LUMEN ET VIRTUS

Management and complications of gestational diabetes mellitus: a systematic review

https://doi.org/10.56238/levv15n39-190

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ABSTRACT

Objective: The general objective of the present study is to analyze the scientific production on gestational diabetes mellitus, seeking to identify the main complications, as well as the main methods used in the treatment of this pathology. Methodology: It is a systematic review focused on understanding the main aspects of gestational diabetes mellitus. The research was guided by the question: "What are the complications and management of Gestational Diabetes Mellitus, based on the evidence available in the scientific literature?". To find answers, searches were performed in the PubMed database using four descriptors combined with the Boolean term "AND". This resulted in 408 articles. 31 articles were selected for analysis and 15 articles were used to compose the collection. Results: GDM significantly increases the risk of the mother developing type 2 diabetes after pregnancy. Without appropriate interventions, a considerable portion of women with GDM can be diagnosed with diabetes mellitus within a few years of giving birth. The insulin resistance and increased inflammation seen in GDM are key factors contributing to this prolonged risk. Conclusion: Gestational diabetes mellitus (GDM) is a condition characterized by glucose intolerance during pregnancy, increasing the risk of complications such as preterm birth and macrosomia. GDM occurs due to insulin resistance, and can lead to the development of type 2 diabetes in the future. Effective management involves continuous monitoring, dietary control, and medical interventions, which are essential to protect the health of the mother and fetus.

Keywords: Gestational Diabetes Mellitus, Complications, Pregnant.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic condition of pregnancy that presents as newly developing hyperglycemia in pregnant women who did not have diabetes before becoming pregnant and typically resolves after delivery. About 9% of pregnancies worldwide are affected by this prevalent prepartum condition As of 2020, the prevalence of GDM among pregnant women has increased significantly, reaching up to 15%. Although it is possible to develop GDM at any time throughout the course of pregnancy, it is usually seen between weeks 24 and 28 of pregnancy. In recent decades, the incidence of GDM has increased, mainly due to the increasing prevalence of obesity and advanced maternal age. During pregnancy, obese women have a 2.4 times higher risk of developing gestational diabetes mellitus (GDM) when compared to thin women (GRECO et al., 2024) (DINIZ et al., 2023) (NAKSHINE; JOGDAND, 2023) (ZHANG et al., 2024)

Gestational diabetes is caused by a deficit in insulin production in pregnant women, whose pancreas is unable to generate the insulin needed to meet the insulin needs of pregnancy. Normally, in the first trimester of pregnancy, there is a marked increase in insulin sensitivity, promoting glucose uptake by adipose tissue. However, as pregnancy progresses, placental hormones such as human chorionic gonadotropin (hCG), progesterone, estrogen, and human placental lactogen (hPL) increase, many of which cause insulin resistance. On the other hand, there is usually increased pancreatic beta cell proliferation and reduced pancreatic beta cell apoptosis, so that the beta cell mass undergoes hypertrophy and hyperplasia, leading to increased insulin release, which maintains normal glucose levels. If beta cell dysfunction occurs, the compensatory effect is lost, resulting in gestational diabetes (SÁNCHEZ-GARCÍA et al., 2023).

It is essential to detect and treat GDM during pregnancy because of the detrimental impact it has on the mother and fetus, both in the short and long term. Short-term consequences include increased risk of preeclampsia, which itself is an established risk factor for cardiovascular disease (CVD), as well as increased need for cesarean section, and difficulty during delivery. Women who had GDM during pregnancy have an increased risk of type 2 diabetes and cardiovascular disease later in life, compared with those with normoglycemic pregnancies and increased CVD risk. In addition, fetal complications such as macrosomia, polycythemia, fetal hyperglycemia, neonatal hypoglycemia, shoulder dystocia, neonatal respiratory distress syndrome, and increased perinatal mortality (NAKSHINE; JOGDAND, 2023) (FISKÅ et al., 2023) (SLOUHA et al., 2023)

This systematic review article aims to compile and analyze the scientific evidence on the management of gestational diabetes mellitus (GDM), as well as its main complications. The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis

of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of diagnostic and therapeutic approaches

METHODS

This is a systematic review that seeks to understand the main aspects of Gestational Diabetes Mellitus, as well as to demonstrate the main complications associated with the condition. For the development of this research, a guiding question was elaborated through the PVO strategy (population, variable and objective): "What are the complications and management of Gestational Diabetes Mellitus, based on the evidence available in the scientific literature?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Diabetes Mellitus, Gestational, Pregnancy, Diabetes, Gestational, Prenatal Diagnosis. The search strategy used in the PMC database was: Diabetes Mellitus, Gestational AND Pregnancy , Diabetes, Gestational AND Prenatal Diagnosis. From this search, 408 articles were found, which were subsequently submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 408 articles were found. After applying the inclusion and exclusion criteria, 31 articles were selected from the PubMed database, and a total of 15 studies were used to compose the collection.

DISCUSSION

Gestational diabetes mellitus (GDM) is a frequent complication of pregnancy and its incidence is growing globally. GDM is characterized as glucose intolerance with onset or first detection during pregnancy, although the methods and criteria for diagnosing GDM have evolved over time and vary among institutions. Pregnancies affected by GDM are more likely to result in poor obstetric outcomes, including preterm birth, cesarean section, macrosomia, and shoulder dystocia (EHLERS et al., 2021).

The cause of GDM is attributed to the inability of the maternal pancreas to adapt to the increased demand for insulin during pregnancy. During pregnancy, the body becomes less sensitive to insulin, which leads to an increase in insulin production by pancreatic beta cells. Insulin, released by these beta cells, plays an essential role in promoting glucose uptake by peripheral tissues, decreasing glucose production in the liver, and controlling the release of lipids from adipose tissue.

However, if normal insulin levels fail to achieve the expected response of insulin receptors, insulin resistance can occur. As a result, beta cells must produce more insulin than usual to maintain normal maternal blood glucose levels. This insulin resistance is a natural part of a healthy pregnancy and is induced by placental hormones to ensure that the fetus receives the nutrition it needs for proper growth and development. Maternal beta cells respond by increasing their number, production, and release of insulin to maintain glucose balance despite insulin resistance. However, when maternal beta cells fail to adapt to the metabolic changes associated with pregnancy, gestational diabetes mellitus (GDM) results in hyperglycemia (NAKSHINE; JOGDAND, 2023).

Hyperglycemia increases the activity of the sorbitol pathway and the accumulation of phosphate trioses (glyceraldehyde 3-phosphate and dihydroxyacetone phosphate) due to inhibition of the glycolytic enzyme glyceraldehyde 3-phosphate dehydrogenase (G3PDH), which is able to glycosylate proteins for the formation of advanced glycation products (AGEs) by increasing protein kinase C (PKC) and activating the hexosamine pathway that generates uridine diphosphate-N-acetyl glucosamine (UDP-GlcNAc), which has the ability to bind to proteins and regulate their functions. The activation of these mechanisms, added to glucose autooxidation and mitochondrial dysfunction, results in greater production of free radicals and oxidative stress. Oxidative stress and inflammation are interrelated; the production of reactive oxygen species (ROS) can activate inflammatory cells and increase the production of inflammatory mediators. Inflammation, in turn, leads to an increased release of ROS, initiating a vicious circle (SAUCEDO et al., 2023).

In addition, GDM promotes epigenetic changes directly in the endothelial cells of the fetoplacental vasculature. Fetoplacental endothelial cells isolated after pregnancies with GDM reveal altered transcriptome and DNA methylation profiles, and differentially methylated and expressed genes are particularly clustered in the functional pathways 'cell morphology' and 'cell movement'. In fact, fetoplacental endothelial cells exposed to DMG show a different actin filament organization and an altered barrier function. In human umbilical vein endothelial cells isolated from pregnancies with GDM, several miRNAs, including miRNA-101, exhibit altered expression. Notably, miRNA-101 targets the zester enhancer-homologum-2 (EZH2), a histone methyltransferase. Dysregulation of miRNA-101-mediated EZH2 repression is thought to have significant implications for the migration and budding properties of primary endothelial cell cultures, highlighting the crucial role of DMG-induced histone modifications in fetoplacental endothelial cell function. In addition, epigenetic mechanisms play a key role in the phenomenon known as "hyperglycemic memory" (DINIZ et al., 2023).

Glucose is the main energy substrate required for fetal and placental growth. As fetal gluconeogenesis is minimal during pregnancy, pregnant women undergo several physiological changes in their metabolic, renal, immune, cardiovascular, hematological and respiratory systems to

ensure a continuous and adequate supply of glucose to the fetus. Regarding changes in metabolism, the onset of physiological insulin resistance, which increases as pregnancy progresses, is necessary to establish a maternal-fetal glucose transfer system via facilitated diffusion, primarily through glucose transporter 1 (GLUT1). In pregnant women, several factors increase the risk of disturbance of physiological insulin resistance. These include family and personal history of diabetes mellitus, obesity, ethnicity (primarily Indigenous worldwide, African Americans, and Hispanics), and advanced maternal age (CALVO et al., 2024).

Several risk factors can contribute to gestational diabetes mellitus (GDM), with a significant problem being polycystic ovary syndrome (PCOS). PCOS is the most prevalent endocrine condition that begins before puberty and, due to marked hormonal changes, is only diagnosed after puberty. The prevalence of GDM has increased considerably in women with PCOS when compared to healthy controls, and some studies indicate that phenotype A may be more likely to lead to GDM. Risk factors for GDM in women with PCOS include low levels of preconception sex hormone-binding globulin, elevated body mass index (BMI) (> 25 kg/m²), and impaired glucose intolerance before conception. Although maternal outcomes are similar to those seen in women with GDM alone, those with GDM and PCOS are even more likely to develop pregnancy-induced hypertension and early miscarriage. Newborns born to mothers with GDM and PCOS are more likely to be born with low birth weight, compared to children of mothers with isolated GDM, who often have high birth weight (SLOUHA et al., 2023).

GDM causes several complications both in the short and long term regarding maternal health. Women diagnosed with GDM are significantly more likely to develop diabetes mellitus later in life. Approximately 10% of these women are diagnosed with diabetes mellitus soon after delivery. In the absence of specific interventions to reduce the risk of developing diabetes mellitus, the remaining have a 20% to 60% chance of developing the disease within 5 to 10 years of early pregnancy. Weight gain, insulin resistance, increased C-reactive protein levels, and reduced adiponectin levels are risk factors for beta cell decline at relatively high rates, leading to diabetes mellitus (NAKSHINE; JOGDAND, 2023).

In addition, there is growing evidence to suggest a strong relationship between GDM and risk of mental disorders, with an emphasis on its association with depression. A recent meta-analysis involving 10 cohort studies with a total population of 2,000,002 identified a significantly increased risk of developing postpartum depressive symptoms in women with GDM. It is worth noting the risk of depression in women with GDM, since physical and mental health are closely intertwined. When mental health issues coexist with physical health issues, health outcomes, disability, and costs tend to be much more severe (JIN et al., 2024).

There is evidence that diabetes and depression may share common biological risk factors. For example, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis has been observed in both people with diabetes and depression. Women with GDM are more likely to experience increased inflammation and elevated levels of adipokines, which are also related to depression. The very event of having GDM can result in depressed mood. In addition, it was found that GDM and mental disorders share several common risk factors, such as age, education level, and occupation. Women of advanced maternal age or unemployed and housewives are more likely to have GDM and mental disorders. Several studies have also found a relationship between depressive symptoms and difficulties adapting to diabetic complications, as well as adverse obstetric outcomes such as cesarean delivery and preterm birth (JIN et al., 2024).

The placenta plays a crucial regulatory role in maintaining fetal growth and development during pregnancy, possessing various functions such as nutrient transport and endocrine functions. Changes in placental functions can also induce a variety of fetal diseases and complications, such as fetal overnutrition or growth restriction. Previous studies have shown that metabolic abnormalities in patients with GDM can impair the structure, morphology, and functions of the placenta, leading to pathological changes and affecting energy conversion between mother and fetus, which impacts fetal development. Recently, a growing number of studies have shown that the placenta is associated with diseases such as obesity in the offspring, cardiovascular disease, and neurodevelopmental impairment, highlighting the importance of the placenta during fetal development (YI et al., 2024).

The growing fetus is only able to produce a limited amount of glucose; therefore, it gets most of its glucose from its mother's blood. Pedersen's modified theory states that regardless of glucose stimulation, greater fetal insulin production results from extra glucose carried by the placenta at elevated and uncontrolled maternal glucose levels. This is supported by the placental expression of glucose transporter proteins (GLUTs), which is higher in pregnancies with diabetes mellitus. In addition, insulin has the ability to activate mTOR, a potent regulator of cell proliferation. The amino acid transporters of the A and L systems of the placenta increase cell division and the supply of essential nutrients to the fetus due to elevated maternal insulin, which also results in increased activity of placental mTOR. Maternal hyperglycemia and hyperinsulinemia can lead to fetal changes similar to those found in GDM, resulting in neonatal obesity. An increase in neonatal size at birth, known as macrosomia, is a result of excessive nutrient storage. The fat is predominantly localized to the abdomen and fetal shoulders. Macrosomic babies are born in 15% to 45% of pregnancies with GDM (NAKSHINE; JOGDAND, 2023).

Pregestational diabetes mellitus (GDM) has been known for decades as a risk factor for congenital heart defects (CAD). The pathophysiology of the effects of maternal diabetes on the fetal heart is multifactorial and not yet fully understood. Structural anomalies can result directly from the

hyperglycemic environment, activating a cascade of cellular events and changes in gene expression. Morphological changes in the fetal heart were associated with fetal hyperinsulinemia and insulin-like growth factor I (IGF-1). IGF-1 promotes hypertrophy in cardiomyocytes, leading to decreased myocardial compliance and functional impairment (DEPLA et al., 2021) (ZHANG et al., 2022)

Gestation begins with fertilization and organogenesis begins during the third to eighth week post-conception and continues until delivery. Therefore, the first trimester of pregnancy is the most critical period for organogenesis. In women with pregestational diabetes mellitus (GDM), there is a long period of sustained hyperglycemia before and during pregnancy, which can significantly impact organogenesis and contribute to cardiac changes in the offspring. This differs from gestational diabetes mellitus (GDM), which is usually diagnosed between 24 to 28 weeks of gestation. Therefore, in a woman with GDM, blood glucose levels may be normal or only slightly elevated during the first trimester, leading to minimal influence on organogenesis. This may partially explain why the children of women with GDM have a higher risk of cardiac anomalies compared to the children of women with GDM. However, women who develop GDM during pregnancy often have evidence of metabolic dysfunction before pregnancy, such as pancreatic beta cell defects and increased insulin resistance, which may contribute to the development of hyperglycemia and consequently increase the rate of malformations in infants, although further studies are needed to elucidate the potential mechanisms involved (ZHANG et al., 2022).

Ideally, GDM rates in the population could be reduced through individual and societal measures designed to promote healthy lifestyle changes, including adequate dietary intake and increased physical activity in the general population, with a focus on the health and fitness of women of childbearing age. Maternal age at conception is an important marker of pregnancy complications, including GDM, but it is strongly influenced by both individual choices and social factors, and is unlikely to be an effective target for preventive measures. Maternal overweight and obesity are also very important risks that need to be addressed before pregnancy through lifestyle measures (MCINTYRE et al., 2020).

A comprehensive approach is needed to best manage an individual with GDM. This involves educating patients on how to manage weight gain during pregnancy, dietary adjustments, nutritional monitoring, and regulating blood sugar levels. With enough exercise, dietary changes, and lifestyle adjustments, up to 70%-85% of people with gestational diabetes can be cured. Most organizations recommend daily monitoring of self-blood glucose at home. Currently, daily self-monitoring of postprandial and fasting blood glucose levels is encouraged. The American Diabetes Association (ADA) recommends that target blood sugar levels be 95 mg/dL fasting and 140 mg/dL or 120 mg/dL over one to two hours, respectively, after a meal (NAKSHINE; JOGDAND, 2023).

A clinical dietitian should provide dietary guidance to all women with GDM, as dietary guidance is the mainstay of GDM treatment. Some of the dietary strategies mentioned in the literature include the DASH diet (dietary techniques to treat hypertension), calorie-restricted diets, low-glycemic index diets, low-carbohydrate diets, low-unsaturated fat diets, high-fiber and soy diets, diets based on. The emphasis of nutritional guidance should be on a balanced diet with reasonable portions, healthy fats, complex carbohydrates, and 20% protein. Even in pregnant women with GDM, physical activity and regular exercise have been promoted and encouraged. The benefits of moderate exercise during pregnancy include a lower risk of gestational diabetes, a lower potential for larger-than-normal newborns, and a lower risk of hypertension problems, preterm birth, and fetal growth restriction. In addition, pregnancy-related lifestyle modifications affect the postpartum period, reducing the chance of postpartum depression (NAKSHINE; JOGDAND, 2023).

In about 15% to 30% of patients with GDM, glycemic control is insufficient, despite suggested changes in diet and lifestyle, requiring the use of medications. Typically, if hyperglycemia still persists throughout the day after 10-14 days of nutritional and daily life changes, courses of medication should be considered. Insulin is the preferred medication in gestational diabetes mellitus to control hyperglycemia. Insulin offers the safest contour during pregnancy. Oral medications investigated include metformin and sulfonylureas, such as glibenclamide. Large molecules, such as insulin, cannot cross the placenta. For this reason, it is the drug of choice in most cases. Metformin and glibenclamide have been shown to have the ability to cross the placental barrier and reach the fetus (NAKSHINE; JOGDAND, 2023).

Insulin (INS) is the commonly used drug for the treatment of GDM, known for its established efficacy and high safety profiles. However, INS is considered to be used when cases of GDM do not respond adequately to dietary or exercise interventions. However, the convenience factor plays a central role, as INS therapy requires injections and presents challenges in terms of storage, making it significantly less convenient. As biguanide, MET exerts its effects by inhibiting gluconeogenesis in the liver, consequently reducing hepatic sugar production. In addition, it exerts actions on peripheral tissues, reducing free fatty acids (FFA), facilitating muscle glycogen synthesis and increasing GLP-1 levels in intestinal cells, thus inhibiting glucose absorption by intestinal wall cells, but its use is only present when good control is not achieved with insulin (ZHANG et al., 2024).

Although there are no definitive reports from reliable sources confirming the adverse effects of TEM in neonates, its clinical use has been the subject of controversy due to its ability to cross the placental barrier. It is hypothesized that MET can permeate placental tissue and potentially result in unfavorable fetal and neonatal outcomes, thus requiring further research to determine its long-term impacts on pregnant women and fetuses (ZHANG et al., 2024).

CONCLUSION

Gestational diabetes mellitus (GDM) is a growing condition that affects many pregnant women, characterized by glucose intolerance diagnosed during pregnancy. Its prevalence is increasing and is associated with several obstetric complications, such as preterm birth, cesarean section, and macrosomia. The main cause of GDM is the difficulty of the maternal pancreas in meeting the increased demand for insulin during pregnancy, resulting in insulin resistance and hyperglycemia. In addition to the immediate risks to maternal health, GDM is linked to an increased likelihood of developing type 2 diabetes in the future. Without appropriate interventions, a significant proportion of women with GDM can be diagnosed with diabetes mellitus within a few years of pregnancy. Insulin resistance and increased inflammation contribute to this prolonged risk.

Early and multidisciplinary management of GDM should include ongoing monitoring, appropriate diet management, and medical interventions to minimize risks to mother and baby. In summary, GDM is a complex condition that requires a comprehensive approach to ensure the health and well-being of both the mother and the fetus, highlighting the importance of follow-up and early intervention.

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