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ABSTRACT

The pathophysiology of obesity includes adipose tissue dysfunction, alterations in adipokine secretion and chronic inflammation, which contribute to insulin resistance. During pregnancy, this increases the risk of complications such as gestational diabetes, preeclampsia, miscarriage, premature delivery and fetal death. In addition, obesity is linked to an increased risk of cesarean section, anesthetic complications, postoperative infections and venous thromboembolism. Management of obesity in this setting focuses on behavioral and lifestyle interventions, limiting excessive weight gain. The use of weight-reducing medications is contraindicated, while bariatric surgery may be an option if performed in the preconceptional state.

Keywords: Obesity, Overweight, Pregnancy, Pregnancy Complications (source: MeSH NLM).

RESUMEN

La fisiopatología de la obesidad incluye disfunción del tejido adiposo, alteraciones en la secreción de adipocinas e inflamación crónica, lo que contribuye a la resistencia a la insulina. Durante el embarazo, esto aumenta el riesgo de complicaciones como diabetes gestacional, preeclampsia, aborto espontáneo, parto prematuro y muerte fetal. Además, la obesidad está vinculada a un mayor riesgo de cesáreas, complicaciones anestésicas, infecciones posoperatorias y tromboembolismo venoso. El manejo de la obesidad en este contexto se enfoca en intervenciones conductuales y de estilo de vida, limitando el aumento excesivo de peso. El uso de medicamentos para reducir peso está contraindicado, mientras que la cirugía bariátrica puede ser una opción si se realiza en el estado preconcepcional.

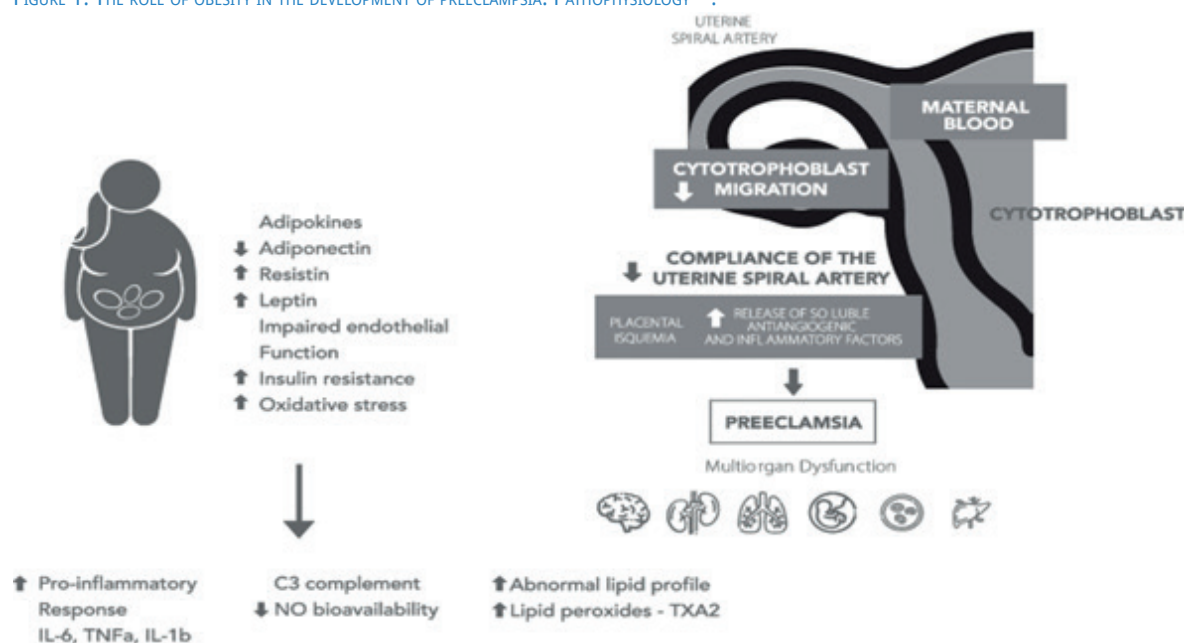
Palabras clave: Obesidad, Sobrepeso, Embarazo, Complicaciones del embarazo (fuente: DeCS BIREME).

PATHOPHYSIOLOGY

From a pathophysiological perspective, obesity is characterized by a dysfunction of adipose tissue, which includes alterations in the secretion of adipokines, such as leptin and adiponectin, and a chronic inflammatory state⁽¹⁾. These alterations contribute to insulin resistance, which is a key factor in the development of gestational and other metabolic complications during pregnancy. Additionally, maternal obesity is associated with an increase in the transfer of nutrients to the fetus through the placenta, which can lead to excessive fetal growth and a higher risk of obesity and metabolic disorders in the offspring⁽²⁾.

Placental dysfunction is another important mechanism linking maternal obesity to complications during pregnancy. Obesity can induce structural and functional changes in the placenta, affecting the exchange of nutrients and oxygen between mother and fetus. This is due in part to chronic inflammation, oxidative stress and mitochondrial dysfunction in the placenta⁽³⁾. These changes may contribute to the development of conditions such as fetal growth restriction and preeclampsia.

In summary, maternal obesity affects pregnancy through multiple pathophysiologic pathways, including adipose tissue dysfunction, insulin resistance, and placental dysfunction, increasing the risk of complications for both mother and fetus (Figure 1). Understanding these mechanisms is crucial for developing effective strategies for the prevention and management of obesity during pregnancy.

FIGURE 1. THE ROLE OF OBESITY IN THE DEVELOPMENT OF PREECLAMPSIA. PATHOPHYSIOLOGY⁽¹³⁾.

OBSTETRIC CONSEQUENCES

1. ANTEPARTUM COMPLICATIONS

• Gestational diabetes

Several studies have shown that women with obesity have a higher risk of developing gestational diabetes compared to those with a normal body mass index (BMI). The risk has been reported to be 3 to 4 times higher, increasing the likelihood of maternal and fetal complications⁽⁴⁾. Moreover, gestational obesity has been associated with the presence of pregestational type 2 diabetes mellitus (DM2) and with an increased maternal risk of developing DM2 in the long term, reaching up to 70% incidence in 25 years after pregnancy⁽⁵⁾. Gestational diabetes, by itself, is linked to an increased risk of fetal macrosomia, neural tube closure defects, fetal conotruncal heart anomalies, sudden intrauterine death, polyhydramnios, neonatal hypoglycemia, cesarean delivery, and increased maternal-fetal morbidity⁽⁶⁾.

Clinical guidelines recommend screening for diabetes during gestation at two key times. At the first prenatal check-up, ideally during the first trimester, the presence of pregestational DM2 should be assessed by fasting glucose measurement or, in case of high risk, with a glucose tolerance test⁽⁷⁾. Subsequent-

ly, between 24 and 28 weeks of gestation, a second evaluation for gestational diabetes is recommended. In overweight or obese women, most guidelines suggest the preferential use of the glucose tolerance test instead of the fasting glucose dose, due to its better diagnostic performance⁽⁸⁾. For the prevention and management of gestational diabetes, the first line of treatment should always include lifestyle modifications, such as healthy diet and regular exercise. If pharmacological treatment is required, insulin is a safe option during pregnancy, as the routine use of oral antidiabetics is not recommended due to lack of sufficient evidence on their fetal safety⁽⁹⁾.

• Hypertensive disorders of pregnancy

Obesity in gestation has been shown in numerous studies to carry an increased risk of developing preeclampsia and has even been identified as an independent risk factor for preeclampsia, with the risk increasing proportionally with body mass index (BMI)⁽¹⁰⁾. The literature suggests that the mechanisms involved include systemic inflammation and endothelial dysfunction characteristic of obesity, which alter the environment in which the placenta develops. Specifically, these mechanisms negatively affect trophoblastic invasion necessary for spiral artery remodeling, a key defect in the genesis of preeclampsia⁽¹¹⁾.



Recommendations for preventing preeclampsia in obese women include first and foremost general weight control measures before and during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and other medical societies recommend interventions such as regular exercise and a balanced diet to reduce the risk of preeclampsia. These interventions not only help limit weight gain during pregnancy, but also improve metabolic conditions that may influence the pathogenic sequence of preeclampsia⁽¹²⁾.

Prevention of preeclampsia also includes the use of pharmacological measures such as the use of low-dose aspirin before 16 weeks⁽¹³⁾. However, this prophylaxis has been demonstrated in women at high risk of developing the disease. There are multiple risk factors associated with preeclampsia, so in recent years there has been an attempt to reach a consensus on the criteria for administering this drug. A very useful and practical scheme is the one that stratifies the risk factors in risk levels: high, moderate and low⁽¹⁴⁾. It is proposed that in the presence of at least 1 high-risk factor, aspirin prophylaxis should be initiated, whereas 2 or more moderate-risk factors are required to initiate prophylaxis (Table 1).

Obesity (BMI ≥ 30 kg/m²) has been considered as a moderate risk factor. Therefore, other factors such as nulliparity, family history of preeclampsia, maternal age ≥ 35 years, among others, would be required to administer prophylaxis. However, other trends point out that obesity in itself would be a sufficient factor to initiate it. There is still no consensus on this recommendation, so in clinical practice the recommendation of prophylaxis will depend on medical criteria.

• Miscarriage

Overweight and obese women have an increased risk of miscarriage compared to those with a BMI within the normal range. A meta-analysis reported that the risk of miscarriage in women with BMI ≥ 25 was significantly higher, with an odds ratio (OR) of 1.67⁽¹⁵⁾. In addition, an observational cohort study in women with a history of recurrent early pregnancy

TABLE 1. HIGH, MODERATE, AND LOW RISK FACTORS FOR PREECLAMPSIA⁽¹⁴⁾.

Risk	Risk factors
High	<ul style="list-style-type: none"> - History of preeclampsia, especially when accompanied by an adverse outcome - Multifetal gestation - Chronic hypertension - Diabetes type 1 or 2 - Kidney disease - Autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid syndrome)
Moderate	<ul style="list-style-type: none"> - Nulliparity - Obesity (IMC >30 kg/m²) - Family history of preeclampsia (mother or sister) - Sociodemographic characteristics (e.g., African-American race, low socioeconomic status) - Age greater than or equal to 35 years - Personal obstetrical history factors (e.g., low birth weight or small for gestational age, previous adverse pregnancy outcome, interval between pregnancies > 10 years)
Low	<ul style="list-style-type: none"> - BMI less than 30 kg/m², without other risk factors

loss found that the risk of euploid miscarriage in obese women was 58%, compared with 37% in non-obese women⁽¹⁶⁾.

These findings suggest that obesity may be associated with alterations in implantation and early pregnancy development, possibly due to metabolic and inflammatory factors.

• Prematurity and fetal death

Obese women are at increased risk of preterm delivery, whether indicated by maternal or fetal complications or spontaneous delivery. Chronic inflammation, characteristic of obesity, has been proposed to play a role in the pathophysiology of preterm delivery, although the specific mechanisms are not yet fully elucidated⁽¹⁷⁾.

A systematic review and meta-analysis demonstrated a direct relationship between increased maternal BMI and the risk of perinatal mortality. For every five-unit increase in maternal BMI in overweight or obese women, the relative risk (RR) was 1.21 for fetal death (95% CI: 1.09-1.35), 1.24 for stillbirth (95% CI: 1.18-1.30), 1.16 for perinatal death (95% CI: 1.00-1.35), 1.15 for neonatal death (95% CI: 1.07-1.23) and 1.18 for infant death (95% CI: 1.09-1.28)⁽¹⁸⁾. These data highlight the importance of rigorous prenatal control in women with obesity to reduce adverse perinatal outcomes.



2. INTRAPARTUM COMPLICATIONS

• Cesarean delivery

There is a dose-response relationship between body mass index (BMI) and the need for cesarean section. Women with BMI >35 have been reported to have a significantly increased risk of cesarean delivery (OR = 3.38) compared to those with a BMI within the normal range⁽¹⁹⁾. This increased cesarean section rate is associated with multiple complications, including anesthesia difficulties and an increased risk of surgical site infections⁽²⁰⁾.

Broad-spectrum antimicrobial prophylaxis is recommended in all cesarean deliveries to reduce the risk of postoperative infections⁽²¹⁾. However, there is no consensus on optimal antibiotic dosing based on BMI. Compared with women of normal weight, the risk of surgical site infections is higher in women who are overweight (OR = 1.6; 95% CI: 1.2-2.2), class I obese (OR = 2.4; 95% CI: 1.7-3.4), and class II and III obese (OR = 3.7; 95% CI: 2.6-5.2)⁽²²⁾. Strategies such as skin preparation, different closure techniques and the use of supplemental oxygen have failed to significantly decrease the rate of post-cesarean section infections in obese women; however, subcutaneous tissue closure when fat exceeds 2 cm has been shown to significantly reduce the incidence of wound dehiscence⁽²³⁾.

• Anesthesia

Maternal obesity significantly increases the risk of anesthetic complications, regardless of the type of anesthesia used.

For regional anesthesia, obese women have a higher risk of epidural anesthesia failure compared to those who are normal weight or overweight. Obesity is also associated with an increased risk of maternal hypotension and prolonged fetal heart rate decelerations after administration of spinal anesthesia⁽²⁴⁾. In addition, the combination of spinal anesthesia and obesity significantly impairs maternal respiratory function for up to two hours post procedure⁽²⁵⁾.

On the other hand, we have general anesthesia. Its use in pregnant women with obesity

has been shown to carry a higher risk due to difficulties in endotracheal intubation and the higher prevalence of obstructive sleep apnea, which increases the risk of hypoxia and intra-operative complications⁽²⁶⁾.

The Royal College of Obstetricians and Gynaecologists (RCOG) recommends that all women with a pregestational BMI >40 be evaluated in an antenatal consultation with an obstetric anesthesiologist to optimize anesthetic safety during delivery⁽²⁷⁾.

3. POSTPARTUM COMPLICATIONS

• Increased risk of infections

Women with obesity are at increased risk of infections during the peripartum period, including postpartum endometritis and surgical wound infections after cesarean section. Increased adipose tissue and reduced tissue perfusion favor bacterial proliferation and altered immune response, contributing to the increased risk of infections⁽²⁸⁾.

In the case of endometritis, it has been observed that women with obesity have a 2- to 3-fold increased risk compared to women of normal weight⁽²⁹⁾. Similarly, surgical wound infections after cesarean section occur more frequently in women with obesity, with a relative risk of 1.6 in overweight women, 2.4 in class I obesity, and up to 3.7 in severe obesity⁽³⁰⁾.

To reduce this risk, administration of broad-spectrum prophylactic antibiotics prior to surgical incision is recommended⁽³¹⁾. However, optimal dosing is still a matter of debate, as some studies suggest that increased volume of distribution in obese women may require higher doses of prophylactic antibiotics⁽³²⁾.

• Venous thromboembolism

Maternal obesity is a well-established risk factor for venous thromboembolism (VTE) in the postpartum period. Women with obesity have been reported to have a significantly increased risk of developing deep vein thrombosis (DVT) and pulmonary embolism, with an adjusted odds ratio of 14.9 compared with non-obese women⁽³³⁾.



The U.S. Pregnancy and Thrombosis Working Group recommends individual assessment of the need for thromboprophylaxis, noting that there is insufficient evidence to recommend routine use of pharmacologic prophylaxis after cesarean section in all obese patients⁽³⁴⁾.

The American College of Obstetricians and Gynecologists (ACOG) suggests placement of pneumatic compression devices before and after cesarean delivery to reduce the risk of VTE in obese women⁽³⁵⁾.

On the other hand, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends the use of prophylactic low molecular weight heparin (LMWH) for seven days postpartum in obese women with at least one additional risk factor, such as smoking or a history of VTE. In addition, in women with two or more risk factors, it suggests considering the use of LMWH from early pregnancy until six weeks postpartum⁽³⁶⁾.

MANAGEMENT

1. WEIGHT MANAGEMENT WITH LIFESTYLE

Current recommendations on the management of obesity in pregnancy focus on behavioral and lifestyle interventions to limit excessive gestational weight gain (GWG) and improve health outcomes.

According to a report by the US Preventive Services Task Force, interventions that combine diet, exercise, and behavioral counseling can reduce the risk of gestational diabetes, emergency cesarean sections, macrosomia, and large-for-gestational-age babies. These interventions are also associated with a modest reduction in gestational weight gain and a reduced likelihood of exceeding National Academy of Medicine (NAM) weight gain recommendations⁽³⁷⁾.

ACOG suggests that obese women should receive preconception counseling about the risks of obesity in pregnancy and be encouraged to follow a weight reduction program before conceiving. During pregnancy, body mass index (BMI) should be recorded and weight gain recommendations should be reviewed periodically⁽³⁸⁾.

2. USE OF WEIGHT REDUCTION DRUGS

The use of weight-loss medications during pregnancy is contraindicated because of the potential risks to the fetus and the lack of benefit of weight loss during this period. According to the clinical practice guidelines of the American Association of Clinical Endocrinologists and the American College of Endocrinology, all weight loss drugs are classified as category X by the FDA, meaning they are contraindicated during pregnancy⁽³⁹⁾.

This includes drugs such as orlistat, which although it did not show teratogenicity in pre-clinical studies, its use is discouraged due to possible risks to the fetus.

Liraglutide and semaglutide are glucagon-like peptide type 1 (GLP-1) receptor agonists that have been approved by the FDA for the treatment of obesity and type 2 diabetes. However, their use during pregnancy is not recommended due to lack of safety data in this population and potential risks to the fetus.

Other medications such as the phentermine/topiramate combination have specific fetal toxicity warnings, as exposure to topiramate during the first trimester may increase the risk of oral malformations. Therefore, it is recommended that women of childbearing age use effective contraception while taking these medications and have regular pregnancy tests.

In summary, current evidence discourages the use of weight loss medications during pregnancy because of the potential risks to the fetus and lack of benefit to the mother in this setting. Interventions should focus on lifestyle changes and behavioral management to control gestational weight gain.

3. OTHER DRUGS

Statin use during pregnancy is important to mention in this review because of the close association of obesity with dyslipidemias. Historically, statins have been contraindicated during pregnancy because of teratogenicity concerns based on case reports of congenital malformations following first-trimester statin exposure⁽⁴⁰⁾. However, more recent cohort



studies have not demonstrated a significant increase in the risk of teratogenicity, although an increased risk of miscarriage has been observed⁽⁴¹⁾.

In 2021, the FDA revised its position on statins, removing the absolute contraindication for all pregnant women, allowing that in very high-risk cases, such as women with homozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease, their use may be considered after careful risk-benefit assessment⁽⁴²⁾. Despite this, the general recommendation remains to discontinue statins before conception and during pregnancy, because cholesterol is essential for normal fetal development and atherosclerosis is a chronic process that will not be significantly affected by temporary discontinuation of treatment. It is noteworthy that all malformations occurred in infants whose mothers were exposed to lipophilic statins, whereas no adverse birth outcomes were reported in infants whose mothers used hydrophilic statins such as pravastine⁽⁴³⁾.

4. SURGICAL INTERVENTIONS FOR WEIGHT REDUCTION

Bariatric surgery, including gastric bypass, is an intervention that has been used to treat obesity in women of reproductive age, and has significant implications for maternal and fetal health in the preconception setting. Evidence suggests that bariatric surgery can improve fertility and reduce the risk of obesity-related complications during pregnancy, such as gestational diabetes and hypertension⁽⁴⁴⁾. However, it is also associated with an increased risk of nutritional deficiencies, which may affect fetal development⁽⁴⁵⁾.

Gastric bypass, in particular, has been shown to reduce the risk of preeclampsia compared with women with obesity who have not undergone surgery⁽⁴⁶⁾. However, it has also been associated with an increased risk of fetal growth restriction and having small-for-gestational-age (SGA) babies⁽⁴⁷⁾. This is due, in part, to malabsorption of essential nutrients that can occur after malabsorptive procedures such as gastric bypass.

It is recommended that women who have undergone bariatric surgery wait at least 12-18 months before conceiving to allow weight and nutritional status to stabilize⁽⁴²⁾. In addition, close monitoring of nutritional status and fetal growth during pregnancy is crucial to mitigate potential risks⁽⁴⁸⁾.

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