Maternal Obesity and Impact on Fetal Brain Development

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Obesity is preventable. Obesity is the most common medical condition in women of reproductive age. It is such a common condition that the implications relative to pregnancy often are unrecognized, overlooked, or ignored because of the lack of specific evidence-based treatment options. The management of obesity requires long-term approaches ranging from population-based public health and economic initiatives to individual nutritional, behavioral, or surgical interventions. Therefore, an understanding of the management of obesity during pregnancy is essential, and management should begin before pregnancy and continue through the postpartum period. Although the care of the obese woman during pregnancy requires the involvement of the obstetrician, maternal and child healthcare professional, and additional healthcare professionals, such as nutritionists, can offer specific expertise, related to complications of obesity.

The purpose of this document is to offer an integrated approach to the management of obesity in women of reproductive age who are planning a pregnancy. The problems go beyond fetal metabolic programming. Maternal obesity has effects on fetal neurodevelopment. Impaired dopaminergic signaling has been implicated in the development of certain psychiatric disorders in humans. The effect of maternal obesity, high fat diet, and gestational weight gain on fetal neurodevelopment and offspring behavior is also the focus of this review.

EPIDEMIOLOGY

Incidence, Definition and Trends

In the United States (U.S.), more than 60% of reproductive age women are overweight and 35% are obese, representing a 70% increase in pre-pregnancy obesity (1). Obesity is commonly classified based on body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m^2). Recommendations for patients with a BMI greater than 35 are not yet completely based on clear evidence (2). Women should set pregnancy weight gain goals on their pre-pregnancy BMI or the BMI during the first antenatal visit. Ethnic differences exist. The physiologic increase in BMI during pregnancy in about 50% of women caused as an indicator of body fat (3). In 2009, the Institute of Medicine (IOM) in the US revised the pregnancy recommendations not regarding ethnicity, age, smoking behavior and parity (*see Table 1 below)* . Trimester specific recommendations for weight were defined and evidence-based absolute and relative risks (RR) for mother and child were finally used for recommendations (4).

According to the World Health organization (WHO) worldwide obesity has nearly triples since 1975. In 2016, more than 1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese. 39% of adults aged 18 years and over were overweight in 2016, and 13% were obese. Most of the world's population live in countries where overweight and obesity kills more people than underweight. 39 million children under the age of 5 were overweight or obese in 2020. Over 340 million children and adolescents aged 15-19 were overweight or obese

in 2016 (5). WHO defined overweight – is a BMI greater than or equal to 25; and obesity is a BMI greater than or equal to 30.

Criteria	BMI (kg/m^2)	Recommended Weight Gain		
		Course of Pregnancy		2nd & 3rd trimesters
		Singleton Pregnancy	Twin Pregnancy	Singleton pregnancy
Underweight	<18.5	12.5 – 18 kg	No information	0.51 (0.44-0.58) kg/gestational week
Normal weight	18.5 – 24.9	11.5 – 16 kg	17 – 25 kg	0.42 (0.35-0.50) kg/gestational week
Overweight	25 – 29.9	7 – 11.5 kg	14 – 23 kg	0.28 (0.23-0.33) kg/gestational week
Obesity Class I	30 – 34.9	5 – 9 kg	11 – 19 kg	0.22 (0.17-0.27) kg/gestational week
Obesity Class II	35 – 39.9	5 – 9 kg	11 – 19 kg	0.22 (0.17-0.27) kg/gestational week
Obesity Class III	>40	5 – 9 kg	11 – 19 kg	0.22 (0.17-0.27) kg/gestational week

Table 1. Weight classification / World Health Organization (WHO), with modified criteria of the Canadian Guidelines and Recommended weight gain according to the Institute of Medicine (IOM). References 2, 3, 4, 5.

In new guidelines, waist circumference and co-morbidity are used as criteria for weight reduction in obese non-pregnant patients. Regardless of the BMI, women who followed the weight gain guidelines (*stated above in Table 1.*) had fewer adverse outcomes (cesarean delivery, gestational hypertension, birth weight <2,500 g or >4,000 g) (3). Early counseling by pediatricians, general practitioners, at schools and universities should be promoted. In adolescents between 11 and 15 years of age, a good breakfast and physical activity were the main negative predictors for obesity (6).

BMI Calculator:
https://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/english_bmi_calculator/bmi_calculator.html

The primary weight management strategies during pregnancy are dietary control, exercise, and behavior modification. These strategies have been used either alone or in combination to avoid excessive gestational weight gain.

Pre-Conception Counseling

Optimal control of obesity begins before pregnancy. Weight loss before pregnancy, achieved by surgical or non-surgical methods has been shown to be the most effective intervention to improve medical comorbidities. Because even small weight reduction before pregnancy in women with obesity may be associated with improved pregnancy outcomes, weight loss before pregnancy should be encouraged. Motivational interviewing has been used successfully withing the clinical setting to promote weight loss, dietary modification, and exercise (7). The goal of motivational interviewing is to help patients move through the states of dealing with unhealthy

behavior. Although achieving a normal BMI is ideal, a weight loss of 5-7% over time can significantly improve metabolic health (8). The U.S. Preventive Services Task Force recommends that all adults aged 18 years and older with a BMI of 30 or greater be offered or referred to intensive multicomponent behavior interventions for weight loss and weight loss maintenance (9).

Medications for weight loss management are NOT recommended during the pre-pregnancy time or during pregnancy because of safety concerns and adverse effects. These types of drugs include typical anorectics, which alter the release and reuptake of neurotransmitters that suppress appetite, and other drugs that decrease intestinal fat absorption by inhibiting pancreatic lipase. Metformin, which is used to treat type 2 diabetes, decreases hepatic glucose production and has been associated with decreased gestational weight gain in some studies when used to treat mild gestational diabetes (10). In pregnant patients who are overweight or obese but do not have diabetes, metformin in addition to diet and lifestyle advice starting at 10 to 20 weeks did not improve pregnancy or birth outcomes (11).

Maternal Obesity and Perinatal Outcomes

Maternal obesity has negative effects on the mother and fetus both during pregnancy and delivery, as well as the offspring during the neonatal period and later in life (12). It is summarized below (*see figure* 1). Obese women have an increased risk of fetal structural congenital anomalies (13).

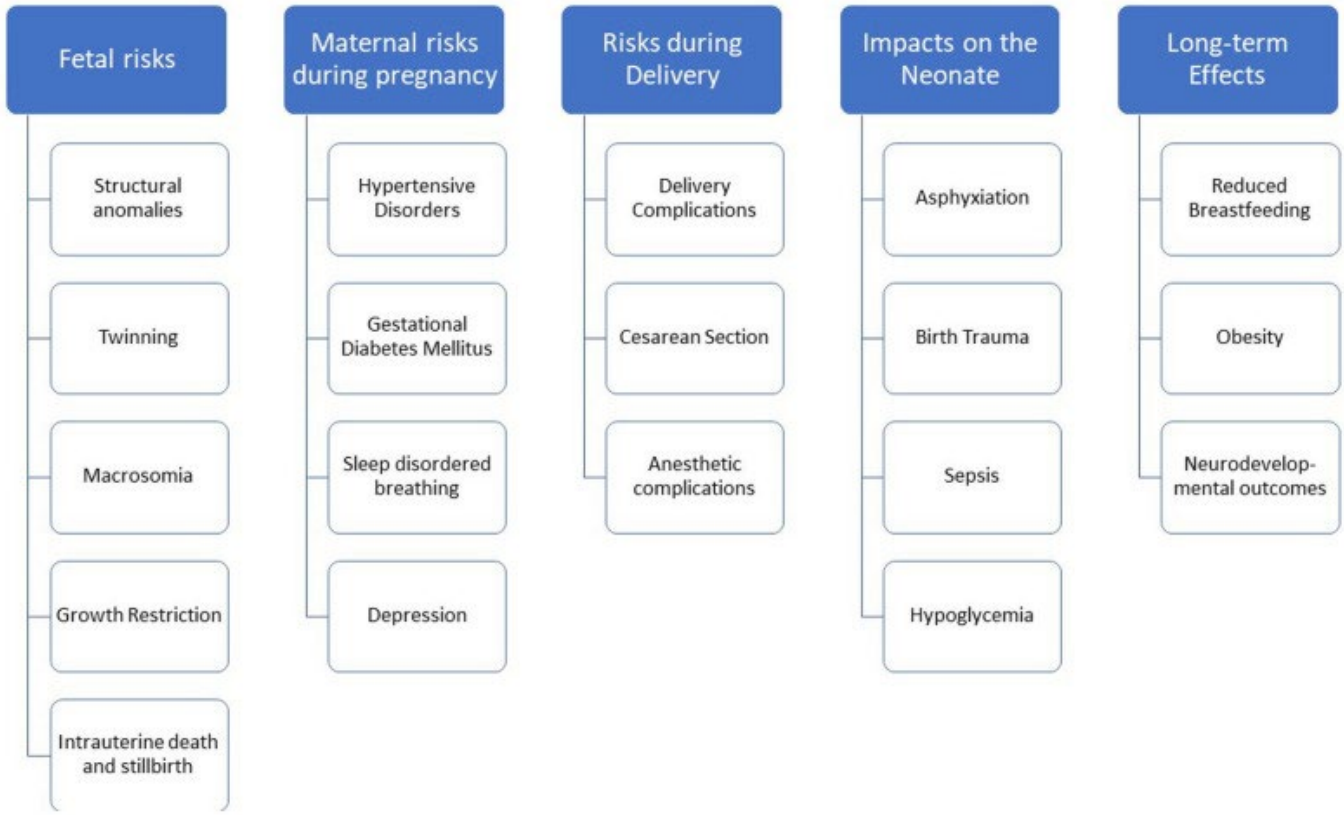

Figure 1. Summary of perinatal outcomes associated with maternal obesity.

The overall rate of major organ malformations increased from 3.5% in normal weight mothers, to 4.7% with class III obesity, in this large systemic review (14), and effects were greater in multiple gestations (14). Structural defects reported to be significantly associated with maternal obesity include malformations in the central nervous system, cardiac structures, digestive systems, limbs and genital organs. The largest risk was reported in the nervous system with neural tube defects (NTDs), cardiovascular anomalies, orofacial clefts, and other anomalies. The largest risk was reported in the nervous system, with and adjusted risk ratio of 1.15 in overweight women compared to 1.88 in women with class III obesity (14,15).

Maternal Obesity and Effects on Fetal Neurodevelopment

Data from large epidemiologic studies have demonstrated an association between maternal obesity and neurodevelopment morbidities in offspring. Impaired dopaminergic signaling has been implicated in the development of certain psychiatric disorders in humans. Maternal obesity may increase the risk for intellectual disability or cognitive deficits in offspring from 1.3- to 3.6-fold (16). Maternal obesity has been linked to decreases in offspring cognition (e.g., 2 – 5 points lower IQ [intelligent quotient] in offspring of obese women compared to non-obese counterparts), with every increase of 1 unit in maternal pre-pregnancy BMI found to be associated with a significant reduction in offspring IQ and non-verbal IQ, suggesting a dose-response relationship (17). Of note, extremely low maternal pre-pregnancy BMI (<18.5 kg/m^2) has also been significantly associated with lower offspring IQ, although the reported decrement is less than in the setting of maternal obesity (16,18). Maternal obesity may increase odds of autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD) and cerebral palsy (CP).

Physiology of Obese Pregnancy

The aforementioned studies defined maternal pre-pregnancy obesity as a reported pre-pregnancy or measured early pregnancy BMI >30 kg/m^2 or absolute pregnancy weight >90 kg. These definitions do not identify percent of weight due to body fat and/or the distribution of body fat, both of which may have bearing on maternal and fetal health (19). Epidemiological studies are also limited by their inability to demonstrate causation or to elucidate mechanism; the fact that some these data are from large US or European population-level studies in the 1970s – 1990s, when obesity was less prevalent; and the fact that many of these studies suffer from attrition, sampling biases for control groups, reliance on parental report to evaluate post exposure and offspring diagnosis, lack of satisfaction-power, and inability to adjust for confounders (20).

The primary mechanism that have been proposed to underlie the risk of neurodevelopmental morbidity in offspring of obese women include:

1. Inflammation-induced mal-programing;
2. Relative excess and/or deficiencies of circulating nutrients;
3. Metabolic hormone-induced mal-programming; and
4. Impaired development of serotonergic and dopaminergic signaling.

These mechanisms are not necessarily distinct from one another, and feature several interconnections (*see figure 2*).

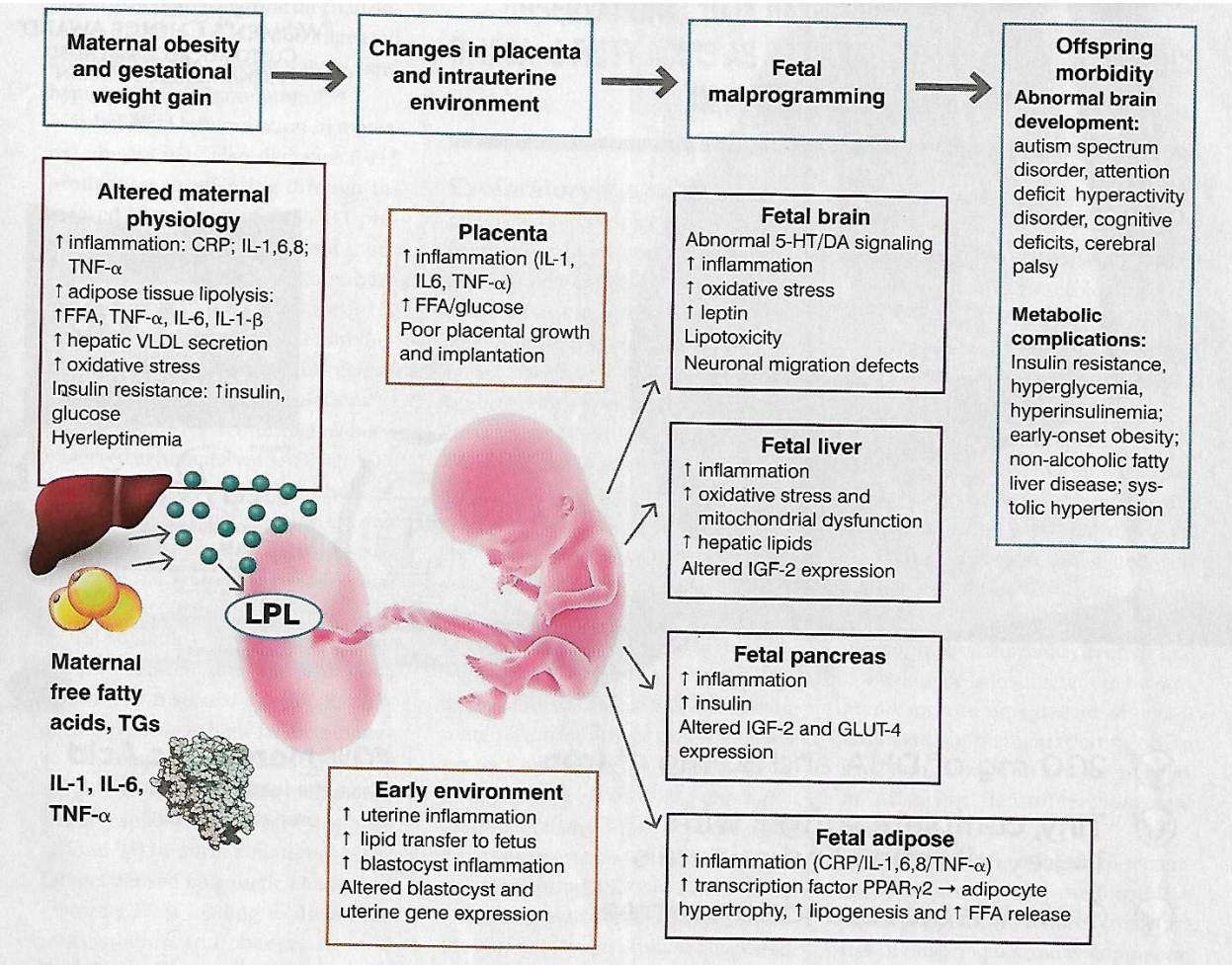

Figure 2. Mechanism underlying intrauterine mal-programming and offspring morbidity in maternal obesity. Abbreviations: 5-HT (serotonin); CRP (C-reactive protein); DA (dopamine); FFA (free fatty acid); GLUT-4 (glucose transporter type 4); IGF-2; (insulin-like growth factor 2); IL (interleukin); LPL (lipoprotein lipase); PPARγ2 (peroxisome proliferator-activated receptor gamma 2); TG (triglycerides); TNF (tumor necrosis factor); VLDL (very low-density lipoprotein).

Inflammation-induced mal-programming

Both maternal obesity and pregnancy itself are associated with chronic systemic inflammation (21). Obese women have been demonstrated to have exaggerated physiologic responses to pregnancy, with increased circulating levels of pro-inflammatory cytokines compared to their normal weight counterparts (22). Maternal BMI has been shown to be directly correlated with maternal blood concentrations of cytokines and with activation of pro-inflammatory pathways in the placenta (23). Placental and intrauterine inflammation are associated with altered fetal cytokine expression. Elevated levels of maternal pro-inflammatory cytokines during gestation have been linked to increased risk for autism spectrum disorders (ASD) and neurodevelopment delays in children (24). Children with ASD have also been shown to have elevated plasma markers of inflammation.

It is postulated that underlying maternal and placental inflammation in the setting of maternal obesity plays a key role in fetal brain inflammation and subsequent abnormal offspring neurodevelopment. This concept has been corroborated by animal studies (25).

Relative excess or deficiency of circulating nutrients

Maternal obesity is associated with increased circulating free fatty acids and glucose, due to diet, increased insulin resistance, and increased adipose tissue lipolysis. The fetus is exposed to excess of certain circulating nutrients. Obesity has also been shown to coexist with states of subclinical malnutrition characterized by excess energy intake with a relative deficiency in circulating micronutrients (26). Excess free fatty acids and glucose in maternal circulation, and deficiencies of vitamin D, B12, folate, and iron have been implicated in abnormal neurodevelopment of the fetus. Obese pregnant women were also found to have lower levels of nutritional antioxidants, suggesting that fetuses of obese women may be exposed to more oxidative stress and inflammation than those of lean women (27).

Metabolic hormone-induced mal-programming

Fetuses of obese women may be chronically exposed to insulin resistance and glucose-rich environment, even in absence of diagnosed gestational or pre-gestational diabetes. The fetal pancreas compensates by producing increased insulin, and the pro-inflammatory environment compounds fetal insulin resistance via inflammatory changes in fetal adipose tissue. Insulin acts on fetal brain as a growth factor, and excess insulin exposure can cause disruptions in neural circuitry, brain development, and behavior. Maternal hyperinsulinemia in the setting of Type 2 diabetes and gestational diabetes have been shown to be associated with increased risk of ASD and neurodevelopmental delay (28).

Leptin levels are also elevated in obese women. Leptin functions as a critical neurotrophic factor, and leptin signaling abnormalities during fetal development have been associated with decreased neuronal stem cell differentiation and growth. Leptin receptors are widely distributed in brain regions involved in behavior regulation, so derangement in leptin signaling during the key developmental periods is another potential mechanism underlying abnormal neurodevelopment in fetuses of obese women (29).

Impaired development of serotonergic and dopaminergic signaling

Maternal obesity may also increase the risk of neurodevelopmental and psychiatric disorders through abnormal development of serotonergic (5-hydoxytryptamine [5-HT]) and dopaminergic (DA) systems. 5-HT signaling plays a significant role in neuronal migration, cortical neurogenesis, and synaptogenesis during fetal brain development (29,30). Subclinical inflammation in maternal obesity may also decrease 5-HT production to offspring through increased breakdown of the 5-HT precursor tryptophan. Suppressed 5-HT synthesis has been observed in humans with ADHD, ASD, anxiety, and depression (31). Thus, altered 5-HT production may be one mechanism by which maternal obesity increases risk for neurodevelopmental disorders in offspring. Impaired dopaminergic signaling has been implicated

in the development of ASD, ADHD, disordered eating, and other psychiatric disorders in humans (31).

Effects of maternal obesity on the offspring at birth and long-term are summarized below in figure 3.

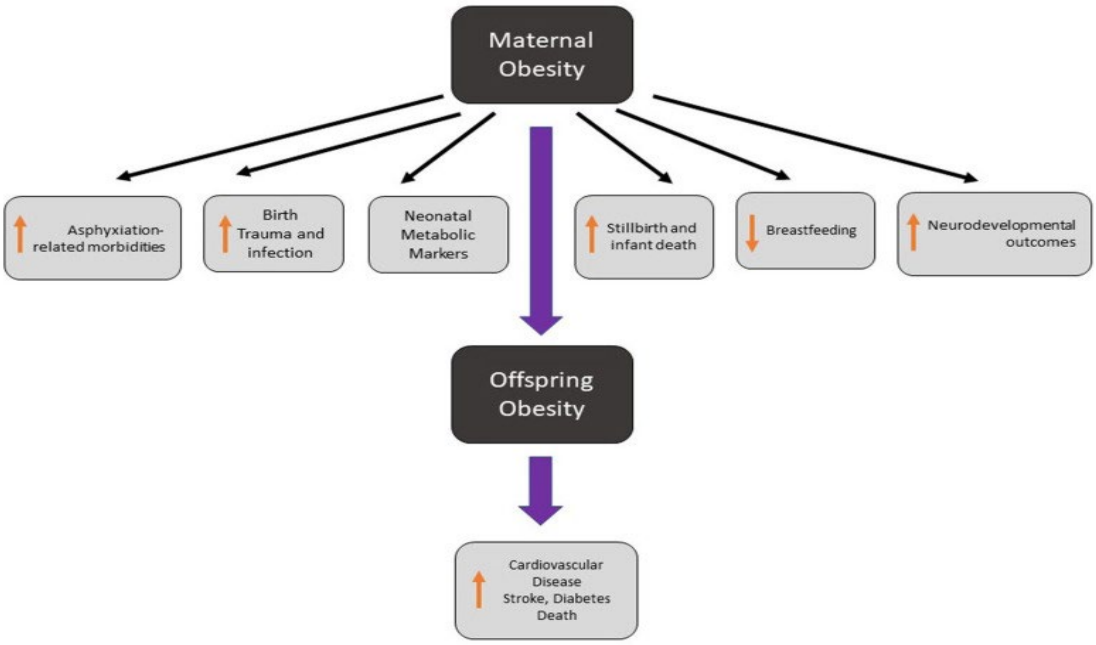

Figure 3. Long-term outcomes of offspring exposed to maternal obesity.

Clinical Considerations and Recommendations

Obese women have an increased risk of fetal structural congenital anomalies. Detection of congenital anomalies by ultrasonography is significantly reduced with increasing maternal BMI. Obese women should be counseled about the limitations of ultrasound in identifying structural anomalies. To optimize ultrasonographic image quality in obese pregnant women include a vaginal approach in the first trimester or using the maternal umbilicus as an acoustic window, as well as tissue harmonic imaging. Fetal magnetic resonance imaging obviates many of these technical problems, but because its use is limited by cost and availability, magnetic resonance imaging is not recommended for routine screening (32). Maternal obesity also affects measures of serum analytes because of the increased plasma volume in obese pregnant women. Although weight adjustment for analytes improves detection of neural tube defects and trisomy 18, this adjustment does not improve detection of Down Syndrome (32).

Metabolic disorders of Pregnancy: Women with obesity are at increased risk of metabolic syndrome. Increased insulin resistance during pregnancy may cause pre-existing but subclinical cardiometabolic dysfunction to emerge as preeclampsia, gestational diabetes, and obstructive sleep apnea (OSA). These complications are associated with adverse pregnancy outcomes. All pregnant patients should be screened for gestational diabetes mellitus based on medical history, clinical risk factors, or laboratory screening test results to determine blood glucose levels. Routine screening generally is performed at 24 – 28 weeks of gestation. Early pregnancy

screening for glucose intolerance (gestational diabetes or overt diabetes) should be based on risk factors (33). If the initial early diabetes screening result is negative, a repeat diabetes screening generally is performed at 24 – 28 weeks of gestation (33).

Stillbirth and Antenatal Fetal Surveillance

For patients with pre-pregnancy BMI of 35.0 – 39.9, weekly antenatal fetal surveillance may be considered beginning of 37/07 weeks of gestation. For patients with pregnancy BMI 40 or greater, weekly antenatal fetal surveillance may be considered beginning at 34 0/7 weeks of gestation (34).

Intrapartum Care for overweight and obese women: Maternal obesity alone is NOT an indication for induction of labor; however obese women are at increased risk of a prolonged pregnancy and have an increased rate of labor induction. Pregnant patients with higher BMI have higher rates of complications with an elective repeat cesarean delivery as well as with a trial of labor after cesarean. Obesity is not a contraindication to labor after cesarean: the decision to undergo after cesarean depends on the patients preferences, and such a decision should rely on tenets of shared medical decision (35). Compared with normal weight pregnant women, pregnant women with class III obesity have a significantly increased risk of postpartum atonic hemorrhage (bleeding greater than 1,000 mL) after a vaginal delivery (5.2%), but not after cesarean delivery (7,35).

Anesthesia during Labor - Epidural or Spinal Anesthesia: The use of epidural or spinal anesthesia for intrapartum pain relief is recommended but may be technically difficult because of body habitus and loss of landmarks. The risk of epidural analgesic failure is greater in obese women compared with normal-weight and over-weight women; therefore early labor epidural catheter placement should be considered after discussing risks and benefits with the patient. Epidural catheters placed for labor may reduce the decision-to-incision interval for an emergency cesarean delivery. The combination of spinal anesthesia and obesity significantly impairs respiratory function for up to 2 hours after the procedure (36). General anesthesia also poses risks for obese women because of potential difficulties with endotracheal intubation due to excessive tissue and edema. General anesthesia is not contraindicated in obese pregnant women, but consideration should be given to pre-oxygenation, proper patient positioning, and having fiberoptic equipment available for intubation (36).

Antibiotics:

Broad-spectrum antimicrobial prophylaxis is recommended for all cesarean deliveries unless the patient is already receiving antibiotics for conditions such as chorioamnionitis. Some recommendations based on general procedures would suggest a 2-g prophylactic cefazolin dose for women who weigh more than 80 kg (175 lb), with an increase to 3 g for those who weigh more than 120 kg (265 lb) (37). Conclusive recommendations for weight-based dosage are difficult to establish because of lack of evidence demonstrating different adipose tissue concentrations and decreases surgical site infections with higher dosage strategies in an obese cohort.

Incision

The optimal skin incision for primary cesarean delivery in class II and III obese patients has not been determined. Closure of the subcutaneous tissue with depth greater than 2 cm can significantly decrease the incidence of wound disruption. However, the use of subcutaneous drain with bulb suction in obese women with at least 4 cm of subcutaneous fat was not effective in preventing wound complications in this study, and may have increased post-cesarean wound complications and should not be used routinely (38). Pre-operative skin cleaning before cesarean delivery with an alcohol-based solution should be performed unless contraindicated. A reasonable choice is chlorhexidine-alcohol skin preparation. Vaginal cleansing before cesarean delivery in laboring patients and those with ruptured membranes using either povidone-iodine or chlorhexidine gluconate may be considered. Skin closure techniques and supplemental oxygen have not proved useful in decreasing the rate of post-cesarean infectious morbidity.

Postpartum Care

Because of increased risk of venous thromboembolism in obese women, it is recommended pneumatic compression devices to be placed before a cesarean delivery and continued postpartum for all women not already receiving thromboprophylaxis. The American College of Chest Physicians currently recommends low-molecular-weight (LMW) heparin for the prevention and treatment of venous thromboembolism instead of unfractionated heparin (39). The optimal prophylactic dose of LMW heparin has not been determined, but enoxaparin 40 mg daily is commonly used (39). Venous thromboembolism prophylaxis is usually start 12 hours after cesarean delivery using weight-based (0.5 mg/kg enoxaparin every 12 hours) dosage or BMI stratified (BMI of 40 – 59.9 receiving enoxaparin 40 mg every 12 hours and BMI of 60 or greater receive enoxaparin 60 mg every 12 hours) dosage.

Clinicians should encourage behavioral interventions focused on improving both diet and exercise, which have been shown to improve outcomes compared with programs focused on exercise alone. Nutrition and exercise counseling should continue postpartum and before attempting another pregnancy. For women who are breastfeeding, more evidence is required to confirm whether diet, exercise, or both provides the most benefits for postpartum weight loss.

Summary

BMI calculated at the first prenatal visit should be used to provide diet and exercise counseling. Because even small weight reduction before pregnancy in women with obesity may be associated with improved pregnancy outcomes, weight loss before pregnancy should be encouraged. Clinicians should encourage behavioral interventions focused on improving both diet and exercise, which has been shown to improve outcomes compared to programs focused on exercise alone. Obese women should be counseled about the limitations of ultrasound in identifying structural anomalies. Early pregnancy screening for glucose intolerance (gestational diabetes or overt diabetes) should be based on risk factors, including maternal BMI of 30 or greater, known impaired glucose metabolism, or previous gestational diabetes. For patients with pre-pregnancy BMI of 35.0 – 39.9, weekly antenatal fetal surveillance may be considered beginning by 37 0/7 weeks of gestation. For patients with prepregnancy BMI 40 or greater,

weekly antenatal fetal surveillance may be considered beginning at 34 0/7 weeks of gestation. Weight-based dosage for venous thromboembolism thromboprophylaxis may be considered rather than BMI-stratified dosage strategies in class III obese women after cesarean delivery. Consultation with anesthesia service should be considered for obese pregnant woman with obstructive sleep apnea, because they are at an increased risk of hypoxemia, hypercapnia, and sudden death.

Suggested Reading

Obesity in Pregnancy
http://www.womenshealthsection.com/content/obsmd/obsm013.php3

Gestational Diabetes: A Comprehensive Review
http://www.womenshealthsection.com/content/obsmd/obsm011.php3

Healthy Mother Healthy Infant Through Nutrition
http://www.womenshealthsection.com/content/obs/obs029.php3

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