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PATHOPHYSIOLOGY OF DIABETES MELLITUS AND MECHANISMS OF MAJOR MATERNAL COMPLICATIONS: A SYSTEMATIC REVIEW

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Luiz Filipe Brasileiro Miranda dos Santos[1], Eris Araújo Oliveira[2], Warla Bruna Barbosa da Costa[3], Larissa Medeiros da Fonseca[4], Sibele Santos Bezerra[5], Graciete Mendes das Graças[6], Roberta Ticiana Rocha Pontes de Castro[7], Sarah Oliveira Resende[8] and Luana Carolina Rodrigues Guimarães[9].

ABSTRACT

Objective: The main objective of this study is to review the scientific literature on the pathophysiology of Diabetes Mellitus (DM) and the mechanisms underlying associated maternal complications. Methodology: This research is a systematic review aimed at understanding the essential aspects of Diabetes Mellitus and its maternal complications. The research was guided by the question: "What are the main mechanisms that lead to maternal complications in diabetes mellitus, and what scientific evidence supports these findings?" To answer this question, we searched the PubMed Central (PMC) database using four descriptors combined with the Boolean operator "AND". This resulted in 408 articles. After applying the inclusion and exclusion criteria, 28 articles were selected for analysis, of which 8 were used to compose this review. Results: Diabetes Mellitus significantly increases the risk of maternal complications, such as preeclampsia, preterm birth, and fetal macrosomia. Without appropriate interventions, many women with DM can develop serious complications during pregnancy. Insulin resistance and increased inflammation seen in DM are crucial factors contributing to these complications. In addition,

[1] Physician graduated from the Pernambuco Faculty of Health (FPS)
E-mail: luizfbmirandasantos@gmail.com
[2] Undergraduate student in Medicine at Universidade Potiguar (UNP)
E-mail: erisaraujoop15@gmail.com
[3] Undergraduate student in Medicine at Uninassau de Campina Grande
E-mail: warlabruna@hotmail.com
[4] Physician graduated from Potiguar University (UNP)
E-mail: larissampf@hotmail.com
Lattes: http://lattes.cnpq.br/2351231355180221
[5] Graduanda at universidad internacional tres fronteiras (UNINTER DE PY)
E-mail: sibelesantos2@gmail.com
[6] Medical student at the Pontifical Catholic University of Minas Gerais (PUC Minas) - Betim
E-mail: gracietedasgraca@yahoo.com.br
[7] Physician graduated from the Faculty of Medicine of Juazeiro do Norte-CE
E-mail: robertaticianarocha@gmail.com
[8] Physician graduated from the Faculty of Dracena – UNIFADRA
E-mail: dra.sarahoresende@gmail.com
[9] Guidance counselor
Physician from the Faculty of Medicine of Itajubá (FMIT) - Itajubá/SP; Gynecologist and Obstetrician and Master in Health Promotion, Professor and preceptor in the discipline of Gynecology and Obstetrics at the University of Franca - UNIFRAN
E-mail: luanarodriguesgo@gmail.com

DM is associated with neonatal complications such as neonatal hypoglycemia and respiratory distress syndrome. Conclusion: Diabetes Mellitus is a condition characterized by chronic hyperglycemia that can lead to several maternal and neonatal complications. Understanding pathophysiological mechanisms, such as insulin resistance and inflammation, is essential for effective disease management and for protecting maternal and fetal health.

Keywords: Diabetes Mellitus. Maternal Complications. Pathophysiology. Clinical Management.

INTRODUCTION

During pregnancy, significant changes occur in the mother's metabolism to ensure an adequate supply of nutrients to the fetus. In early pregnancy, there is an increase in insulin sensitivity to promote energy storage in the form of fat and glycogen. However, as pregnancy progresses, especially in the second and third trimesters, progressive insulin resistance occurs (Calvo et al., 2024).

This insulin resistance is a normal and necessary physiological mechanism. It allows more glucose to remain available in the mother's bloodstream to be transferred to the fetus. Several placental hormones, such as human placental lactogen (hPL), placental growth hormone (PGH), progesterone, cortisol, and prolactin, play a critical role in promoting this insulin resistance. These hormones are produced by the placenta and have counterinsulin effects, increasing hepatic gluconeogenesis and lipolysis, as well as decreasing insulin sensitivity in peripheral tissues (Calvo et al., 2024).

Studies show that maternal pancreatic beta cells undergo compensatory adaptations to maintain glycemic homeostasis during pregnancy, including an increase in beta cell mass due to hyperplasia (an increase in the number of cells) and hypertrophy (an increase in cell size). These processes are mediated by hormones such as estrogen, progesterone, hPL, prolactin, and cortisol, which promote beta cell proliferation and hypertrophy to increase insulin secretion (Calvo et al., 2024).

Genetic predisposition plays a significant role in the development of GDM. Several genetic polymorphisms are associated with an increased risk of developing the disease, especially those related to pancreatic beta cell function and insulin resistance. In addition, familial inheritance of type 2 diabetes mellitus (T2DM) is a strong risk indicator for the development of GDM (Calvo et al., 2024). In addition to the genetic components, several environmental factors influence the etiology of GDM. Among them, maternal obesity is one of the most important. Excess adipose tissue leads to the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which can interfere with insulin signaling and contribute to insulin resistance (Calvo et al., 2024). A high-carbohydrate, high-fat diet and lack of physical activity are also well-documented risk factors (Calvo et al., 2024).

Early screening for hyperglycemia during pregnancy by measuring HbA1c levels. Hyperglycemia is recognized as a significant risk factor for several obstetric complications, such as macrosomia, large for gestational age (LGA), preeclampsia, and preterm delivery. The study indicates that elevated HbA1c levels (> 39 mmol/mol), even if below the diagnostic threshold for diabetes, can predict these complications (Mañé et al., 2024).

Early screening for hyperglycemia through HbA1c measurement is valued for its pre-analytical stability and convenience of not requiring fasting, making it a practical and effective tool to identify pregnant women at risk (Mañé et al., 2024). Early interventions based on these outcomes can mitigate obstetric complications, promoting better maternal health outcomes (Mañé et al., 2024).

In addition to affecting the baby, hyperglycemia poses a significant risk to the mother's health. Complications such as preeclampsia and premature birth are serious conditions that can compromise maternal health. Preeclampsia, for example, is characterized by high blood pressure and can lead to damage to vital organs such as the liver and kidneys, as well as increase the risk of cardiovascular disease in the long term (Mañé et al., 2024). Preterm birth, in turn, puts the mother at risk of complications related to early labor and postpartum recovery (Mañé et al., 2024)

METHODOLOGY

This study is a systematic review that aims to understand the main aspects of the pathophysiology of Diabetes Mellitus (DM) and the mechanisms of the main associated maternal complications. To develop this research, we formulated a guiding question using the PVO (population, variable and objective) strategy: "What are the pathophysiological mechanisms of Diabetes Mellitus and its main maternal complications according to scientific evidence?"

The searches were carried out in the PubMed Central (PMC) database. We used four descriptors in combination with the Boolean operator "AND": Diabetes Mellitus, Maternal Complications, Pathophysiology, Mechanisms. The search strategy applied was: Diabetes Mellitus AND Maternal Complications, Diabetes AND Pathophysiology AND Mechanisms. We found 408 articles, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published between 2018 and 2024 and that addressed the themes proposed for this research. In addition, we considered review, observational and experimental studies, available in full. The exclusion criteria were: duplicate articles, available only as abstracts, that did not directly address the topic studied, or that did not meet the inclusion criteria.

After applying the descriptors in the searched databases, we found a total of 408 articles. After applying the inclusion and exclusion criteria, we selected 31 articles from the PubMed database, of which 8 studies were used to compose this systematic review.

RESULTS

TABLE 1: MAIN MATERNAL COMPLICATIONS DESCRIBED BY EACH AUTHOR SELECTED FROM THE SYSTEMATIC REVIEW.

Author(s)	Main Complications	Full Description
Foo et al. (2024)	Insulin resistance, Hepatic steatosis, Nonalcoholic steatohepatitis (NASH), Chronic inflammation, Oxidative stress, Adipokine changes	**Insulin resistance**: Persistent after delivery, preventing the inhibition of lipolysis and resulting in an influx of free fatty acids into the liver. - **Hepatic steatosis**: Accumulation of triglycerides in the liver, leading to hepatic fat. - **EHNA**: Inflammation and damage to liver cells. - **Chronic inflammation and oxidative** stress: Production of reactive oxygen species (ROS) and elevation of pro-inflammatory cytokines such as IL-6, IL-1, IL-18 and TNF-α. - **Changes in adipokines**: Reduced levels of adiponectin, an adipokine that regulates glucose and fatty acid oxidation.
Calvo et al. (2024)	Genetic predisposition, Maternal obesity, Diet high in carbohydrates and saturated fats, Advanced maternal age, Family history of T2DM	**Genetic predisposition**: Genetic polymorphisms and familial inheritance of type 2 diabetes as strong risk indicators. - **Maternal obesity**: Production of pro-inflammatory cytokines that interfere with insulin signaling. - **Diet rich in carbohydrates and saturated** fats: Well-documented risk factors that contribute to the development of GDM. - **Advanced** maternal age: Decreased pancreatic beta cell function and increased insulin resistance. - **Family histories of T2DM:** Increased likelihood of developing GDM in subsequent pregnancies.
Xu et al. (2018)	Inadequate sleep duration, Intermittent hypoxemia	**Inadequate sleep duration**: Sleeping less than 7 hours or more than 9 hours per night, with short sleep duration associated with increased inflammatory stress and endothelial dysfunction. Excessive sleep can result in hormonal dysregulation, elevated cortisol levels, and impact on weight gain. - **Intermittent hypoxemia**: Frequent in cases of sleep apnea, exacerbating insulin resistance due to increased inflammation and oxidative stress.
Mercado-Evans et al. (2024)	Group B streptococcal (GBS) rectovaginal colonization	**Rectovaginal GBS colonization**: Hyperglycemia and immune dysregulation associated with GDM increase susceptibility to GBS colonization, with a 16% higher risk in women with GDM. Hyperglycemia affects immune cell function, vaginal microbiota, and vaginal mucosal barrier integrity, creating an environment conducive to GBS colonization and proliferation.
Jin et al. (2024)	Perinatal depression (prenatal and postpartum)	**Perinatal depression**: Women with GDM are nearly twice as likely to develop perinatal depressive symptoms. Potential mechanisms include dysregulation of the HPA axis, chronic inflammation, increased adipokines, and significant stress associated with the diagnosis and management of GDM. Prevalence is highest in low- and middle-income countries, where access to quality health care and psychological support is limited.
Bucci et al. (2024)	Cardiovascular complications	**Cardiovascular complications**: Women with GDM are at increased risk of heart failure, myocardial infarction, and ischemic stroke, due to insulin resistance, endothelial dysfunction, and chronic inflammation. These factors contribute to the development of cardiovascular diseases in the long term.

SOURCE: TABLE CREATED BY THE AUTHOR

DISCUSSION

The placenta is an essential organ for transporting nutrients between mother and fetus, ensuring the proper growth of the baby. In the case of GDM, glucose transport is particularly affected. Maternal hyperglycemia results in an increase in the expression of glucose transporters, such as GLUT-1, GLUT-4, and GLUT-9, in the placenta. This leads to an increased transfer of glucose to the fetus, resulting in macrosomia, a condition where the baby is born with excessive weight (YI et al., 2024). However, anomalies in transport can also result in fetal hypoglycemic conditions if GLUTs levels are insufficient, which negatively impacts fetal growth (YI et al., 2024).

The placenta exerts a fundamental endocrine function during pregnancy, regulating the production and release of hormones that are crucial for both the mother and the fetus. Changes in the hormonal function of the placenta due to gestational diabetes mellitus (GDM) have significant implications for fetal development and the metabolic health of the offspring.

Human placental lactogen (HPL) and growth hormone (GH) levels increase significantly in pregnancies complicated by GDM, especially in the third trimester (YI et al., 2024). HPL, produced by the placenta, plays an important role in modulating maternal glucose and lipid metabolism, preparing the mother for the energy demands of pregnancy. In women with GDM, elevated HPL production is associated with increased insulin resistance, which may result in maternal hyperinsulinemia (YI et al., 2024).

This increase in maternal insulin resistance favors the passage of more nutrients, such as glucose and amino acids, to the fetus, resulting in excessive fetal growth (macrosomia). In addition, HPL can directly influence the production of IGF-1 in the fetus, a hormone that stimulates growth and fat deposition (YI et al., 2024). In animal models, targeted reduction of HPL was associated with intrauterine growth restriction, underscoring the importance of this hormone for fetal development (YI et al., 2024).

The IGF-1/IGF-2 axis is also instrumental in regulating fetal growth. Free IGF-1 levels are elevated in the placenta of women with GDM, due to the lower binding capacity of IGFBP proteins, which normally bind to IGF-1, reducing its bioavailability (YI et al., 2024). This increase in IGF-1 bioavailability is correlated with exaggerated fetal growth and macrosomia (Yi et al., 2024).

In addition, increased expression of IGF-2 in the placenta is directly associated with the development of macrosomia, as IGF-2 is a potent fetal growth factor (YI et al., 2024). Changes in DNA methylation that affect IGF-1 and IGF-2 expression contribute to these changes in fetal growth and obesity rates in offspring of mothers with GDM (YI et al., 2024).

Adipokines, such as leptin, resistin, and adiponectin, are also secreted by the placenta and play important roles in modulating maternal and fetal metabolism (YI et al., 2024). Leptin and resistin have elevated levels in the umbilical cord blood of fetuses of mothers with GDM, and these levels are positively correlated with birth weight (YI et al., 2024). These hormones are associated with an increased risk of obesity and insulin resistance in offspring (YI et al., 2024).

In contrast, maternal adiponectin levels are generally reduced in pregnancies with GDM, which is associated with higher insulin resistance and obesity in offspring (YI et al., 2024). Adiponectin is known for its anti-inflammatory and insulin-sensitizing properties, and its reduction contributes to the development of metabolic disorders (YI et al., 2024).

DNA methylation is a crucial epigenetic process that involves the addition of methyl groups to the DNA molecule, usually at position 5 of the cytosine ring, forming 5-methylcytosine. This process can modify the activity of a DNA segment without altering the sequence. In the context of the placenta in women with gestational diabetes mellitus (GDM), DNA methylation plays a key role in gene expression regulation and fetal development.

Studies have shown that GDM can alter the overall methylation of DNA in the placenta, resulting in changes in fetal development and the long-term health of the offspring. For example, global hypermethylation in the placenta of GDM patients is associated with insulin resistance and increased birth weight, indicating fetal reprogramming that may predispose offspring to obesity and metabolic disorders (YI et al., 2024).

Imprinted genes are genes that are expressed in a parent-of-origin dependent manner, that is, their expression is determined by the genome of one of the parents. In the context of GDM, the methylation of imprinted genes in the placenta is of particular interest due to its impact on fetal growth and development.

- **MEG3 (Maternally Expressed Gene 3):** MEG3 methylation in the placenta of women with GDM is significantly increased on the maternal side of the placenta and is positively correlated with maternal blood glucose levels and fetal birth weight. This hypermethylation can lead to lower MEG3 expression, negatively influencing fetal programming and increasing susceptibility to metabolic diseases (YI et al., 2024).
- **MEST (Mesoderm-Specific Transcript):** MEST methylation is reduced in women with GDM, which is associated with the development of macrosomia.

This hypomethylation can be transmitted to offspring, increasing the risk of obesity in adulthood (YI et al., 2024).

- **DLK1 (Delta-Like 1):** Hypermethylation of the DLK1 gene in the placenta of patients with GDM results in a significant decrease in its gene expression. DLK1 methylation is positively correlated with fetal weight and maternal blood glucose, indicating that hypermethylation of this gene may be a mechanism for obesity and metabolic disorders (YI et al., 2024).

In addition to imprinted genes, methylation of metabolic genes in the placenta can significantly affect the regulation of fetal metabolism:

- **LEP (Leptin):** Leptin is an adipokine important for the regulation of energy homeostasis and fetal growth. In GDM, the mean level of LEP methylation at 23 CpG sites is increased in the placenta of women with GDM, which is associated with insulin resistance and increased levels of leptin in umbilical cord blood, contributing to increased birth weight (YI et al., 2024).
- **ADIPOQ (Adiponectin):** Adiponectin is known for its anti-inflammatory and insulin-sensitizing properties. In GDM, ADIPOQ methylation is increased in the placenta, which is associated with reduced adiponectin levels in umbilical cord blood and increased insulin resistance in offspring (YI et al., 2024).
- **LPL (Lipoprotein Lipase):** LPL promoter methylation in the placenta is reduced in women with GDM, which is correlated with increased levels of triglycerides and low-density lipoprotein (LDL) in maternal and umbilical cord blood, contributing to fat deposition and increased birth weight (YI et al., 2024).

DNA methylation in the placenta in women with GDM plays a crucial role in fetal programming and the development of metabolic diseases in the offspring. Understanding these epigenetic changes is essential to develop interventions that can mitigate the risks of obesity, diabetes, and other metabolic diseases in offspring. Continued research on the impacts of DNA methylation offers promise for future prevention and treatment strategies (YI et al., 2024).

MicroRNAs (miRNAs) are small non-coding RNA molecules that play a crucial role in the post-transcriptional regulation of gene expression. They work by binding to specific messenger RNAs (mRNAs), leading to degradation of the mRNA or inhibiting its translation. In the placenta, miRNAs regulate a number of vital biological processes, including cell proliferation, trophoblastic invasion, and nutrient metabolism.

In the setting of gestational diabetes mellitus (GDM), the expression of miRNAs in the placenta can be altered, resulting in significant effects on fetal development. Studies

have shown that maternal hyperglycemia influences the expression of various miRNAs in the placenta, affecting proliferation, trophoblast infiltration, and glucose and lipid metabolism (YI et al., 2024).

A notable example is the miR-132. High concentrations of glucose have been found to inhibit cell viability and reduce miR-132 expression levels in the placenta. The reduction of miR-132 can promote the proliferation of trophoblastic cells, which are responsible for the invasion of the maternal endometrium and the formation of the fetal component of the placenta. This can contribute to the development of macrosomia, a condition where the fetus grows excessively due to increased nutrient transfer (YI et al., 2024).

Another significant miRNA is miR-21, which is downregulated in the placenta of patients with GDM. miR-21 is involved in lipid and glucose homeostasis, and its downregulation can lead to increased expression of PPARγ, a nuclear receptor that regulates lipid and glucose metabolism. This alteration may contribute to fat accumulation and metabolic disorders in the offspring (YI et al., 2024).

miR-29b is another miRNA that is downregulated in the DMG. Studies have shown that decreasing miR-29b levels in the placenta promotes trophoblastic activity and increases glucose uptake. Downregulation of miR-29b leads to increased expression of hypoxia-inducible factor 3 (HIF3A) beta subunit, which is associated with adaptation to intrauterine hyperglycemia (YI et al., 2024).

miR-98 and miR-199a are upregulated in the placentas of patients with GDM. These miRNAs indirectly regulate glucose uptake by targeting the Mecp2-Trpc3 pathway. Activation of this pathway may increase insulin resistance and contribute to glucose metabolism disorders in the fetus (YI et al., 2024).

The regulation of miRNAs in the placenta is an essential mechanism that can be affected by GDM, directly influencing fetal development and the risk of metabolic diseases in the offspring. Understanding these mechanisms is vital for developing prevention and treatment strategies that can mitigate the adverse effects of GDM on the long-term health of offspring (YI et al., 2024).

Understanding the epigenetic and functional changes of the placenta in women with GDM is essential to identify interventions that can mitigate the risks of chronic diseases in the offspring. The research highlights the importance of epigenetics in fetal programming and provides a foundation for future prevention and treatment strategies (YI et al., 2024).

TABLE 2: HORMONES AND GENES INVOLVED IN THE PATHOPHYSIOLOGY OF GDM:

Hormone/Gene	Role in the pathophysiology of GDM	Reference
Human Placental Lactogen (hPL)	Produced by the placental syncytiotrophoblast, it has diabetogenic effects, increasing insulin resistance in maternal tissues. It	Calvo et al., 2024

	promotes pancreatic beta cell proliferation and hypertrophy by increasing insulin secretion to compensate for insulin resistance.	
Placental Growth Hormone (PGH)	It replaces pituitary growth hormone during pregnancy, regulates placental growth, and promotes a state of physiological insulin resistance. It influences the synthesis of adiponectin, an anti-inflammatory hormone and insulin sensitizer.	Calvo et al., 2024
Leptin	Produced by adipose tissue and syncytiotrophoblast, it has significantly elevated levels in pregnant women with GDM. Hyperleptinemia is associated with insulin resistance and may exacerbate the inflammatory state of the placenta. In GDM, LEP methylation is increased, associated with insulin resistance and elevated levels of leptin in umbilical cord blood, contributing to increased birth weight.	Calvo et al., 2024; YI et al., 2024
Resistina	Produced by the placenta, associated with insulin resistance. In pregnant women with GDM, elevated levels of resistin can interfere with insulin signaling and negatively affect glucose and lipid transport.	Calvo et al., 2024
Adiponectin (ADIPOQ - Gene)	Known for its anti-inflammatory and insulin sensitizing properties. In GDM, ADIPOQ methylation is increased, associated with reduced levels of adiponectin in umbilical cord blood and increased insulin resistance in offspring.	YI et al., 2024
Lipoprotein Lipase (LPL - Gene)	LPL promoter methylation is reduced in women with GDM, correlated with elevated triglyceride and LDL levels in maternal and umbilical cord blood, contributing to fat deposition and increased birth weight.	YI et al., 2024
MEG3 (Maternally Expressed Gene 3 - Gene)	MEG3 methylation is significantly increased on the maternal side of the placenta, positively correlated with maternal blood glucose levels and fetal birth weight. Hypermethylation can lead to lower MEG3 expression, negatively influencing fetal programming and increasing susceptibility to metabolic diseases.	YI et al., 2024
MEST (Mesoderm Specific Transcript - Gene)	MEST methylation is reduced in women with GDM, associated with the development of macrosomia. This hypomethylation can be transmitted to offspring, increasing the risk of obesity in adulthood.	YI et al., 2024
DLK1 (Delta-Like 1 - Gene)	Hypermethylation of the DLK1 gene in the placenta results in a significant decrease in its gene expression. Positively correlated with fetal weight and maternal blood glucose, hypermethylation of this gene may be a mechanism for obesity and metabolic disorders.	YI et al., 2024

SOURCE: CREATED BY THE AUTHOR

MATERNAL COMPLICATIONS

Insulin resistance is one of the main pathogenic factors in NAFLD, especially in patients with a history of gestational diabetes mellitus (GDM). During pregnancy, the placenta secretes counterinsulin hormones, such as human placental lactogen, which increases insulin resistance. This resistance is a normal physiological response to ensure adequate glucose supply to the developing fetus (FOO et al., 2024). However, in some women, this insulin resistance exceeds what is needed, resulting in hyperglycemia and eventually the development of GDM.

After childbirth, many women continue to experience insulin resistance. This prolonged resistance prevents inhibition of lipolysis, resulting in an influx of free fatty acids into the liver. Insulin normally inhibits lipolysis in adipose tissue, but in states of insulin resistance, this inhibition is attenuated, leading to an increase in circulating fatty acid levels (FOO et al., 2024).

Excess free fatty acids are transported to the liver, where they are converted into triglycerides, leading to the accumulation of liver fat (steatosis). The liver tries to compensate for this overload by increasing the export of triglycerides in the form of very low-density lipoproteins (VLDL), but the export capacity is limited. In addition, insulin resistance also promotes de novo lipogenesis (the synthesis of new fatty acids) in the liver, further exacerbating fat accumulation (FOO et al., 2024).

The continuous accumulation of fat in the liver leads to a situation where the liver cells become full of triglycerides. This hepatic steatosis is an early stage of NAFLD and can progress to nonalcoholic steatohepatitis (NASH) if left uncontrolled. NASH is characterized by inflammation and damage to liver cells, as well as fat accumulation (FOO et al., 2024).

The accumulation of fat in the liver causes chronic inflammation and oxidative stress. Lipid-overloaded liver cells produce reactive oxygen species (ROS), leading to oxidative stress. Inflammation is mediated by pro-inflammatory cytokines such as IL-6, IL-1, IL-18, and TNF-α, which are elevated in patients with NAFLD. This inflammatory and oxidative environment perpetuates the cycle of liver damage and inflammation, resulting in the progression of liver disease (FOO et al., 2024).

Insulin resistance also affects the secretion and action of adipokines, hormones produced by adipose tissue. For example, women with GDM have reduced levels of adiponectin, an adipokine that regulates glucose and fatty acid oxidation. Low adiponectin levels are associated with increased inflammation and progression of fatty liver. The combination of insulin resistance, liver fat accumulation, chronic inflammation, and oxidative stress contributes significantly to the development and progression of NAFLD (FOO et al., 2024).

Women with GDM have reduced levels of adiponectin, a hormone that regulates glucose and fatty acid oxidation. Low adiponectin levels are associated with increased inflammation and progression of fatty liver. In addition, changes in adipokine levels, such as elevation of pro-inflammatory cytokines, exacerbate inflammation and oxidative stress (FOO et al., 2024).

Hormonal changes play a crucial role in the pathophysiology of nonalcoholic fatty liver disease (NAFLD) in patients with gestational diabetes mellitus (GDM). During pregnancy, the placenta secretes several counterinsulin hormones, such as human placental lactogen (HPL), cortisol, and estrogen, which increase insulin resistance. This increase in insulin resistance is a physiological adaptation aimed at ensuring the availability of glucose to the growing fetus. However, in some women, this resistance becomes excessive, leading to hyperglycemia and GDM (FOO et al., 2024).

After childbirth, many women continue to experience insulin resistance, which has important consequences for lipid and liver metabolism. Insulin normally inhibits lipolysis in adipose tissue, but insulin resistance prevents this inhibition, resulting in elevated levels of free fatty acids in the circulation. These fatty acids are transported to the liver, where they are converted into triglycerides, leading to the accumulation of liver fat (FOO et al., 2024).

In addition, levels of adiponectin, a hormone produced by fat tissue, are reduced in women with GDM. Adiponectin has anti-inflammatory properties and increases insulin sensitivity. Low adiponectin levels are associated with increased inflammation and worsening of fatty liver. The reduction in adiponectin also contributes to the increase in hepatic lipogenesis, further promoting the accumulation of fat in the liver (FOO et al., 2024).

Another relevant hormone is leptin, also produced by adipose tissue. Women with GDM often have elevated leptin levels, which is associated with insulin resistance and inflammation. Leptin may promote liver inflammation through the activation of macrophages in the liver, contributing to the progression of steatosis to nonalcoholic steatohepatitis (NASH) (FOO et al., 2024).

These hormonal imbalances create a metabolic environment conducive to the development and progression of NAFLD. Therefore, proper management of hormone levels and insulin resistance is crucial to prevent liver complications in women with a history of GDM.

For fetuses, the risks are also significant. Maternal hyperglycemia during pregnancy can result in elevated glucose levels in the fetus, leading to fetal hyperinsulinemia. This condition can cause accelerated fetal growth and a higher risk of obesity in the future. Intrauterine exposure to an altered metabolic environment may predispose offspring to metabolic disorders, including insulin resistance. Children of mothers with GDM may have altered liver development, with a greater propensity for fat accumulation in the liver and liver inflammation throughout life. In addition, studies indicate that children of mothers with GDM have a significantly higher risk of developing type 2 diabetes and metabolic syndrome, conditions strongly associated with NAFLD (FOO et al., 2024).

Evidence suggests that GDM has a lasting impact on intergenerational liver health, reinforcing the need for ongoing monitoring and early interventions to prevent complications associated with NAFLD. An interdisciplinary approach, combining clinical care, lifestyle changes, and ongoing research, will be key to addressing the challenges posed by this metabolic condition (FOO et al., 2024).

Genetic predisposition is one of the main risk factors for the development of GDM. Several genetic polymorphisms are associated with an increased risk of developing the

disease. For example, variants in genes related to the function of pancreatic beta cells, which are responsible for insulin production, may affect the body's ability to compensate for insulin resistance during pregnancy (Calvo et al., 2024). In addition, familial inheritance of type 2 diabetes mellitus (T2DM) is a strong indicator of risk for developing GDM, suggesting that family history plays a crucial role (Calvo et al., 2024).

In addition to genetic components, several environmental and lifestyle factors significantly influence the etiology of GDM. Among these factors, maternal obesity is one of the most important. Excess adipose tissue leads to the production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), which can interfere with insulin signaling and contribute to insulin resistance (Calvo et al., 2024). Diet high in refined carbohydrates and saturated fats, as well as lack of physical activity, are also well-documented risk factors (Calvo et al., 2024).

Advanced maternal age is another significant risk factor for GDM. Women who become pregnant after the age of 35 have a higher likelihood of developing GDM compared to younger women. This can be attributed to several physiological changes that occur with aging, including decreased pancreatic beta cell function and increased insulin resistance (Calvo et al., 2024).

Women who have had GDM in previous pregnancies have a significantly higher risk of developing the condition again in subsequent pregnancies. In addition, a family history of type 2 diabetes mellitus also increases the likelihood of developing GDM (Calvo et al., 2024). These risk factors are particularly important in screening and monitoring women during pregnancy.

During pregnancy, the production of placental hormones, such as human placental lactogen (hPL) and placental growth hormone (PGH), increases significantly. These hormones have diabetogenic effects, increasing insulin resistance in maternal tissues to ensure an adequate supply of glucose to the fetus (Calvo et al., 2024). However, this resistance can outpace the compensating capacity of the maternal pancreas, leading to the development of GDM. Chronic low-grade inflammation, often associated with obesity, exacerbates insulin resistance. Inflammatory cytokines, such as TNF-α and IL-6, produce a pro-inflammatory environment that negatively affects pancreatic beta cell function by reducing their ability to secrete insulin in response to increased resistance (Calvo et al., 2024).

Insulin resistance is a normal and necessary physiological mechanism during pregnancy, allowing more glucose to remain available in the maternal bloodstream to be transferred to the fetus. Several placental hormones, such as human placental lactogen

(hPL), placental growth hormone (PGH), progesterone, cortisol, and prolactin, play a critical role in promoting this insulin resistance (Calvo et al., 2024). However, when this resistance exceeds the compensatory capacity of the maternal pancreas, the hyperglycemia characteristic of GDM occurs.

Sleep duration during pregnancy is a key aspect for the health of both mother and fetus, with studies indicating that both sleep deprivation and oversleeping can increase the risk of gestational diabetes mellitus (GDM). Pregnant women who sleep less than 7 hours per night have a 1.50-fold increased risk of developing GDM, possibly due to increased inflammatory stress and endothelial dysfunction caused by sleep deprivation. Short sleep duration can trigger complex pathophysiological mechanisms, including hormonal dysregulation and insulin resistance, factors that contribute significantly to the development of GDM. On the other hand, sleeping more than 9 hours per night is also associated with a 1.28-fold increased risk of GDM. Prolonged sleep duration can lead to hormonal dysregulation, affecting the hypothalamic-pituitary-adrenal axis and resulting in elevated levels of cortisol, a hormone that raises blood glucose levels and contributes to insulin resistance. In addition, excessive sleep can increase the inflammatory response and alter the secretion of hormones that regulate appetite, such as leptin and ghrelin, impacting weight gain and, consequently, the risk of GDM.

The relationship between sleep duration and GDM development involves complex and multifaceted pathophysiological mechanisms. Prolonged sleep duration can be an indicator of poor sleep quality, characterized by fragmentation and frequent episodes of microarousals, which negatively affect endothelial function and increase oxidative stress. Intermittent hypoxemia, which is common in cases of sleep apnea, can also exacerbate insulin resistance due to increased inflammation and oxidative stress. Therefore, monitoring and adjusting sleep duration during pregnancy, keeping it between 7 and 9 hours per night, is crucial. Sleep hygiene strategies and behavioral interventions can help promote healthy sleep patterns, reducing the risk of GDM, and promoting maternal and fetal health. These findings underscore the importance of a holistic and personalized approach to sleep management in pregnant women, considering both the quantity and quality of sleep, with a view to preventing complications such as GDM and promoting overall well-being during pregnancy (Xu et al., 2018).

Other risk factors include ethnicity, with women of certain ethnicities, such as Asians, African Americans, Hispanics, and Native Americans, being more likely to develop GDM. Excessive weight gain during pregnancy is also a significant risk factor, as is polycystic ovary syndrome (PCOS), which is associated with insulin resistance (Calvo et al., 2024).

Gestational Diabetes Mellitus is a multifaceted condition with numerous genetic, environmental, hormonal and metabolic risk factors. Early identification of these risk factors is essential for the implementation of effective preventive and management strategies. In-depth understanding of the underlying mechanisms that contribute to the development of GDM can help improve health outcomes for both mother and baby.

The research by Bucci et al. (2024) offers an in-depth analysis on maternal health complications from gestational diabetes (GDM). This study reveals that GDM, often seen as a temporary pregnancy problem, can have significant and long-lasting implications on the cardiovascular health of affected women.

Bucci et al. (2024) demonstrate that women with GDM have a substantially higher risk of cardiovascular events, including heart failure, myocardial infarction, and ischemic stroke, compared to women who have not suffered from this condition. Insulin resistance, endothelial dysfunction, and chronic inflammation, all risk factors associated with GDM, are mentioned as contributors to the development of cardiovascular disease in the long term. These findings underscore the critical need for continuous monitoring and targeted interventions to mitigate these risks.

The study emphasizes that early recognition and proper management of GDM are essential to minimize long-term risks (Bucci et al., 2024). Education and awareness among healthcare professionals and patients are highlighted as key aspects to improving long-term health outcomes. Implementing postpartum monitoring programs and lifestyle changes are recommended as effective strategies to promote cardiovascular health.

In addition, Bucci et al. (2024) identify that gestational complications should be viewed not only as temporary concerns during pregnancy, but as predictors of future health problems. Women with GDM, especially those who also develop gestational hypertension, are at an even higher compound risk of cardiovascular complications. This underscores the importance of ongoing and personalized interventions for these women to reduce the risk of cardiovascular events.

Gestational diabetes (GDM) has been identified as a significant risk factor for maternal rectovaginal colonization by group B streptococci (GBS). This association is extremely important, since GBS colonization is a known risk factor for severe perinatal diseases, including sepsis and neonatal meningitis. The systematic review and meta-analysis conducted by Mercado-Evans et al. (2024) revealed that women with GDM are 16% more likely to be colonized by GBS compared to women without GDM.

Maternal rectovaginal colonization by group B streptococci (GBS) is a critical issue in obstetrics, as it is directly linked to serious perinatal complications. The relationship

between GBS colonization and severe perinatal diseases is remarkable. GBS, when present in the mother's vaginal and gastrointestinal tract, can be transmitted to the neonate during delivery. This transmission process is particularly dangerous, as newborns have an immature immune system, making them highly vulnerable to infections.

Recognizing and mitigating the risk factors that contribute to GBS colonization is crucial. One such factor, as discussed by Mercado-Evans et al. (2024), is gestational diabetes (GDM). GDM not only alters the mother's glycemic homeostasis but also affects her immunity and vaginal microbiota, creating an environment conducive to GBS colonization and proliferation. Therefore, women with GDM have a 16% increased risk of being colonized by GBS compared to women without GDM. In addition, pre-pregnancy diabetes was also associated with a significantly higher risk of 76%, further highlighting the importance of metabolic control during pregnancy (Mercado-Evans et al., 2024). In summary, rectovaginal GBS colonization in mothers with gestational diabetes poses a significant threat to neonatal health, requiring surveillance and appropriate clinical intervention to prevent serious neonatal infections (Mercado-Evans et al., 2024).

The mechanisms by which DMG increases susceptibility to GBS colonization are not fully understood. But it is known that first, GDM is characterized by a state of increased insulin resistance and hyperglycemia, which means that blood glucose levels are elevated. These conditions can lead to immune dysregulation, where the maternal immune system becomes less effective at fighting infections. Hyperglycemia can affect the function of immune cells such as neutrophils, NK (natural killer) cells, and macrophages, by decreasing their responsiveness to pathogens such as GBS (Mercado-Evans et al., 2024).

In addition, GDM alters the microbial composition of the vagina. Under normal conditions, the healthy vaginal microbiota is dominated by Lactobacillus, which help maintain an acidic environment and inhibit the growth of pathogenic bacteria. However, GDM can result in a lower abundance of Lactobacillus and an increase in other less desirable bacteria, such as Bacteroides and Klebsiella. This change in the microbiota may create a more favorable environment for GBS colonization and growth (Mercado-Evans et al., 2024).

Another factor to consider is the integrity of the vaginal mucosal barrier. GDM can cause chronic inflammation, which affects the vaginal mucosa, making it more susceptible to infections. Chronic inflammation can damage the mucosal barrier, facilitating GBS adhesion and penetration into the vagina and rectum (Mercado-Evans et al., 2024).

In addition, GDM is often associated with other metabolic conditions, such as obesity, which are also risk factors for GBS colonization. These conditions may share similar

pathological mechanisms, amplifying the risk of colonization in pregnant women with GDM (Mercado-Evans et al., 2024).

Therefore, it is crucial to recognize GDM as a significant risk factor for GBS colonization, not only by hyperglycemia, but also by immune dysregulation, changes in the vaginal microbiota, and mucosal barrier impairment. The inclusion of GDM in screening guidelines may improve prevention and treatment strategies by reducing the incidence of serious neonatal complications associated with GBS (Mercado-Evans et al., 2024).

Another important aspect is the overlap between GDM and other metabolic conditions, such as obesity and type 2 diabetes, which are also associated with an increased risk of GBS colonization. These conditions may share similar pathogenic mechanisms, amplifying the risk of colonization in pregnant women. Therefore, it is crucial to consider GDM as an independent risk factor and to conduct efforts to detect and monitor GBS colonization in these patients during prenatal care (Mercado-Evans et al., 2024).

In addition to these physical complications, there is growing evidence suggesting a strong link between GDM and the risk of perinatal depression, which includes both prenatal and postpartum depression. The systematic review and meta-analysis conducted by Jin et al. (2024) revealed that women with GDM are almost twice as likely to develop perinatal depressive symptoms compared to those who do not have GDM, with a pooled odds ratio of 1.92 (95% CI 1.24-2.97).

The increased risk of perinatal depression in women with GDM can be explained by several potential mechanisms. First, biochemical changes directly associated with GDM, such as dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is seen in both individuals with diabetes and individuals with depression, may play an important role. Dysregulation of the HPA axis can lead to increased inflammation and an elevated concentration of adipokines, which are associated with depression (Jin et al., 2024). In addition, the diagnosis of GDM itself can be a significant stressor for pregnant women, resulting in depressed mood. Pregnant women with GDM have to deal with dietary changes, close monitoring of glucose levels, and in some cases, insulin administration, which can increase stress and anxiety during pregnancy.

Another important aspect is that both GDM and perinatal depression share common risk factors, such as advanced maternal age, obesity, and low income. Women who are older or facing financial difficulties are more likely to develop GDM and perinatal depression (Jin et al., 2024). In addition, the prevalence of GDM is higher in low- and middle-income countries, where pregnant women have less access to quality health care and psychological support. These countries also have a higher incidence of perinatal depression

compared to high-income countries, suggesting that a lack of resources and adequate support may exacerbate mental health problems in pregnant women with GDM (Jin et al., 2024).

The relationship between GDM and perinatal depression is of particular concern in low- and middle-income countries, where health systems may not be equipped to provide integrated support to pregnant women facing these conditions. The review by Jin et al. (2024) highlights the urgent need for GDM prevention and management strategies that also address the mental health of pregnant women. This includes early screening for depressive symptoms, appropriate nutritional interventions, and community-based programs that offer emotional and psychological support.

These findings have significant implications for public health, especially in countries with limited resources. Health policies that integrate physical and mental care can help reduce the impact of GDM and perinatal depression, improving health outcomes for pregnant women and their babies. Additionally, education and awareness of the relationship between GDM and perinatal depression can help identify and treat symptoms early, promoting a healthier pregnancy and a better quality of life for affected women (Jin et al., 2024).

In summary, GDM is a complex condition that not only affects the physical health of pregnant women, but is also strongly associated with increased risk of perinatal depression. Understanding this relationship and implementing effective prevention and treatment strategies is essential to improve maternal and child health outcomes, especially in low- and middle-income countries (Jin et al., 2024).

Gestational diabetes (GDM) is one of the most common complications in pregnancy, affecting up to 25% of pregnant women worldwide. In addition to physical health impacts, such as increased risk of gestational hypertension, preeclampsia, and type 2 diabetes, GDM is closely linked to increased risk of mental disorders, particularly perinatal depression. Women with GDM have a significantly increased risk of developing perinatal depressive symptoms, especially in low- and middle-income countries. Lack of access to adequate care can exacerbate this risk, leading to a significant increase in the prevalence of perinatal depression. This scenario demands attention from public health policies for the creation of specific programs for the diagnosis and treatment of depression in pregnant women with GDM (Jin et al., 2024).

The combination of GDM and perinatal depression can generate an increase in demand for health services, including obstetric and psychiatric care. Low- and middle-income countries, which already face resource-limited challenges, may experience

additional burdens on their health systems. Public health strategies must consider the integration of physical and mental care for pregnant women, optimizing the use of available resources. The article by Jin et al. (2024) highlights the urgent need to develop GDM prevention and management programs, aiming to reduce the risk of perinatal depression. Early intervention strategies, such as mental health education, screening for depressive symptoms during pregnancy, and nutritional support, can be crucial. Implementing community-based programs that provide emotional and psychological support to pregnant women can improve health outcomes and reduce the burden of perinatal depression (Jin et al., 2024).

Awareness of the relationship between GDM and perinatal depression is critical for health professionals and pregnant women. Educational programs can help identify and treat depressive symptoms early, improving the quality of life for women and their families. A concerted effort between governments, health organizations, and communities is needed to promote education about these risks. The study by Jin et al. (2024) reveals that the risk of perinatal depression is higher in low- and middle-income countries compared to high-income countries. This underscores the need for public health policies that aim to reduce health inequalities by ensuring that all pregnant women have access to quality care. Initiatives such as subsidies for antenatal care, social assistance programs, and improvements in health infrastructure can play a crucial role in mitigating these risks (Jin et al., 2024).

Untreated perinatal depression can have adverse consequences for women's socioeconomic well-being, impacting their ability to work, care for their children, and actively participate in society. Therefore, investing in the mental health of pregnant women is not only a public health issue, but also a strategy to promote gender equality and sustainable socioeconomic development. Understanding the public health implications of GDM and perinatal depression is essential for developing effective policies and programs. Based on the findings of Jin et al. (2024), public health initiatives must address both the prevention and treatment of these conditions, with a special focus on low- and middle-income countries. Improving access to integrated health care and promoting education about these risks can contribute significantly to improving maternal and child health outcomes.

These public health implications point to the need for a multidisciplinary and integrated approach in the management of GDM and perinatal depression. Public health programs should include prevention, early diagnosis, and effective treatment, in addition to promoting education and emotional support for pregnant women. Collaboration between governments, health organizations, and communities is essential to ensure that pregnant

women receive the care they need and to reduce the prevalence of perinatal depression associated with GDM. Ultimately, addressing these challenges will contribute to improved maternal and child health and sustainable socio-economic development in low- and middle-income countries (Jin et al., 2024).

CONCLUSION

Gestational diabetes mellitus (GDM) is a multifaceted condition that not only impacts the physical health of pregnant women, but is also closely linked to a range of metabolic, cardiovascular, and mental complications. Postpartum insulin resistance leads to a dangerous accumulation of liver fat, promoting the progression of nonalcoholic fatty liver disease (NAFLD). In addition, GDM not treated properly can result in adverse cardiovascular health consequences for both mothers and their offspring, with significant intergenerational impacts.

Risk factors, including genetic predisposition, obesity, and hormonal changes during pregnancy, exacerbate women's vulnerability to GDM. Aspects such as inadequate sleep duration and group B streptococcal (GBS) colonization are indicative of how pregnant women with GDM face several additional challenges that require careful clinical management. Additionally, the association between GDM and perinatal depression emphasizes the need for a holistic and integrated approach to maternal health care. Prevention, early diagnosis, and appropriate treatment of both conditions are essential to improve maternal and child health outcomes. Therefore, public health policies must address the interrelationship between the physical and mental aspects of GDM, especially in low- and middle-income countries, where resources may be limited. Investments in education, early screening, and community-based interventions are key to mitigating risks and promoting the health and well-being of pregnant women and their families.

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