Review Article
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Obesity a risk factor for dramatic adverse outcomes in pregnancy: a narrative review

Abstract

Obesity represents one of the greatest threats to public health today. During pregnancy, obese women face various and catastrophic maternal/perinatal adverse outcomes. The risks associated with being overweight and obese also compromise the future health of both the woman and her offspring. This narrative review includes systematic reviews, meta-analyses, and cohort or case-control studies that describe the considerable and serious harm to which an obese woman is exposed during pregnancy, as well as the pathophysiological mechanisms that cause these effects. Obese women and healthcare providers must be aware of these consequences when planning a pregnancy. Based on the results of this review, it is ideally recommended that women who wish to become pregnant should start with a normal weight. Understanding the pathophysiological mechanisms behind these damages will allow for the development of more effective specific treatments during pregnancy.

Keywords: obesity and pregnancy, adverse outcomes, pathophysiology, gestational diabetes, perinatal death and obesity

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Introduction

Obesity is the most common health problem and the greatest threat to women of reproductive age in the 21st century.[1] Obesity rates are increasing globally, and it is estimated that if current trends continue, one billion people will be obese by 2030. In the United Kingdom, more than 50% of women of reproductive age are overweight or obese.[1] In a public hospital in Chile, nearly 50% of pregnant women were overweight or obese at the beginning of their pregnancy.[2] Maternal obesity, along with numerous associated conditions, has a severe impact on the health of the mother, the child, and the child's future development. During the early weeks of pregnancy, obese women have a higher frequency of congenital anomalies and second-trimester miscarriages due to ascending infections. Comorbidities associated with obesity, such as gestational diabetes mellitus (GDM) and hypertension (preeclampsia, PE), increase the risk of immediate and long-term adverse outcomes for both the mother and the child. At the end of pregnancy, obese women are more likely to have large-for-gestational-age (LGA) newborns due to excessive fetal growth caused by insulin resistance and glucose intolerance. This results in an increased risk of complications during delivery, such as shoulder dystocia, cesarean section, and infections in surgical wounds. Additionally, these women are at higher risk for preterm birth (PTB), whether spontaneous, mainly due to ascending infections, or medically induced, as well as stillbirth (SB). During the postpartum period, they face a higher risk of venous thromboembolism, hemorrhage, depression, and breastfeeding difficulties. The newborns of obese women have a higher percentage of body fat, which increases the risk of childhood obesity. It is estimated that up to 30% of pregnancy complications may be attributed to overweight/obesity or excessive gestational weight gain, which can affect the mother-newborn pair throughout life.[13–11]

Although there is no single mechanism that explains the adverse perinatal outcomes associated with maternal obesity, available data suggest that pre-pregnancy maternal insulin resistance, hyperinsulinemia, inflammation, and oxidative stress contribute to fetal and placental dysfunction. Furthermore, maintaining overweight and obesity during the postpartum period increases future cardiometabolic risks and obesity in subsequent pregnancies.[3–7] The aim of this narrative review is to analyze the multiple and serious maternal and perinatal adverse outcomes to which an obese woman is exposed during pregnancy, as well as the mechanisms that cause them. Understanding the magnitude of these harms will promote the prevention of obesity in women who wish to become pregnant and allow for the development of more effective treatments when prevention is not possible.

Methodology

This review selected systematic reviews, meta-analyses, and notable manuscripts such as cohort or case-control studies with very low or low risk of bias and a high or moderate likelihood of establishing a causal relationship. The search was conducted in PubMed, Elsevier, Science Direct, Wiley, Scopus, Ovid, and Scielo, from the year 2000 onwards.

Epidemiology

Obesity is the most common chronic metabolic disorder affecting women of reproductive age. The World Health Organization (WHO) defines it as a chronic disease characterized by excess adiposity that may harm health.[1] It uses the body mass index (BMI) as a surrogate marker for obesity and defines normal weight as a BMI < 25 kg/m², overweight as a BMI between 25 and 29.9 kg/m², and obesity as a BMI ≥ 30 kg/m². Within obesity, Class I obesity is distinguished (BMI 30.00-34.99 kg/m²), Class II obesity (BMI 35.00-39.99 kg/m²), and Class III obesity (BMI > 40 kg/m²).[7]

Prevalence

Between 1980 and 2020, the prevalence of obesity in women nearly tripled, rising from 6% to 16%.[3] Among women of childbearing age, overweight has fluctuated between 29% and 50%, while obesity has ranged between 10% and 25%.[3] Among pregnant women, there is significant variability. In the United States, in 2020, 27% of parturients were overweight, and 30% were obese.[3] In Qatar, a study showed that at the beginning of pregnancy, 31% of pregnant women were overweight, and 41% were obese.[8] Data from 14,568 deliveries

in Saudi Arabia indicated that 33% of the women were overweight, and 36% were obese.[8] In India, obesity affects between 12% and 71% of pregnant women, depending on the region.[8] In a public hospital in Chile, nearly 50% of pregnant women presented with overweight or obesity at the beginning of pregnancy.[2] The current WHO BMI limits underestimate the prevalence of obesity as a condition of excess adiposity associated with health problems.

Review

Adverse pregnancy outcomes associated with obesity

Obesity during pregnancy is associated with several adverse risks and complications for both the mother and the newborn. Evidence shows a clear relationship between excess weight and an increased incidence of problems during pregnancy compared to women with normal weight. The following is a summary of the most relevant findings from the studies mentioned:

- UK Study,[9] 30,298 pregnancies included. Risks associated with: Overweight/Class I Obesity: hypertensive disorders, OR 1.9 (1.7-2.3); gestational diabetes mellitus: OR 1.7 (1.3-2.3), labor induction, OR 1.2 (1.1-1.3; cesarean section, OR 1.4 (1.3-1.5); postpartum hemorrhage, OR 1.4 (1.3-1.5); macrosomia, OR 1.5 (1.3-1.6). Class III Obesity: preterm birth: OR 1.6 (1.1-2.5); fetal death: OR 3.0 (1.0-9.3); neonatal unit admission: OR 1.6 (1.0-2.6).

- Chinese Study,[10] 29,303 pregnant women included: Increased BMI: Risks associated with preeclampsia, gestational diabetes, cesarean section, preterm birth, small for gestational age (SGA), large for gestational age (LGA), and perinatal death. Risks were generally higher in chinese women compared to caucasian women. Median BMI increased with maternal age and parity ($P < 0.001$).

- Meta-analysis,[11] included 39 cohorts from Europe, North America, and Oceania, with 265,270 births: BMI and gestational weight: Risks associated with hypertensive disorders, gestational diabetes, and large-for-gestational-age at birth. Preterm birth increased with higher BMI and gestational weight gain. Obese mothers with high weight gain during pregnancy had the highest risk of complications: OR 2.51 (2.31-2.74).

- Spanish Cohort,[12] with 16,609 women included: Comparison between obesity (BMI ≥ 30 kg/m²) and normal weight (BMI 20-24.9 kg/m²): Risks associated with preeclampsia: OR 2.199 (1.46-3.29); rectovaginal colonization by Group B *Streptococcus*: OR 1.299 (1.14-1.47); labor induction: OR 1.593 (1.44-1.75); cesarean section: OR 2.755 (2.46-3.08); fetal weight ≥ 4000 g: OR 2.090 (1.803-2.422) and neonatal ICU admission: OR 1.341 (1.12-1.59)

These studies highlight the significant negative impact of obesity on pregnancy, showing an increase in the risk of multiple complications. It is essential for women planning pregnancy to maintain a healthy BMI and appropriate weight gain during gestation to minimize theserisks.

Physiopathological problems of obesity

Obesity during pregnancy is linked to various issues that affect both the mother and the fetus. Two key aspects are described here: gut dysbiosis and changes in fat deposition and inflammation.

- Gut dysbiosis in obese pregnant women.[13]

Definition and effects. Gut microbiota dysbiosis: In obese women, the composition of the intestinal microbiota changes, showing reduced diversity and alterations in bacterial types. Microbiota hypothesis: It is postulated that lean individuals have more efficient microbiota in extracting energy from the diet, while obese individuals have microbiota that promote adiposity.Impact on the fetus: Maternal dysbiosis can affect the fetal intestinal microbiome in utero, altering its development and potentially leading to metabolic problems and cardiometabolic diseases in adulthood.

Clinical considerations: Maternal-infant health: To improve maternal health and the well-being of the baby, it is recommended that pregnant women maintain a balanced diet and a healthy BMI. Future research: Although bacterial DNA has been identified in obese women, the active presence of commensal bacteria has not been demonstrated. More research is needed to understand how specific microbial changes affect pregnancy and develop treatments to correct these changes.

- Fat Deposition and Metabolic Changes,[8]

Fat deposition: Subcutaneous vs. Visceral fat: In overfeeding conditions, fat accumulates first in subcutaneous adipose tissue. When this storage is exceeded, fat accumulates in visceral and hepatic adipose tissue. Metabolically healthy vs. Unhealthy fat: Metabolically healthy obese individuals have more subcutaneous fat and less visceral and hepatic fat. Conversely, metabolically unhealthy lean individuals may have excess visceral and hepatic fat.

- Inflammation and Insulin Resistance:[14]

Inflammatory cytokines: Excess visceral and hepatic fat is associated with increased secretion of inflammatory cytokines, chronic low-grade inflammation, and insulin resistance. Effect on obese pregnant women: Women who are obese before pregnancy may have greater amounts of pre-existing visceral and hepatic fat. Excessive weight gain during pregnancy can exacerbate these deposits and worsen gestational diabetes.

Clinical implications: Weight and metabolism control: It is crucial for obese women to control weight gain during pregnancy to avoid exacerbating metabolic problems. Gestational diabetes management: Visceral and hepatic fat accumulation can complicate the management of gestational diabetes, requiring more intensive strategies to control glucose and inflammation. Obesity during pregnancy not only affects the immediate health of the mother and newborn, but changes in intestinal microbiota and excess visceral and hepatic fat are two key mechanisms contributing to these risks. Maintaining a healthy BMI, a balanced diet, and adequate weight management during pregnancy are essential to minimize these risks and promote maternal-infant health. Ongoing research is essential to better understand these mechanisms and develop effective interventions.

Pathophysiology of adverse outcomes. metabolic complications responsible for damage

Obesity is a significant factor in the pathophysiology of various metabolic complications during pregnancy. The expansion of adipose tissue and associated inflammatory alterations have a profound impact on maternal and fetal health. Here is a summary of the pathophysiology behind these issues and how they contribute to adverse outcomes:

- Biology of Adipose Tissue:[14]

Adipose Tissue Expansion:

Adipose Tissue in Development: In the fetus, adipose tissue begins to develop between 14 and 16 weeks of gestation, with more advanced development at 28 weeks. In adulthood, obesity can result in the expansion of both adipocyte size (fat cells) and number in childhood.

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Types of Adipose Tissue: White Adipose Tissue (WAT): Mainly stores lipids and is associated with metabolic diseases.Brown Adipose Tissue: Its primary function is thermogenesis, although its presence in humans is limited compared to WAT.

Inflammation and Metabolism:

Visceral vs. Subcutaneous Adipose Tissue: Visceral adipose tissue (located around internal organs) is more closely associated with metabolic syndrome compared to subcutaneous adipose tissue. Visceral adipose tissue significantly contributes to chronic inflammation and insulin resistance due to its direct venous drainage to the liver.

- Adipose Tissue as an Endocrine Organ:[14]

Adipokine Production:

Inflammatory adipokines: Adipocytes produce various adipokines that affect metabolism and inflammation. For example:TNF-α: Stimulates lipolysis and increases insulin resistance by interfering with insulin receptor substrate (IRS1).Leptin: Regulates appetite and fatty acid oxidation, and also induces the secretion of IL-1R.

Anti-inflammatory adipokines: Although adipose tissue also produces adiponectin and IL-10, in obesity, the production of these anti-inflammatory molecules may be outweighed by the pro-inflammatory ones.

Related Enzymes:

11β-Hydroxysteroid dehydrogenase Type 1: Increases in obese individuals and modulates the local availability of corticosteroids, affecting inflammation within adipose tissue.

- Interactions in the Placenta of Obese Pregnant Women:[15,16]

Immune Cells and Inflammation:

Change in cellular composition: Maternal obesity increases the accumulation of macrophages in the placenta, especially pro-inflammatory M1 types, contributing to an exacerbated inflammatory state.

Pro-inflammatory cytokines: The placenta can release pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF, contributing to systemic inflammation and placental dysfunction.

-Chronic Inflammation (Metainflammation):[15]

Meta inflammation: Obesity is associated with chronic low-grade inflammation, driven by excess lipids and adipocyte hypertrophy. This persistent inflammation affects placental function and is implicated in insulin resistance and other metabolic problems.

- Impact on Insulin Resistance and Metabolism:[3,15]

Insulin Resistance:

Contributing factors: Insulin resistance in obese women is exacerbated by factors such as human placental lactogen, placental growth hormone, placental microRNAs, and pro-inflammatory cytokines.

Postpartum recovery: While insulin resistance may improve quickly after delivery, the placenta plays a crucial role in maintaining this resistance during pregnancy. Obesity during pregnancy is intrinsically linked to a series of metabolic complications due to the expansion of adipose tissue, the production of inflammatory adipokines, and the impact on the placenta and metabolism. Chronic inflammation, insulin resistance, and altered placental function are key factors contributing to adverse outcomes in obese pregnant women. Maintaining a healthy BMI and managing weight gain during pregnancy are crucial for mitigating these risks and improving maternal-infant health outcomes (Table 1).

Table 1 Pathophysiology of major events causing adverse outcomes associated with obesity during pregnancy

Event	Pathophysiology
Gestational diabetes (GDM)	Hormonal changes and increased insulin resistance during pregnancy contribute to impaired glucose metabolism and increased fetal exposure to high glucose.
Uncontrolled type 2 diabetes with vasculopathy and placental insufficiency	Unmanaged blood sugar levels lead to vascular damage, placental dysfunction, and poor nutrient/oxygen transfer to the fetus.
Maternal intestinal microbial dysbiosis	Alteration in gut microbiota composition, potentially impacting metabolic and immune responses during pregnancy.
Obesity and excessive gestational weight gain	Excessive weight gain results in increased insulin resistance, inflammation, and complications like macrosomia and preeclampsia.
Hyperinsulinemia	Chronic high insulin levels, often resulting from insulin resistance, exacerbate metabolic disorders and increase the risk of gestational diabetes.
Beta-cell function deterioration	Progressive decline in pancreatic beta-cell function with advancing gestational age leads to worsening glucose control.
Increased insulin resistance and oxidative stress	Pre-pregnancy insulin resistance leads to inflammation, oxidative stress, and higher risk for gestational diabetes and placental dysfunction.
Fetal macrosomia	Maternal hyperglycemia leads to increased fetal insulin secretion, resulting in excessive fetal growth (macrosomia).
Nutrient and micronutrient deficiency Small-for-gestational-age	Caloric intake limitations can lead to insufficient supply of essential nutrients for fetal growth.
Maternal hypertriglyceridemia	Elevated triglyceride levels contribute to increased cardiovascular risk and metabolic disorders during pregnancy.
Preeclampsia	Excess body fat increases systemic inflammation and oxidative stress, causing endothelial dysfunction and the development of hypertension and kidney damage.
Subcutaneous and visceral fat, inflammation, and insulin resistance	Accumulation of fat leads to chronic inflammation, insulin resistance, and metabolic disturbances, affecting both mother and fetus.

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Table 1 Continued...

Event	Pathophysiology
Adipocyte expansion, inflammation, and cardiovascular diseases	Large increase in fat cells contributes to systemic inflammation, insulin resistance, and an increased risk of cardiovascular diseases.
Meta-inflammation	Chronic low-grade inflammation involving triglycerides and insulin resistance contributes to metabolic complications and placental dysfunction.
Altered vascular and fibrinolytic function	Vascular dysfunction, including impaired blood flow and coagulation, heightens the risk of thromboembolic events and placental insufficiency.
Prothrombotic state	Obesity contributes to a prothrombotic environment, increasing the risk of clot formation and vascular complications during pregnancy.
Preterm birth	Chronic inflammation, ascending bacterial infection and hormonal alterations associated with maternal obesity may induce spontaneous preterm labor.
Congenital defects	The risk of congenital defects increases due to metabolic alterations and inadequate glucose levels during embryonic development.
Fetal death	Placental insufficiency, ascending bacterial infection and fetal hypoxia related to maternal obesity contribute to the risk of fetal. death
Increased macrophages and altered immune cells in placenta	Excessive inflammation and immune cell activation in the placenta disrupt its function, affecting fetal development and increasing adverse outcomes.
Placental structural and functional changes	Histological changes in the placenta impair its function, leading to inadequate nutrient and oxygen transfer to the fetus.
Microbiota imbalance and inflammation	Decreased abundance of beneficial bacteria (e.g., Lactobacillus) with increased vaginal infections leads to systemic and placental inflammation.
Chorioamnionitis and group B Streptococcus infection	Inflammation and infection in the amniotic membranes or fetus can result from ascending bacterial infections, increasing preterm labor and fetal risks.
Ascending bacterial infections	Infections ascending from the vagina can lead to chorioamnionitis, funisitis, and increased risk of preterm birth and fetal infection.

Obesity and placental dysfunction

Maternal obesity is a significant risk factor for placental dysfunction during pregnancy, which can have serious consequences for both the mother and the fetus. Associated complications include preeclampsia (PE), gestational diabetes mellitus (GDM), preterm birth (PTB), and small for gestational age (SGA) newborns. The underlying mechanisms of placental dysfunction in obese women include chronic inflammation, oxidative stress, and dysregulation of metabolic pathways, all of which contribute to an adverse environment for fetal development.[16]

-Mechanisms of Placental Dysfunction:[16]

Chronic inflammation and oxidative stress: Obesity is associated with a chronic inflammatory state and oxidative stress, which can alter placental function. These factors may damage placental cells, affecting their ability to exchange nutrients and oxygen between the mother and fetus.

Epigenetic changes: It has been suggested that obesity may induce epigenetic changes in the placenta, such as DNA methylation, which alters gene expression and, consequently, placental function. These changes may contribute to fetal growth restriction and other adverse outcomes.

Alterations in metabolic mediators: Obesity can affect the production and function of key mediators such as leptin and apelin, which are important for placental vascular tone and angiogenesis. These alterations may impair oxygen and nutrient exchange, jeopardizing fetal development.

- Placental Lesions Associated with Obesity:[17–24]

Common placental lesions in obese women include: Edema and delayed villous maturation: These lesions are frequent in gestational diabetes and cases of maternal hypoperfusion. Avascular terminal villi: Primarily associated with gestational diabetes. Massive fibrinoid deposition: This can cause placental insufficiency and is associated with SGA newborns and stillbirth in the third trimester. Fetal thrombotic vasculopathy: Thrombi in the umbilical arteries may affect fetal blood flow and are associated with gestational diabetes.

- Impact on Vascular and Fibrinolytic Function:[14]

In non-pregnant obese women, obesity profoundly alters vascular and fibrinolytic function. Clinically, this is reflected in an increased risk of hypertension, atherosclerosis, ischemic heart disease, and the likelihood of heart attack or stroke.

Vascular: Increased vascular stiffness, reduced vessel dilation, and altered response to vasodilators are observed. Perivascular adipose tissue contributes to these changes by releasing inflammatory mediators.

Fibrinolytic: Obesity is associated with a prothrombotic state, characterized by elevated levels of coagulation factors and alterations in platelet function and fibrinolysis.

During pregnancy, these vascular and fibrinolytic dysfunctions are exacerbated, contributing to the observed placental lesions and an increased risk of complications.[14]

-Prevention and management:[14] Preventing and managing maternal obesity is crucial to reducing the risk of placental dysfunction. This includes:

Lifestyle modifications: Interventions promoting a healthy diet and regular exercise can help manage weight and improve metabolic health during pregnancy.

Early detection and management: Early detection of associated conditions such as gestational diabetes and preeclampsia, and appropriate management, can reduce risks for both mother and fetus.

- Research and Future Directions:[14] Further research is needed to better understand the exact mechanisms through which obesity affects

placental function and to develop effective interventions. Research should focus on how lifestyle modifications and other interventions can mitigate these risks and improve pregnancy outcomes in obese women. Maternal obesity is clearly linked to a range of serious complications during pregnancy, many of which are due to placental dysfunction. Although the effects of physical activity on the placenta have been documented, the role of reducing sedentary behavior in placental development and function has not yet been studied.[25] Identifying specific mechanisms and implementing preventive and management strategies are essential to improving maternal and fetal health in this context.

Obesity and diabetes

Diabetes Mellitus (DM), both type 2 and Gestational Diabetes Mellitus (GDM), are metabolic disorders closely associated with obesity and present significant complications during pregnancy.[8]

- Type 2 Diabetes Mellitus (T2DM) During Pregnancy:[8] The prevalence of T2DM in pregnancy has increased markedly in recent decades, partly due to the rising number of obesity cases. T2DM is characterized by progressive deterioration of pancreatic beta-cell function, resulting in hyperglycemia and requiring strict medical management. This condition is associated with a higher risk of serious complications for both mother and fetus, including:

Congenital malformations: The rate of congenital malformations is significantly higher in women with T2DM compared to the general population. In one study in England, the rate of congenital malformations in women with T2DM was 40.5 per 1,000 births, nearly double the rate observed in the general population.[26]

Additional complications: Women with T2DM have an increased risk of gestational hypertension, preeclampsia, cesarean delivery, and giving birth to large-for-gestational-age (LGA) newborns. Complications can increase by 50% to 100% compared to women without T2DM.[8]

Pregnancy outcomes in women with obesity and diabetes are affected by several factors, including pre-pregnancy BMI, pre-pregnancy and third-trimester HBA1c levels, and gestational weight gain (GWG).[8,27]

- Gestational Diabetes Mellitus (GDM): GDM is a type of diabetes that develops during pregnancy and affects approximately 14% of all pregnancies. It is related to increased insulin resistance and/or reduced insulin secretion.[28]

The prevalence of GDM increases with pregestational BMI. Studies show that overweight, obese, and severely obese women are more likely to develop GDM compared to women with normal weight. Meta-analyses found that the likelihood of developing GDM is significantly higher in overweight and obese women.[11,29] GDM is more common among Hispanic, non-Hispanic Black, Native American, or Asian or Pacific Islander women than non-Hispanic White women [3]. Additionally, during pregnancy, increased secretion of placental hormones such as human placental lactogen (HPL), cortisol, and growth hormone further increases maternal insulin resistance.[8]

Risks associated with GDM include:[3]

Gestational hypertension and PE: Women with GDM have a higher risk of developing gestational hypertension and PE.

Cesarean delivery: The likelihood of cesarean delivery also increases.

Childhood obesity and T2DM in offspring: The offspring of women with GDM are at an increased risk of developing childhood obesity and T2DM in adulthood.

Adverse outcomes: Women with GDM and excessive gestational weight gain are at higher risk for fetal macrosomia, PTB, and excessive fetal growth.

Impact of Gestational Weight Gain (GWG) : Excessive GWG during pregnancy is closely linked to GDM. Women who gain more weight than recommended during pregnancy are at a higher risk of developing GDM.[8,11]

Underlying mechanisms and risk factors: The underlying mechanisms that explain the increased risk of GDM in obese women include:[3,8,30,31]

Insulin resistance: Obesity increases insulin resistance and decreases pancreatic beta-cell response, leading to higher insulin production and increased resistance during pregnancy.

Systemic inflammation: Obesity is associated with chronic inflammation and elevated levels of inflammatory markers, contributing to metabolic dysfunction.

Visceral adiposity: Excess visceral fat is associated with a higher risk of GDM compared to subcutaneous and general adiposity, due to increased very-low-density lipoproteins (VLDL), which lead to beta-cell insufficiency.

Progression to T2DM: Approximately 50% of women with GDM progress to T2DM within five years after the index pregnancy, and it is estimated that up to 70% of these women will develop diabetes between 22 and 28 years after pregnancy.

Offspring risks: The children of women with GDM also have a higher future risk of childhood obesity and early-onset T2DM.

Prevention and management strategies: To mitigate the risks associated with diabetes during pregnancy, it is recommended:[3,8]

Weight control: Maintaining a healthy weight before and during pregnancy can help reduce the risk of GDM and its complications.

Strict monitoring and management: Regular monitoring of blood glucose levels and proper diabetes management during pregnancy are essential to prevent complications.

Lifestyle modifications: Adopting a healthy diet and regular physical activity can improve glucose control and reduce the risk of developing GDM. The relationship between obesity and diabetes during pregnancy is complex and multifaceted. Obesity increases the risk of T2DM and GDM, and these conditions pose significant risks for both mother and fetus. Proper weight management, glucose monitoring, and early interventions are crucial to improving pregnancy outcomes in women with diabetes.

Obesity, macrosomia, and large for gestational age (LGA) birth weight

A large for gestational age newborn is defined as one whose birth weight is above the 90th percentile for gestational age and sex. Macrosomia, on the other hand, refers to a birth weight over 4000 g. Gestational diabetes mellitus (GDM) occurring in late pregnancy can induce short-term fetal changes in obese women. If maternal hyperglycemia, hyperinsulinemia, or dyslipidemia exceed the placenta's capacity to adapt, excessive fetal growth can occur.[3]

Nonetheless, a dose-dependent relationship between maternal obesity and an increased rate of LGA newborns has been documented, independent of the presence of GDM or excessive gestational weight gain (GWG). A U.S. study including 820,000 deliveries in obese women without GDM or excessive GWG showed an increase in LGA newborn rates, reaching 8.6% in class I obesity, 11.5% in class II, and 13.9% in class III.[32] In a meta-analysis, odds ratios (OR) of 2.28 (2.15-2.41) and 2.36 (2.17-2.56) were reported for the association between maternal obesity and macrosomia and LGA, respectively.[33] Furthermore, GDM is still associated with a higher risk of LGA even in non-obese women without excessive GWG.[32] Among obese women, a dose-response relationship between GDM and LGA has been observed,[11] with higher LGA rates in women with type 2 diabetes (T2D) compared to those without diabetes.[27] In women with T2D, LGA is linearly associated with body mass index (BMI), GWG, and glycosylated hemoglobin (HbA1c) in the first and third trimesters.[8]

- Hyperinsulinemia and Fetal Weight: Insulin stimulates fetal glucose aerobic metabolism, increasing oxygen demand. If oxygen supply is insufficient due to the high affinity of HbA1c for oxygen, thickening of the placental basement membrane, and reduced uteroplacental or fetoplacental blood flow, fetal hypoxemia may occur. Fetal hypoxia triggers hypoxia-sensitive transcription factors, which in turn stimulate angiogenesis. In women with type 1 diabetes (T1D), upregulation of placental glycosylation and acylation pathways, as well as increased placental weight, has been observed.[16]

- Hypertriglyceridemia and Fetal Weight: In the absence of diabetes, LGA newborns are primarily mediated by maternal hypertriglyceridemia [34]. However, in obese women, hyperinsulinemia also increases placental triglyceride levels, contributing to fetal adiposity [34]. In cases of GDM and T2D, LGA is secondary to both hyperglycemia and hypertriglyceridemia.[8,35]

Obesity and small for gestational age (SGA) newborns

SGA newborns have a birth weight below the 10th percentile for gestational age and sex. Poorly controlled T2D can be associated with maternal vasculopathy, affecting placentation and leading to fetal growth restriction with SGA size.[36] GDM can also affect placental structure, altering its function and leading to placental insufficiency and SGA [37]. Tighter glycemic control in T2D and GDM has been associated with a higher risk of SGA.[8] In a retrospective cohort study of 974 women with pregnancies complicated by SGA, obese women had a higher likelihood of severe SGA and uterine artery Doppler abnormalities. Hypertensive disorders and T2D were significantly more common in obese women, and the risk of severe SGA was significantly higher in these women.[37] Doppler abnormalities increased with worsening obesity: 31.4%, 34.4%, and 46.2% for non-obese, class I obesity, and class II or III obesity, respectively ($p < 0.01$). After adjusting for potential confounders, women with class I obesity had higher odds of severe SGA (aOR = 1.4 (1.0-2.1)). Additionally, the likelihood of abnormal Doppler was higher among women with class II/III obesity compared to non-obese women after adjusting for confounders (aOR = 1.7 (1.2-2.6)).[38]

Restricted intrauterine growth in SGA fetuses in obese women is intriguing since it would be expected that obese pregnant women, who typically have excess circulating nutrients, would give birth to macrosomic newborns. However, some studies have observed a small percentage of SGA newborns in this population, suggesting that not all available nutrients are optimally used for fetal growth.[16] Theories for this phenomenon include the possibility that obese women, despite a high-calorie diet, may lack key nutrients or micronutrients for fetal development, or that consumed nutrients are primarily used to meet maternal metabolic demands rather than support fetal growth.[16]

Additionally, maternal obesity may impact both the placenta and fetus in various ways.[39] While it has been shown that placental nutrient transport capacity increases in obese women, favoring excessive fetal growth (and an increase in LGA newborns), abnormalities such as unbranched placental angiogenesis have also been reported. This condition can reduce blood flow to the placenta, especially in cases of hypertensive complications such as preeclampsia.[16] In obese women, altered insulin signaling has also been suggested, affecting the stimulation of placental nutrient transport systems, thereby reducing nutrient transfer to the fetus and causing growth restriction. In cases of reduced fetal growth, trophoblast invasion is often deficient, limiting blood flow to the placenta. Although no studies have thoroughly analyzed this process in obese women, it is hypothesized that altered trophoblastic invasion could be responsible for growth restriction in this group. Structural alterations in the placental blood vessels of obese women have also been described, which could contribute to tissue ischemia and reduced fetal growth.[40] It is concluded that while maternal obesity is generally associated with excessive fetal growth, in some cases, it may lead to fetal growth restriction due to various placental and metabolic alterations.

Obesity and hypertensive disorders of pregnancy

Gestational hypertension (GH) and preeclampsia (PE) increase the risk of maternal and fetal complications, including preterm birth, SGA, and cesarean section. These risks increase in a dose-response relationship with obesity.[3,11] Insulin resistance appears to play a key role in the relationship between obesity and PE. Studies have shown that obesity is a fundamental risk factor for the development of GH and PE. The link between maternal obesity and complications like gestational hypertension and preeclampsia has been the subject of multiple studies. A modeling study conducted in Poland particularly highlighted that obesity is one of the main risk factors for developing GH and PE.[41] A key factor connecting obesity to these complications is insulin resistance, a common metabolic state in obese individuals that contributes to the development of GH and PE. In a study using the hyperinsulinemic-euglycemic clamp technique, significant increases in insulin resistance, decreased sensitivity to insulin, and reduced beta-cell function were observed in women with GH compared to those with normal blood pressure.[42] Other studies have confirmed this correlation between insulin resistance and GH.[43] Excessive gestational weight gain (GWG) in obese women can worsen insulin resistance, exacerbating the risk of developing GH and PE [44]. Indeed, a dose-response effect has been observed, where greater weight gain during pregnancy increases the risk of GH and PE.[11] Additionally, conditions such as GDM and T2D are also associated with a higher risk of these complications, independent of obesity.[8,39] In summary, maternal obesity, accompanied by insulin resistance and excessive gestational weight gain, plays an important role in the development of GH and PE.

- Pathogenic Mechanisms of PE in Obese Women:[3,8]

The pathogenesis of PE is not completely understood, but chronic inflammation, increased insulin resistance, hyperinsulinemia, and elevated triglyceride levels are thought to play a crucial role in its development.

The metabolic and vascular phenotype associated with obesity during pregnancy may contribute to the higher risk of cardiovascular diseases in the future for women who experience hypertension during pregnancy.

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- Prevention of Preeclampsia: Aspirin administered between weeks 12 and 16 of gestation has been shown to reduce the risk of PE in high-risk obese women. Other risk factors (RFs) include multiple pregnancies, nulliparity or age over 35 years, family history of preeclampsia, history of SGA, and IVF. With RFs, aspirin should be initiated. The recommended dose for obese patients is 100 to 150 mg/day.[27,45]

The most frequent histopathological findings in the placentas of hypertensive pregnant women are:[23] Villous infarction, decidual vessel arteriopathy,retroplacental hematoma,,intervillous hemorrhage, fetal vessel hemorrhagic endovasculitis, fetal thrombotic vasculopathy, intervillous thrombosis, accelerated maturation. These placental changes are representative of vascular dysfunction that affects both nutrient supply to the fetus and maternal health.

Obesity and infection: impact on maternal-perinatal health

A healthy vaginal microbiome is characterized by the dominance of *Lactobacillus*.[46] Obesity has been found to be associated with a lower likelihood of *Lactobacillus* dominance and greater bacterial diversity.[47] This alteration in the microbiota may predispose obese women to infections and complications such as bacterial vaginosis (BV), aerobic vaginitis (AV), and preterm birth (PTB) due to intraamniotic bacterial infection (IBI).[2,47]

- Vaginal Microbiota in Obese Women of Reproductive Age:

Studies in non-pregnant women: A U.S. study of more than 700 reproductive-aged women found that women who were overweight or obese had greater bacterial diversity and less *Lactobacillus* dominance compared to healthy-weight women.[46] These findings have also been observed in Korean cohorts, where *L. crispatus* was inversely associated with BMI, and the dominant type *L. iners* was positively associated with obesity.[48] *Prevotella* and increased bacterial diversity were more prevalent in obese women.[48]

BV prevalence: A cross-sectional study in the U.S. with 6,000 participants found that overweight and obese women had a higher prevalence of BV compared to women with normal weight.[47]

- Vaginal Microbiota in Obese Pregnant Women:

Phenotypic differences: The vaginal microbiome in obese pregnant women shows different characteristics compared to normal-weight women. A prospective study found that a higher pre-pregnancy BMI was associated with a higher incidence of vaginal dysbiosis and lower levels of *Lactobacillus* during pregnancy, as well as a higher incidence of BV.[49,50]

Associations with adverse outcomes: Dominance of *Lactobacillus* in the vaginal microbiota is associated with a lower risk of spontaneous PTB, while a more diverse microbiota is associated with a higher risk. High microbial diversity during pregnancy may influence the risk of cervical shortening, premature rupture of membranes (PROM), and PTB.[50–52] BV, with high diversity, dominance of Gardnerella vaginalis, and other associated bacteria, can increase the risk of spontaneous PTB.[53] Recurrent BV is believed to increase the risk of spontaneous PTB.[54]

Pregnant women with type III obesity at the start of pregnancy, compared to normal-weight pregnant women, had a higher frequency of vaginal taxon associations, including *Atopobium*, *Gardnerella*, *Prevotella*, and *Sneathia*, all bacteria associated with BV.[50,54]

- Mechanisms in Non-Pregnant Women:

Relationship with estrogens: A healthy dominance of Lactobacillus is correlated with higher estrogen levels, which stimulate glycogen deposition in the vaginal epithelium, a carbon source for *Lactobacillus*. In obese women, the relationship between obesity and estrogen levels may differ. Post-menopause, the aromatization of androgens in adipose tissue can elevate estrogen levels, while in premenopausal women, estrogen levels may be lower in obese women, possibly affecting the vaginal microbiota.[48,55]

Gut and vaginal microbiota: Adverse gut microbiota in obese women can affect estrogen metabolism, which may influence the vaginal microbiota.[56]

- Mechanisms in Pregnant Women:

Chronic inflammation: Obesity is associated with a chronic low-level inflammatory state, which may alter the immune system and affect the vaginal microbiota. Obesity can decrease *Lactobacillus* dominance and increase microbial diversity, contributing to a higher risk of infections and adverse outcomes during pregnancy and childbirth.[57,58]

Impact on immune function: Obesity can alter immune function, reducing the immune system's effectiveness and predisposing women to greater vaginal bacterial diversity and a higher risk of infections and PTB due to IBI.[50,59,60]

Previous studies found that maternal obesity was associated with positive inflammatory regulation due to increased production of adipokines (IL-6, C-reactive protein, and leptin). Obese mothers with greater visceral fat mass were more likely to promote systemic inflammation,[61] insulin resistance, and lipotoxicity, which can negatively affect placental sufficiency.[62] An elevated inflammatory state makes obese women more prone to IBA-induced chorioamnionitis, increasing inflammation, the risk of PTB, and perinatal morbidity/mortality.[50,63,64]

Adverse outcomes associated with BV may be related to bacteria that induce a stronger inflammatory response. Additionally, under these conditions, there is dysregulation of innate immune mechanisms in the lower genital tract in women. This includes reduced toll-like receptor 4 (TLR-4) stimulation in Group B *Streptococcus* (GBS) infections and increased cervicovaginal neutrophil activation, along with increased complement and pro-inflammatory cytokines.[50]

The intensity of these inflammatory responses may be exacerbated in women with risk factors such as diabetes, obesity, stress, anxiety, and depression, increasing susceptibility to infections during pregnancy. These factors contribute to alterations in the vaginal environment and the higher prevalence of infections that can have adverse effects on maternal-fetal health.[50]

- Infectious Adverse Outcomes in Obese Pregnant Women Risks associated with infections:

Obese women have a higher risk of adverse maternal and perinatal outcomes related to infections, such as second-trimester miscarriage, preterm birth, infections during childbirth and postpartum, and infectious perinatal mortality (fetal/neonatal).[2,23]

Post-surgical infections: Obesity increases the risk of surgical site infections, with a twofold increase in risk for women undergoing cesarean sections or other gynecological surgeries.[3,65–67]

Rectovaginal colonization by Group B *Streptococcus* (GBS):

Maternal obesity is a significant risk factor for GBS colonization in term pregnancies. Obese pregnant women have a higher prevalence

of GBS colonization compared to non-obese women.[68] These findings highlight the importance of addressing obesity as a significant risk factor for infectious complications and other issues during pregnancy. Proper management of obesity and monitoring the vaginal microbiota can be key strategies to improve maternal-perinatal outcomes (Table 2).

Table 2 Adverse outcomes associated with obesity in pregnancy: documented increased Risk (Odds Ratios - OR)

Adverse Outcome	Description	Odds Ratios (OR)
Gestational diabetes (GDM)	Higher risk of developing glucose intolerance due to increased insulin resistance during pregnancy.	1.5 - 3.6
Large-for-gestational-age (LGA) newborn	Greater likelihood of macrosomia (excessive fetal growth), increasing risk of delivery complications.	2.0 - 2.9
Small-for-gestational-age (SGA) newborn	Higher risk of fetal growth restriction, often due to placental dysfunction or maternal metabolic issues.	1.2 - 1.4
Preeclampsia	Increased risk of hypertension and organ damage, often linked to inflammation and placental dysfunction.	2.5 - 4.5
Hypertensive disorders	Higher incidence of gestational hypertension and chronic hypertension in obese mothers.	2.0 - 3.0
Thromboembolism	Elevated risk of blood clots (deep vein thrombosis or pulmonary embolism) due to hypercoagulability.	2.0 - 4.0
Preterm birth (spontaneous or indicated)	Increased risk of preterm labor, often related to infections, preeclampsia, or placental insufficiency.	1.2 - 1.5
Placental abruption	Elevated risk of placental detachment before birth, which can cause fetal distress and preterm delivery.	1.6 - 2.5
Stillbirth	Increased risk of fetal death, potentially related to placental insufficiency, hypertension, or diabetes.	1.5 - 2.8
Cesarean delivery (C-section)	Greater likelihood of requiring surgical intervention due to labor complications, macrosomia, or dystocia.	1.6 - 2.0
Shoulder dystocia	Increased likelihood of difficult deliveries due to large-for-gestational-age (LGA) newborns.	2.0 - 3.0
Postpartum hemorrhage	Higher risk of excessive bleeding after delivery, often due to uterine atony or prolonged labor.	1.5 - 2.0
Neonatal intensive care unit (NICU) admission	Greater risk of neonatal complications requiring intensive care, linked to preterm birth or birth injuries.	1.3 - 1.6
Congenital malformations	Higher risk of fetal congenital anomalies, particularly neural tube defects and cardiac malformations.	1.2 - 1.8
Neonatal respiratory distress	Increased risk of breathing difficulties in newborns, often linked to preterm birth or delivery complications.	1.3 - 1.7

Obesity and adverse neonatal outcomes

A prospective cohort study highlights that maternal obesity is an independent risk factor (RF) for several adverse outcomes in newborns. Through the analysis of 6,458 women with full-term singleton deliveries (≥37 weeks), of which 51% were obese and had neither hypertension nor diabetes, significant associations were found between maternal obesity and increased neonatal morbidity. After adjusting for race, it was observed that newborns of obese mothers had a significantly higher risk compared to those of non-obese mothers in:

- Composite neonatal morbidity: 9.2% vs. 7.2%, adjusted OR 1.39 (1.15-1.67).
- Neurological morbidity: 0.7% vs. 0.3%, adjusted OR 2.84 (1.22-6.65).
- Hypoxic-ischemic encephalopathy: 0.5% vs. 0.2%, adjusted OR 2.80 (1.02-7.68).
- Treatment with hypothermia: 0.6% vs. 0.2%, adjusted OR 2.92 (1.17-7.30).
- Suspected sepsis: 7.6% vs. 5.8%, adjusted OR 1.45 (1.18-1.79).

These findings emphasize the importance of maternal obesity as a risk factor for neonatal complications, even in the absence of other pre-existing conditions such as hypertension and diabetes. Therefore, addressing maternal obesity is crucial as part of strategies to prevent neonatal morbidity.[69]

Obesity and mood disorders, depression, and anxiety

Maternal obesity has a significant relationship with various mood disorders, including depression and anxiety, as well as the risk of postpartum depression (PP).[3,70,71] Two meta-analyses have documented significant associations between maternal obesity and depressive and anxiety symptoms both before and after childbirth. Reported ORs range between 1.3 and 1.4, indicating a moderate increase in the risk of these disorders in obese women.

Possible underlying mechanisms linking obesity to these disorders include:

I. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, affecting hormonal regulation of stress.

II. Immunological dysregulation, related to the chronic inflammation characteristic of obesity.

III. Body image dissatisfaction, contributing to emotional distress and depressive symptoms.

IV. Experiences of stigmatization, which are more common among obese women and increase the risk of depression and anxiety.

V. Maladaptive eating behaviors, such as binge eating, which may worsen both obesity and emotional problems.

Additionally, the stigma associated with obesity is a significant source of stress. Women who experience repeated weight-related discrimination tend to report more depressive symptoms and unhealthy eating behaviors. There is also a possibility that deteriorating mental health contributes to weight gain, suggesting a bidirectional causal pathway.[3]

Obesity and premature birth

Pre-pregnancy maternal obesity has been identified as a significant RF for preterm birth (PTB) in all its phenotypes, including:

I. Spontaneous PTB (with or without premature rupture of membranes [PROM]).

II. Medically indicated PTB.

In a prospective cohort study involving 43,056 women in China,[72] it was found that the risk of extremely preterm birth (less than 28 weeks), very preterm birth (28 to 31 weeks), and moderately preterm birth (32 to 36 weeks) increased with BMI. Obese women had the highest risk for extremely preterm birth, with an OR of 3.43 (1.07-10.97).[72] Other significant findings include:

I. Maternal obesity was associated with an increased risk of spontaneous preterm labor OR 1.98 (1.13-3.47), PROM OR 2.04 (1.08-3.86), and medically indicated PTB OR 1.39 (1.15-1.67).

II. GDM and PE mediated part of the effect of obesity on PTB, with GDM explaining 13.4% and PE 36.7% of the effect.

III. GDM mediated 32.8% of the spontaneous PTB risk, and PE mediated 64.31% of the medically indicated PTB risk.

Furthermore, obesity is an independent RF for second-trimester miscarriage and spontaneous PTB due to ascending bacterial infections (ABI) from the lower genital tract (LGT). A retrospective cross-sectional study involving 6,150 patients from the Hospital Clínico San Borja Arriarán (HCSBA) found a significant association between obesity and these complications. The OR for second-trimester miscarriage was 3.45 (95% CI, 1.63-7.31; $p < 0.01$) and for spontaneous PTB 2.42 (95% CI, 1.51-3.87; $p < 0.01$)[2] Maternal obesity is linked not only to an increased risk of mood disorders, such as depression and anxiety, but also to a higher incidence of premature birth and its complications, underscoring the importance of addressing these risks in prenatal care.

Obesity and congenital anomalies

Maternal obesity is associated with an increased risk of congenital anomalies in newborns, particularly cardiac defects and neural tube defects. The risk of these anomalies increases proportionally with BMI, suggesting a dose-response relationship. Moreover, the prenatal identification of congenital anomalies in obese women may be more challenging due to the attenuation of ultrasound signals by excess adipose tissue.[3]

- Maternal BMI and Congenital Anomalies: A retrospective cohort study in the United States, which included more than 3 million mother-newborn pairs, found an increase in the incidence of neural tube defects, omphalocele, and cleft lip/palate in neonates of mothers with elevated BMI. As maternal BMI increased before pregnancy, so did the risk of congenital anomalies. It is recommended that women optimize their weight before conception to reduce the risk of congenital anomalies in the fetus.[73] Another cohort study in northern England, which included over 41,000 pregnancies, also revealed that obese women had a higher risk of congenital anomalies compared to those of normal weight. A total of 682 pregnancies had a structural congenital anomaly, with an overall prevalence of 166 per 10,000 births. The most common anomalies included:[74]

•Ventricular septal defects (adjusted OR = 1.56). • Cleft lip (adjusted OR = 3.71). • Ocular anomalies (adjusted OR = 11.36). Maternal obesity during pregnancy is associated with an increased risk of fetal malformations. In an ideal healthcare setting, it is crucial for women planning to conceive to receive counseling about the maternal-fetal risks associated with elevated BMI before pregnancy. This counseling should be multidisciplinary, involving obstetricians, bariatric surgeons, endocrinologists, nutritionists, genetic counselors, and dietitians. Additionally, it is important to inform patients about the limitations in prenatal diagnostic procedures, such as genetic ultrasound and screening, in obese pregnant women. These limitations can affect the early detection of malformations, both in patients with and without diabetes, highlighting the need for a comprehensive approach to minimize risks during pregnancy.[75]

- Obesity and Congenital Heart Disease: Congenital heart disease is the most common structural anomaly in newborns, and recent studies have shown that maternal obesity, along with metabolic disorders such as diabetes mellitus (DM), significantly increases the risk of these malformations. Population-based observations have long described associations between maternal cardio-metabolic disorders and the risk of coronary heart disease in offspring.[76] A meta-analysis of 14 studies concluded that elevated BMI before or at the beginning of pregnancy was associated with an increased risk of congenital heart defects. The dose-response relationship indicated that overweight, moderate obesity, and severe obesity increased the risk of cardiac malformations, with ORs of 1.08, 1.15, and 1.39, respectively.[77]

- Knowledge Gaps about the Origin of Heart Defects and Future Directions: Although it is known that maternal obesity and metabolic disorders, such as diabetes mellitus (DM), are associated with a higher risk of congenital heart disease, the exact mechanisms by which these factors influence fetal heart development remain largely unknown. This lack of clarity represents a weakness in current knowledge about the origin of these defects. From a public health perspective, it is recommended to promote obesity prevention in women planning to conceive, without waiting for a complete understanding of the mechanisms transmitting the risk of malformations. Both obesity and DM are potentially modifiable maternal risk factors to prevent coronary heart disease.[78] Moving forward, research should focus on understanding the causal factors and transmission pathways that alter fetal heart development, allowing for more effective prevention strategies for congenital heart disease. Additionally, in prenatal care, improving early detection of congenital heart disease through more accurate screening, particularly in women with obesity and DM, is essential. This will allow for better pregnancy management and appropriate newborn care in tertiary centers, thus optimizing perinatal outcomes.

- Obesity and Neural Tube Defects (NTDs). A meta-analysis of studies from 1980 to 2007 found that maternal obesity is significantly associated with an increased risk of neural tube defects.[79] The ORs for a pregnancy affected by NTDs were: • 1.22 in overweight women. • 1.70 in obese women. • 3.11 in women with severe obesity, compared

to those with normal weight. Recommendations: Prevention and preconception counseling: It is crucial for women of childbearing age to receive support to achieve a healthy weight before pregnancy to reduce the risk of congenital anomalies. Multidisciplinary approach: It is recommended that a team of specialists, including obstetricians, bariatric surgeons, endocrinologists, nutritionists, and genetic counselors, be involved in the prenatal care of obese women to improve the early detection and management of malformations. In summary, maternal obesity is strongly linked to an increased risk of congenital anomalies, emphasizing the importance of early interventions to optimize weight before pregnancy.

Obesity and fetal death

Obesity and its impact on fetal death (FD): Maternal obesity has been consistently associated with an increased risk of FD. A prospective cohort study in Japan, conducted between 2011 and 2014, found a higher incidence of FD in overweight and obese women compared to those with a normal BMI. The stillbirth rate was 0.33%, and the risk of FD was 1.55 times higher in overweight women and 2.60 times higher in obese women. The risk of early FD (before 28 weeks) was even higher in the obese group, with an adjusted OR of 4.33. These findings underscore the importance of maintaining a healthy BMI before pregnancy to minimize the risk of FD.[80] Various meta-analyses[45,81–83] have indicated that the risk of FD is between 1.3 and 2.1 times greater in obese women compared to those of normal weight. This increased risk is significant for antepartum FD, with an RR of 1.28, but not for intrapartum FD. This could be due to the rigorous medical care obese women receive during labor [81]. In high-income countries, it is estimated that around 8,000 stillbirths (≥22 weeks of gestation) annually are related to maternal overweight and obesity.[82]

- Obesity, Congenital Anomalies, and Fetal Death: Congenital anomalies contribute to approximately 5% of FDs. However, it is likely that other obesity-related mechanisms, such as inflammation, metabolic dysfunctions, and placental abnormalities, also play a significant role in the association between obesity and fetal death.[83]

- Ascending Bacterial Infection and Fetal Death: In a retrospective study of 6,150 patients in Chile, obese women (1,113) had a 4.46 times higher risk of perinatal mortality due to ascending bacterial infection (ABI) compared to women of normal weight. Placental abruption was the final cause of death during birth in 46.9% of cases, and in 93.3% of these, it occurred in pregnancies <27 weeks.[2] ABI was defined as an infectious condition during pregnancy, diagnosed by clinical criteria (obstetric conditions in which intraamniotic infection might occur); laboratory criteria (genital-urinary infection, bacterial vaginosis (BV), or amniotic infection by *S. agalactiae* and/or urinary tract infection present); and histological criteria (acute histological chorioamnionitis (CH), acute funisitis). Genital infections, such as BV and acute CH, are contributing factors.[2]

- Obesity and Fetal Death Due to Chorioamnionitis: A case-control study conducted by NICHD found that overweight and obese women were more likely to experience FD after 20 weeks of gestation compared to women of normal weight. Histological chorioamnionitis was significantly more common in women with FD (33.2%) than in those with live births (15.7%), suggesting an important role for intrauterine infections in FD associated with obesity. When models adjusted for maternal ferritin levels, C-reactive protein, or elevated leukocytes, the OR for FD in obese women changed minimally. However, the relationship between high BMI and CH indicated that the latter contributes to the increased risk of FD in obese women, although obesity remains a significant risk factor.[84]

- Placental Dysfunction and Fetal Death: Placental dysfunction is another cause of fetal death in obese pregnant women, both preterm and term. A study at the HCSBA Maternity Hospital, which included 56,130 births and 479 fetal deaths (a rate of 8.5 per 1,000 births), found that obesity was responsible for 2.9% of these deaths. The most common placental histological findings in these patients included placental immaturity, villous edema, and fetal thrombotic arteriopathy, among others, suggesting that maternal obesity may contribute to placental insufficiency and chronic hypoxia, leading to FD.[23] It is concluded that: Maternal obesity is a significant risk factor for FD, especially in preterm pregnancies and those complicated by infections or placental dysfunction. It is essential for women planning a pregnancy to maintain a healthy BMI before conception to minimize risks. Medical care during pregnancy in obese women should include close monitoring for potential infections and placental dysfunction to reduce the risk of FD.

Obesity and labor complications

Promoting early intervention in overweight or obese women is key to improving perinatal outcomes. Obese women face higher labor complications. Studies and meta-analyses have shown that there is a higher incidence of labor induction, oxytocin use, lack of labor progress, and the need for instrumental delivery compared to women of normal weight.[66] These women also have a higher risk of shoulder dystocia, especially with a BMI ≥ 35, where the risk increases 2 to 2.5 times.[66,85–87] A commonly accepted hypothesis suggests that excess adipose tissue in the pelvis may narrow the birth canal, making the process more complicated, especially in cases of fetal macrosomia.[65] Additionally, obesity is associated with a higher risk of post-term delivery, likely due to hormonal and endocrine imbalances.[65]

- Cesarean Delivery: Although obesity alone is not a direct indication for a cesarean section, there is a clear relationship between elevated BMI and increased rates of both elective and emergency cesarean delivery. Meta-analyses have found that obese women are approximately twice as likely to require a cesarean, particularly emergency ones, compared to women of normal weight.[44,85,88] Factors contributing to this increase include slower cervical dilation, coexisting conditions, and concerns about shoulder dystocia.[40,66,88] Furthermore, obese women face higher risks associated with cesarean sections, such as anesthetic complications, wound infections, hemorrhages, and thromboembolism.[3]

- Postpartum Hemorrhage: Obesity is also linked to an increased risk of postpartum hemorrhage. Two meta-analyses have shown that this risk is higher in women with a BMI greater than 35, with an OR of 1.43.[66] It is believed that obesity can complicate postpartum management, as uterine retractors are distributed over a larger volume, making it harder to identify the uterine fundus and perform bi-manual massages.[89] Obese women also require more blood transfusions after postpartum hemorrhage.[90]

Obesity and cerebral palsy

Maternal overweight and obesity are associated with an increased risk of cerebral palsy in offspring, particularly in term-born children. A cohort study in Sweden, which included 1,423,929 single-term children, found that as maternal BMI increases, so does the risk of cerebral palsy [91]. This risk progressively increases with the degree

of obesity and is related to neonatal complications, such as birth asphyxia. The findings suggest that for every additional unit in BMI, the risk of cerebral palsy increases by 3%.[92]

Obesity and breastfeeding

Obese women are less likely to initiate and maintain breastfeeding. Exclusive breastfeeding rates are lower, and the duration of breastfeeding is shorter compared to women of normal weight.[93,94] Factors such as cesarean delivery, difficulties with latching due to breast size, and elevated progesterone levels can affect the initiation and continuation of breastfeeding.[3,70]

Conclusions

Maternal obesity represents a serious health threat during pregnancy, with broad implications for both mother and fetus. The main concerns include:

-Pregnancy and labor complications: Second-trimester miscarriage due to ascending bacterial infections (ABI). Gestational diabetes mellitus (GDM) and preeclampsia (PE). Rectovaginal colonization by Group B Streptococcus (GBS).Spontaneous and medically indicated preterm birth. Increased likelihood of cesarean section.

-Fetal outcomes: Increased incidence of congenital malformations. Higher risk of macrosomia and large or small for gestational age newborns (LGA and SGA).Increased fetal mortality (FM) and admission to the neonatal intensive care unit (NICU).

-Maternal postpartum outcomes:Higher risk of postpartum hemorrhage.Infections, venous thromboembolism, and cesarean-related complications. Issues with breastfeeding, including a lower likelihood of initiating breastfeeding and a shorter duration of breastfeeding

-Long-term outcomes: Increased risk of obesity, type 2 diabetes (T2DM), ischemic heart disease, hypertension, and childhood obesity in offspring. The pathophysiological mechanisms underlying these issues include maternal insulin resistance, hyperinsulinemia, inflammation, and oxidative stress, which can cause fetal and placental dysfunction.

It is essential that obese women who wish to become pregnant and health professionals are well informed about these risks. Prevention of obesity before pregnancy is fundamental. Furthermore, a detailed understanding of the pathophysiological mechanisms will allow the development of more specific and effective treatments during pregnancy, thus improving outcomes for the mother and the newborn.

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None.

Conflicts of interest

The authors declares that there is no conflicts of interest.

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