% CI) or % vs Normal Weight	P
Early pregnancy		
Spontaneous abortion (miscarriage)		
After spontaneous conception	1.2 (1.1–1.5)	.04
After IVF conception	1.8 (1.1–3.0)	<.05
Recurrent miscarriage	3.5 (1.1–21.0)	.04
Congenital anomalies		
Neural tube defects	1.8 (1.1–3.0)	<.05
Spina bifida	2.6 (1.5–4.5)	<.05
Congenital heart disease	1.2 (1.1–1.3)	<.05
Omphalocele	3.3 (1.0–10.3)	<.05
Late pregnancy		
Hypertensive disorder of pregnancy		
Gestational nonproteinuric hypertension	2.5 (2.1–3.0)	<.0001
Preeclampsia	3.2 (1.8–5.8)	.007
Gestational diabetes mellitus	2.6 (2.1–3.4)	<.001
Preterm birth	1.5 (1.1–2.1)	<.05
Intrauterine fetal demise (stillbirth)	2.8 (1.9–4.7)	<.001

Peripartum		
Cesarean delivery	47.7% vs 20.7%	<.01
Decreased VBAC success	84.7% vs 66%	.04
Operative morbidity	33.8% vs 20.7%	<.05
Anesthesia complications		
Excessive blood loss		
Postpartum endometritis		
Wound infection/breakdown		
Postpartum thrombophlebitis		
Fetal/neonatal complications		
Fetal macrosomia (EFW ≥ 4500 g)	2.2 (1.6–3.1)	<.001
Shoulder dystocia	3.6 (2.1–6.3)	<.001
Birth weight < 4000 g	1.7 (1.4–2.0)	.0006
Birth weight < 4500 g	2.0 (1.4–3.0)	<.0001
Childhood obesity	2.3 (2.0-2.6)	<.05

95% CI, 95% confidence interval; EFW, estimated fetal weight; IVF, in vitro fertilization; OR, odds ratio; VBAC, vaginal birth after cesarean.

Maternal obesity is associated with an increased risk of hypertensive disorders of pregnancy, including preeclampsia (gestational proteinuric hypertension), with an odds ratio (OR) of between 2 and 3.The risk increases linearly as BMI increases. For each increase in BMI of 5 to 7 kg/m^2, there is a corresponding 2-fold increase in the risk of developing preeclampsia**(3).**

Obese women are at increased risk of complications at the time of labor and delivery. The rate of successful vaginal delivery decreases progressively as maternal BMI increases. A meta-analysis of 33 studies showed that the ORs of cesarean delivery were 1.46 (95% CI, 1.34–1.60), 2.05 (95% CI, 1.86–2.27), and 2.89 (95% CI, 2.28–3.79) among overweight, obese, and severely obese women, respectively, compared with normal weight pregnant women. According to Ehrenberg and coworkers, the cesarean delivery rate for women weighing less than 200 lb was 18%, versus 39.6% in women who were classified as extremely obese. This 2- to 3-fold increase in cesarean delivery rate is true for both primigravid and multigravid women. Whether this is secondary to increased fetal size or another maternal characteristic is not known**.(2)**

Table (2): Adjustments to Routine Prenatal Care in Obese Pregnant Women (2)

Risk Factor	Recommended Care
Increased risk of neural tube defect	• Preconception folic acid supplementation (4 mg daily ideally 3 months prior to pregnancy through the first trimester)
	• Maternal serum AFP (15–20 weeks)
• Detailed fetal anatomy survey (18–20 weeks)	
Increased risk of hypertensive disorders of pregnancy, including preeclampsia	• Baseline 24-hour urinalysis in second trimester
	• Baseline liver and renal function tests in second trimester
	• Blood pressure and urine dip for protein at each prenatal visit
• There is no effective way to prevent preeclampsia	
Increased risk of gestational diabetes (GDM)	• Consider early screening with 1-hour nonfasting 50-g glucose load test (GLT) at 16–20 weeks. If positive, check a definitive 3-hour 100-g glucose tolerance test (GTT) to confirm the diagnosis of GDM. If negative, repeated GLT at the usual gestational age of 24–28 weeks
Increased risk of unexplained stillbirth	• Consider weekly antepartum fetal testing with NST and/or BPP beginning at 36 weeks, especially in women with a BMI ≥ 40 kg/m^2 (although this has not been shown to definitively improve perinatal outcome)
Increased risk of anesthesia complications	• ACOG recommends a prelabor or early intrapartum anesthesia consultation for all women with a BMI ≥ 40 kg/m^2
	• Consider early epidural placement in labor
• Recheck epidural placement if the patient is transferred to the operative room for cesarean delivery because of	

increased risk of migration of the epidural catheter	
Failure to lose weight after delivery is associated with subsequent adverse maternal health problems, including complications of future pregnancies	• Continue nutrition counseling and exercise program after delivery
	• Consider consulting a weight loss specialist to optimize postpartum weight loss before attempting another pregnancy
• If complicated by GDM, check 2-hour 75-g GTT at or after 6-week postpartum visit	

Maternal obesity also influences the success rate of attempted vaginal birth after cesarean (VBAC). Carroll and colleagues found that women weighing less than 200 lb had a VBAC success rate of 81.8% compared with 57.1% for women weighing 200 to 300 lb and 13.3% for women heavier than 300 lb. A similar relationship was observed in a subsequent study using BMI rather than absolute maternal weight, with VBAC success rates ranging from 84.7% in women with a BMI lower than 19.8 kg/m^2 to 54.6% in those with a BMI higher than 30 kg/m^2.**(4)**

In addition to an increased rate of operative delivery, obese women are also at increased risk of intraoperative complications, including increased infectious morbidity and thromboembolic events. There is also an increased risk of anesthetic complications, such as failed intubation at the time of general endotracheal anesthesia. A number of specific recommendations have been proposed to minimize intraoperative complications in obese pregnant women (summarized in Table 3).**(5)**

Table (3):Recommendations Before, During, and After Surgery in Obese Pregnant Women(5)

• Consider preoperative cardiac evaluation, especially if the patient has diabetes or chronic hypertension. This should include a baseline electrocardiogram and, if abnormal, an echocardiogram and cardiology consultation.
• Give preoperative broad-spectrum antibiotics 20–30 minutes before the skin incision to reduce the risk of postpartum endometritis and wound infection.
• Consider using a large operating table (especially if the patient is < 300 lb) and having additional personnel in the delivery room.
• Because of the increased risk of intrapartum blood loss, consider having additional blood products available in the operating room.
• If indicated, tape the pannus out of the surgical field to facilitate visualization and avoid a through-and-through skin incision.
• Close the subcutaneous layer. There is extensive evidence that seroma formation and postoperative wound disruption can be decreased in obese women (defined as adipose layer < 2 cm) if the subcutaneous tissues are closed using layers of running sutures.

• Avoid subcuticular skin closure to allow serous fluids from the subcutaneous fat to drain out of the incision rather than accumulate in the subcutaneous layer.
• Place pneumatic compression stockings on the lower extremities of all obese parturients prior to and during surgery as prophylaxis against deep vein thrombosis (DVT).
• The compression stockings should remain in place until the patient is fully ambulatory. Additional prophylaxis against DVT with prophylactic low-molecular-weight heparin should be considered in women with a body mass index ≥ 40 kg/m^2.
• Begin early ambulation to prevent DVT formation.
• Consider delaying removal of staples or sutures for a full week to allow the skin to heal completely.

The reason obese pregnant women are more likely to end up with a cesarean delivery is not known, but a theory is that obese women are more likely to experience dysfunctional labor. For example, Vahratian and colleagues found that the rate of cervical dilation in nulliparous women in spontaneous labor decreased as maternal BMI increased. In this study, normal weight women (BMI 19.8–26.0 kg/m^2) took a median duration of 5.43 hours to dilate from 4 to 10 cm, whereas obese women (BMI > 29.0 kg/m^2) took 6.98 hours. This appears to be true also in women undergoing induction of labor at term**. (2)**

Nuthalapaty and colleagues demonstrated that, although multiparous women progressed faster during induced labor than nulliparous women, in both groups an increase in maternal weight quartile was associated with a decreased rate of cervical dilation and an increase in the duration of labor. Denison and colleagues showed that a higher maternal BMI in the first trimester and a greater increase in BMI throughout pregnancy were associated with a reduced likelihood of spontaneous labor at term, an increased risk of post-term pregnancy, and an increased rate of intrapartum complications**.(6)**

Effect of Maternal Obesity on Perinatal Outcome

Maternal obesity is associated with abnormal fetal growth. Women who are heavier are less likely to have a pregnancy complicated by a small-for-gestational age infant or intrauterine growth restriction, but this protective effect appears to dissipate once the maternal BMI reaches the level of obesity (> 30 kg/m^2). The major concern in obese pregnant women is fetal macrosomia (defined as an estimated fetal weight of greater than or equal to 4500 g), which appears to be increased 2- to 3-fold in obese parturients. Moreover, there appears to be a dose-dependent relationship between maternal obesity and fetal macrosomia**. (7)**

In a recent meta-analysis, the prevalence rates of fetal macrosomia were 13.3% and 14.6% for obese and morbidly obese women, respectively, compared with 8.3% for the normal weight control group. In the United States, the mean birth weight between 1985 and 1998 increased from 3423 to 3431 g among whites and from 3217 to 3244 g among blacks. In Canada during the

same time period, the mean birth weight increased from 3391 to 3427. In Denmark, the mean birth weight between 1990 and 1999 increased from 3474 g to 3519 g (an increase of 45 g) and macrosomia rates increased from 16.7% to 20%. During a similar time period (1992–2001) in Sweden, there was a 3% increase in the incidence of large-for-gestational-age newborns (defined as birth weight > 2 standard deviations from the mean for a given gestational age). Although a number of factors may explain this global increase in the prevalence of fetal macrosomia, the prevailing data suggest that maternal obesity is the main factor, followed by maternal diabetes status.**(5)**

Fetal macrosomia in obese women is associated not only with an increase in the absolute size of the fetus, but also in a change in body composition. Sewell and coworkers found that the average fat mass of infants born to mothers with a normal BMI (< 25 kg/m^2) was 334 g, giving a body fat composition of 9.7%. The offspring of women with a BMI > 25 kg/m^2, on the other hand, had a mean fat mass of 416 g, or a body fat composition of 11.6%. Of note, the majority of this effect appears to be a result of weight gain during pregnancy. Indeed, prepregnancy BMI appears to account for only 6.6% of the observed variation in infantile fat mass and only 7.2% of body fat composition**.(2)**

Maternal obesity is associated also with an increased risk of neural tube defect (NTD) in the offspring, even after controlling for ethnicity, maternal age, education, and socioeconomic status. Watkins and coworkers concluded that a 1 kg/m^2 increase in BMI is associated with a 7% increased risk of having an infant with NTD. A recent meta-analysis by Rasmussen and colleagues reported that the OR for delivering an infant with NTD was 1.22 (95% CI, 0.99–1.49), 1.70 (95% CI, 1.34–2.15), and 3.11 (95% CI, 1.75–5.46) among overweight, obese, and morbidly obese women, respectively, compared with normal weight women. The mechanism underlying the increased risk of NTD in pregnancies complicated by maternal obesity is unknown. However, a number of theories have been proposed, including a reduction in the amount of folic acid reaching the developing embryo due to insufficient absorption and greater maternal metabolic demands, chronic hypoxia, and increased circulating levels of triglycerides, uric acid, estrogen, and insulin (due, in part, to increased insulin resistance)**.(8)**

Maternal Obesity and Diabetes

Maternal obesity is associated with an increased risk of diabetes, both pregestational diabetes and GDM. Compared with normal weight women (BMI < 25 kg/m^2), a recent meta-analysis of 20 studies demonstrated that the OR of developing GDM was 2.14 (95% CI, 1.82–2.53), 3.56 (95% CI, 3.05–4.21), and 8.56 (95% CI, 5.07–16.04) among overweight (BMI 25-30 kg/m^2), obese (BMI > 30 kg/m^2), and severely obese women (BMI > 40 kg/m^2), respectively. A recent study found that weight gain in the 5 years prior to becoming pregnant, even at a rate of 1.1 to 2.2 kg per year, increases the risk of developing GDM, and that this was especially true for women who were not

initially overweight. In addition to prepregnancy BMI, a number of other demographic factors affect the incidence of GDM. Hedderson and colleagues found that GDM was more likely in women who were older than 35 years of age and who were of Hispanic or Asian ethnicity. In this cohort, GDM was also more common in women with 12 years or less of schooling and with 2 or more previous live births.**(9)**

The reason obese women are at higher risk of developing GDM has yet to be fully delineated, but is likely related to an increase in insulin resistance. As a result of the continued production of counter regulatory (anti-insulin) hormones by the growing placenta, insulin resistance increases progressively throughout pregnancy. At any single point in pregnancy, however, obese women have higher insulin resistance (lower insulin sensitivity) than women of normal weight, which results in increased availability of lipids for fetal growth and development. Gene microarray profiling of the placentae of obese women with GDM demonstrates increased expression of genes related to lipid metabolism and transport, which likely accounts for the increase in birth weight and fat mass observed in the offspring of such women**.(10)**

The development of GDM has a number of adverse maternal and fetal implications. For women, these include an increased risk of hyperglycemia, cesarean delivery, and diabetes in later life, with more than 50% of women with GDM acquiring diabetes within 20 years of delivery. The implications for the offspring may be even more severe. Pregnancies complicated by GDM have a 4-fold increased risk of perinatal mortality and a 3-fold increased risk of macrosomia. In addition to being larger, infants born of pregnancies complicated by GDM also have significantly larger skin folds at all areas of measurement (triceps, subscapular, flank, thigh, abdomen) and, as such, are at increased risk of shoulder dystocia and resultant birth injury. Moreover, offspring born of GDM pregnancies are more likely to develop childhood and adult obesity (OR 1.4 [95% CI, 1.2–1.6] for every 1-kg increment in birth weight) as well as type 2 diabetes mellitus**.(11)**

Maternal Obesity and The Health of The Child In Later Life

The "Developmental Origins of Disease" hypothesis, which suggests that elements of heritability can be transmitted in a non-Mendelian way from generation to generation has been proposed for the transmission of obesity risk from mother to child. To date, investigations addressing this in obese pregnancies remain relatively scarce compared with those who have investigated the consequences of fetal growth restriction. However, several cohort studies report an association between maternal early or prepregnancy BMI and offspring BMI assessed at birth, in infancy, childhood, and early adulthood. Others have shown an association with GWG and offspring BMI**. (12)**

Despite the attempts to eliminate confounding, it remains unproven whether these associations represent an intrauterine influence, or more simply, reflect shared

familial, genetic, or lifestyle characteristics. Some authors who have compared maternal-offspring with paternal-offspring adiposity associations have reported stronger relationships with maternal BMI, but others show the maternal and paternal associations to be similar, even after correction for possible nonpaternity. At present, it is concluded that there is no strong evidence of an intrauterine effect (or other maternal specific effects), but with the caveat that the majority of investigations addressing this hypothesis have been carried out in historic cohorts with a low incidence of maternal obesity. One report has assessed obesity in siblings born to women before and after substantial weight loss after bariatric surgery for obesity (BMI 40 kg/m^2). Although a small study that requires replication, the siblings born after maternal weight loss had lower BMI and obesity risk**. (13)**

Thus, given the current level of evidence, we cannot conclude that the current obesity epidemic is driven by intergenerational transmission mediated through the intrauterine environment. However, associations between maternal, paternal, and child obesity urgently need to be addressed in cohorts with an incidence of maternal obesity that reflects contemporary populations. Moreover, better observational studies are needed that exploit within sibling comparisons and perhaps Mendelian randomization approaches with careful follow-up of the offspring. Lifestyle intervention RCTs in obese mothers are likely to be particularly informative. **(14)**

Maternal prepregnancy obesity is strongly associated with risk of GDM, and so, we also considered the association of GDM with offspring health. Observational evidence from different populations constantly shows an association between GDM and macrosomia. Less-profound disturbance of blood glucose, and perhaps other metabolites, may also influence macrosomia and infant body composition as shown by the HAPO study, in which a strong linear association between fasting and postchallenge glucose and the incidence of macrosomia and neonatal adiposity was found in 23,000 nondiabetic mother-baby pairs. Relevant RCTs include the Australian Carbohydrate Intolerance in Pregnant women Study (ACHOIS) in pregnant women with GDM, in which serious perinatal morbidity, including LGA, was reduced by dietary advice and, if needed, insulin (20%). Interestingly, there was 1.4 kg less GWG in the intervention group. This and the recent RCT of similar design in women with mild GDM provide some evidence for a causal relationship between maternal glycemic control and delivery of an LGA and fatter infant**.(15)**

Pima Indians living in the United States (but not in Mexico) have a high incidence of obesity, type 2 diabetes, and GDM, which is associated with greater offspring BMI and obesity risk up to the age of 21y. Evidence from other, in particular, European and North American populations for this association is less consistent. Among the Pima population, evidence that the association reflects, at least in part,

intrauterine mechanisms comes from a sibling study showing increased risk of obesity in offspring born to mothers after their diagnosis of diabetes (i.e. offspring exposure to in utero maternal GDM) compared with their siblings born before the mothers diagnosis (not exposed to in utero maternal GDM). **(16)**

More recent studies from other populations, e.g. from Denmark also provide some support for an influence of GDM on offspring overweight/metabolic syndrome. Inevitably, the interdependence or independence of the relationships between maternal diabetes and obesity with offspring adiposity have proven difficult to define, and these will need to be readdressed if the recommendations of the International Association of Diabetes and Pregnancy Study Groups are adopted because the lowered threshold for diagnosis of gestational diabetes will increase the number of obese women with a diagnosis of GDM**.(11)**

Recommendations to overcome the maternal obesity risks

Assessment of relationships between maternal obesity and offspring health would be facilitated by studies in contemporary birth cohorts with a higher incidence of maternal obesity, and in children born to women in the intervention and control arms of ongoing studies primarily designed to improve pregnancy outcome (e.g. UPBEAT, New Life, LIMIT, and Fit for 2)**.(17)**

- Dietary interventions in future RCTs in obese pregnant women should be better tailored to current theory, e.g. to reduce the maternal glycemic load and prevent insulin resistance, reduce maternal dietary n-6:n-3 ratio, and lower neonatal leptin. Relationships between maternal dietary composition and short- and long-term childhood outcomes should be addressed.
- Recent RCTs designed to address efficacy of an intervention in diabetic pregnancies on maternal and short-term neonatal outcomes, and large observational studies such as HAPO provide an opportunity to interrogate inheritance of obesity through childhood follow-up.
- Long-term follow-up should be included in protocols for studies of obese pregnancies and funding provided to enable follow-up without interruption throughout childhood and into adulthood.
- In interrogation of inheritance of obesity, determination of parental, neonatal, and childhood adiposity and fat distribution using specific methodology may be required, in addition to more conventional measures, e.g. BMI. Measurement of growth trajectories in the fetus would be of value.
- Assessment of inheritance of obesity risk would also be facilitated by collection of paternal and maternal and child DNA in addition to maternal and cord blood biomarkers, methylation status of genes to address epigenetic pathways, placental transport pathways, and nutrient transfer mechanisms.

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