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Repr_Sci_420
5/23/2024

Gestational Diabetes Mellitus: An Exploration of Underlying Mechanisms, Diagnosis, Treatment and Ongoing Research

Gestational Diabetes Mellitus (GDM) affects a substantial number of pregnancies across the world, posing significant risks to both mothers and babies. Typically, GDM arises from insulin resistance that naturally occurs during pregnancy, leading to elevated glucose levels crucial for fetal growth. However, if these levels surpass the baseline requirements for fetal development and remain unregulated, they can harm both mother and baby (CDC, 2023). Beta-cell (β-cell) dysfunction is a primary contributor to GDM, leading to maternal hyperglycemia and elevated fetal glucose levels. Maternal complications due to hyperglycemia range from preeclampsia to the development of type II diabetes post-partum, while fetal complications can include macrosomia (excessive birth weight) and preterm birth (Zhang et al., 2009). Therefore, GDM poses severe risks for both mother and child and requires extensive research into the pathophysiology of the condition to produce impactful interventions and preventative measures. Current research within the field of GDM prevention focuses on refining diagnosis, exploring alternative markers, and assessing early intervention's impact on outcomes, emphasizing the urgent need for effective management strategies.

GDM is one of the most common pregnancy complications, affecting between 1-20% of pregnancies worldwide. The range in prevalence depends upon various diagnostic criteria, but in recent years, there has been a globally positive trend in GDM diagnoses (Amiri et al., 2018). From 1989 to 2004, the frequency of gestational diabetes increased from 1.9% to 4.2% in the United States (Getahun et al., 2008). A study conducted by Zhou et al. (2022) utilized the National Health Interview Survey (NHIS) to examine the prevalence of GDM in 2006, 2016, and 2017 in a cohort of 37,357 women. Their results suggest that the prevalence of GDM increased from 4.6% in 2006 to 8.2% in 2016, a relative increase of approximately 78%. Within this cohort, non-Hispanic white women tended to have a lower increase in prevalence (2.8%) compared to non-Hispanic black women (3.8%), Hispanic women (4.1%), and women of other races and ethnicities (8.4%) over the ten years. Additionally, the increase in prevalence tended to be more evident among women who were overweight (25 ≤ BMI ≤ 30 kg/m2), physically inactive, and with family income below the poverty threshold compared to women in other BMI ranges, more physically active, and with higher family incomes. Collectively, in the ten years between 2006 and 2016, the prevalence of gestational diabetes continuously increased, nearly doubling (Zhao et al., 2018).

As research into gestational diabetes has become more thorough, multiple risk factors have been identified. According to Kouhkan et al. (2021), the significant risk factors that influence GDM diagnosis are maternal age, obesity, family history of diabetes, previous history of GDM, and previous history of a newborn with macrosomia. According to the Centers for Disease Control and Prevention, advanced maternal age is associated with higher rates of GDM. More specifically, the rate for mothers aged ≥ 40 years (15.6%) was nearly six times the rate of mothers aged ≥ 20 years (CDC, 2023). This increase is associated with pancreatic β-cell function and insulin sensitivity decreasing with age (Kouhkan et al., 2010). There is also a 2.5x increase in the risk of developing gestational diabetes associated with obesity, which is related to the elevation of insulin resistance. A family history of Diabetes Mellitus (DM) is also associated with the development of GDM. Specifically, Kouhkan et al. (2021) suggest that there is a 2.9x increase in the risk of developing gestational diabetes if there is a history of diabetes mellitus.

In a normal pregnancy, the mother's body undergoes a series of changes to support the demands of a growing fetus. These physiological changes include adaptations within the metabolic system. Specifically, maternal tissues become progressively less sensitive to insulin. During early pregnancy, insulin sensitivity increases to promote glucose uptake for storage in adipose tissues for demands later in pregnancy. However, as pregnancy develops, the placenta secretes hormones and factors, including estrogen, progesterone, and most importantly, human placenta lactogen (hPL), to promote a state of insulin resistance and chronic hyperglycemia in the mother. The elevated glucose levels are then actively transported across the placenta to fuel the growth of the fetus via GLUT1.

The marked increase in the mother's glucose levels during pregnancy allows the fetus to receive proper nutrients to grow. However, to maintain a healthy glucose level in the mother, it is understood that there must be an increase in pancreatic β-cells mass to support insulin production and, therefore, the regulation of

glucose (Plows, 2018). β-cells produced in the pancreas respond to changes in glucose concentration by varying the insulin synthesis and secretion rate. Insulin facilitates glucose's entry into cells, which can either immediately be used for energy or stored for later use (German, 1993). The homeostasis of glucose levels in the mother is a delicate balance that can be dysregulated, resulting in GDM.

Most GDM cases occur because of β-cell dysfunction, in which the mother cannot produce enough beta cells and insulin to regulate glucose levels in the blood. The resulting high levels of glucose surpass the requirements to support the growing fetus, causing maternal hyperglycemia (Buchanan & Xiang, 2005). Pregnancies affected by GDM impose severe risks to both mother and baby. The mother can develop preeclampsia, have an increased risk of delivery via cessation section (c-section), and have an increased risk of developing diabetes mellitus in the future. The baby may be at risk of macrosomia, preterm birth, breathing difficulties, hypoglycemia (low blood sugar), obesity later in life, and even stillbirth (Mayo et al., 2022). For these reasons, it is imperative to pay rigorous attention to the mechanisms behind the development of GDM and conduct research to develop effective treatments and preventative measures.

In 1964, O'Sullivan and Mahan observed the impact of pregnancy on carbohydrate metabolism, delineating diagnostic criteria for gestational diabetes mellitus (GDM) based on a study involving 752 pregnant women subjected to a 3-hour 100 g oral glucose tolerance test (OGTT). GDM was diagnosed if two or more threshold values for whole blood glucose, as determined by the Somogyi-Nelson method, were surpassed during the OGTT. However, their criteria lacked validation against fetal outcomes, relying instead on the future risk of diabetes development in the subjects (Mishra et al., 2016). In 1973, a study suggested using the 50 g 1-hour oral glucose tolerance test to screen for gestational diabetes. It is currently used by 95% of obstetricians in the United States for GDM screening during pregnancy. (Quintanilla Rodriguez & Mahdy, 2022). In 2014, the U.S. Preventative Service Task Force recommended the oral glucose tolerance test for GDM screening at 24 weeks gestation. (Quintanilla Rodriguez & Mahdy, 2022).

The consensus regarding blood glucose goals for patients with GDM is a fasting and preprandial blood glucose of less than 5.3 mmol/L, 1-hour postprandial blood glucose of less than 7.7 mmol/L, and 2-hour postprandial blood glucose of less than 6.4-6.7 mmol/L (Mukherjee & Dawson, 2022). The treatment of GDM further defines the condition into two categories: A1GDM or GDM A2GDM. Gestational diabetes managed without medication and responsive to nutritional therapy is referred to as diet-controlled gestational diabetes (A1GDM). Gestational diabetes that is unable to be controlled through diet and requires medication to achieve adequate glycemic regulation is A2GDM (Quintanilla et al., 2022). Approximately 15-30% of individuals with GDM need medication in addition to lifestyle modifications to reach target levels of blood glucose (Mukherjee & Dawson, 2022). GDM treatment usually starts with nonpharmacological interventions, assuming an A1GDM status, such as diet modifications, exercise, and glucose monitoring (Quintanilla et al., 2022). Typically, a nutritional counselor or a physician will provide the patient with a personalized plan based on the three central nutritional concepts: caloric allotment, caloric distribution, and carbohydrate intake, alongside a recommendation of 30 minutes of moderate-intensity aerobic exercise at least five days a week.

If this intervention fails, or the patient cannot properly adhere to the recommendation, the patient is pushed from the A1GDM into the A2GDM category. In this case, insulin is the first line of medication employed to achieve glycemic regulation. Insulin is regularly considered standard practice when prescribed alongside diet and exercise. Insulin can better achieve metabolic control by regulating maternal hyperglycemia and reducing excessive amounts of glucose transferred to the fetus while maintaining proper growth (Mukherjee & Dawson, 2022). When food is ingested, it typically breaks down into glucose, which enters the bloodstream. This triggers the pancreas to release insulin, which helps cells absorb glucose for energy and prompts the liver to store excess glucose for later use. As cells use glucose, its concentration in the bloodstream decreases, leading to a reduction in insulin secretion. In turn, this signals the liver to release stored glucose, ensuring a constant energy supply, especially during periods of fasting. This delicate balance between glucose, insulin, and the liver maintains the body's optimal energy levels. However, in gestational diabetes mellitus (GDM), this process is disrupted, leading to elevated blood sugar levels. Introducing exogenous insulin can help regulate blood sugar levels by supplementing the body's natural insulin production, ensuring proper glucose absorption and storage, and maintaining stable energy levels (CDC, 2019).

However, insulin does have disadvantages, specifically, its primary modality of administration as an injectable, which requires education and resources to administer, as well as its ability to cause hypoglycemia when administered improperly or at the wrong time (Mukherjee & Dawson, 2022). Since regular insulin and neutral protamine Hagedorn (NPH) were first approved and used during pregnancy, multiple newer insulin analogs have been approved to treat GDM. Regular insulin is slow-acting and long-lasting, requiring

inconvenient administration 30 minutes before consuming a meal. The development of rapid-acting insulin analogs, such as insulin lispro and insulin aspart, have proved to be equally as safe and more convenient due to their rapid-acting nature (Mukherjee & Dawson, 2022). Additionally, basal insulin analogs, such as Detemir, are safe during pregnancy. Detemir has a low affinity to type 1 insulin growth factor (IGF1) receptors, which suggests that it has a low probability of affecting embryonic transplantation, which has been shown to rely heavily on IGF1. It has also been shown to be as effective in regulating blood glucose levels as NPH concerning glycosylated HbA1C levels at 36 gestational weeks and hypoglycemia (Mukherjee & Dawson, 2022).

In addition to injectable therapies, oral therapies, such as Metformin, have also been shown to improve maternal hyperglycemia in GDM; however, it is a second-line therapy in GDM. Despite its oral administration and more affordable cost in comparison to injectables, it crosses the placenta ubiquitously, causing fetal concentrations that are as high or even higher than maternal concentrations. In contrast, regular insulin does not reach the placenta and remains on the maternal side of the maternal-fetal system (Mukherjee & Dawson, 2022). Despite this, Metformin is safe during pregnancy in individuals with polycystic ovary syndrome (PCOS). The most active areas of research in gestational diabetes involve the mechanisms underlying gestational β-cell compensation and the treatment of GDM based on time of diagnosis, particularly the diagnostic criteria, alternative markers for diagnosis, and effects of early diagnosis and treatment on outcomes (Bremer, 2018).

In a study conducted by Ercument et al. (2019), they explored the role of novel β-cell sources that hold significant therapeutic promise for GDM management. Investigating the presence of a dynamic β-cell reserve, they applied pregnancy conditions to the liver-specific insulin receptor–KO (LIRKO) model of insulin resistance, already demonstrating β-cell hyperplasia, and utilized lineage tracing to monitor the origin of new β cells. While both control and LIRKO mice exhibited increased β-cell mass during pregnancy-induced insulin resistance, the heightened mass in the latter indicated a dynamic source traceable to pancreatic ducts. Their findings were further supported by NOD/SCID-γ LIRKO mice observations, where pregnancy post-co-transplantation of human islets and ducts enhanced β-cell proliferation and increased ductal cells expressing β-cell development-related transcription factors. Additionally, they identified duct cells expressing immature β-cell markers in pancreatic sections from pregnant humans and individuals with type II diabetes. During elevated insulin demand, ductal cells collectively contribute to the compensatory β-cell pool through differentiation or neogenesis (Erucment et al., 2019).

Additionally, a more recent transcriptomics study conducted by Yang et al. (2021) explored the impact of gestational diabetes mellitus (GDM) on placental physiology, focusing on maternal insulin resistance, low-grade inflammation, and endothelial cell dysfunction. Through single-cell RNA sequencing, the research highlights alterations in trophoblast cell subtypes and identifies novel marker genes associated with differentiation pathways. Their research elucidates the functional relevance of differentially expressed genes in GDM placental pathophysiology, emphasizing enrichment in estrogen signaling, antigen processing, and presentation. Additionally, the study revealed changes in immune cell populations, notably natural killer (NK) cells and macrophages. It revealed intricate ligand-receptor interactions between trophoblasts and immune cells within the maternal-fetal interface microenvironment. These findings underscore the complex interplay of cellular mechanisms underlying GDM-associated placental dysfunction and provide insights into potential therapeutic targets. More research is also needed to investigate the effectiveness of precise lifestyle interventions for GDM. Benham et al. (2023) underscore an urgent need for further research within this domain. They identified several precise markers from routine clinical assessments that would prevent escalation from A1GDM to A2GDM. These markers include a history of GDM, Body Mass Index (BMI), and blood glucose concentrations at diagnosis. These clinical measurements were identified as precision markers in the treatment of GDM at diagnosis.

Research on GDM faces several active barriers that complicate the understanding and management of this condition. One significant issue is the heterogeneity in GDM definitions and diagnostic criteria across different regions and institutions, which complicates the comparison and generalization of research findings (Mishra et al., 2016; Metzger, 2010). Additionally, the complex pathophysiology of GDM, involving multiple biological pathways such as insulin resistance, inflammation, and genetic factors, poses a challenge in isolating specific mechanisms (Catalano & Shankar, 2017). The lack of longitudinal studies tracking women before, during, and after pregnancy further limits the understanding of the full impact and progression of GDM (Kim et al., 2007; Kgosidialwa et al., 2024). The genetic and epigenetic complexity, coupled with limited Genome-Wide Association Studies (GWAS) specifically targeting GDM, hinders the identification of definitive markers (Basile et al., 2014). Moreover, population diversity in GDM risk factors and outcomes is often not

adequately represented in studies, reducing the applicability of findings across different ethnic and socioeconomic groups (Hedderson et al., 2010; Farrar et al., 2016). Addressing these barriers requires efforts to standardize diagnostic criteria, procurement and use of the latest research technologies, and recruitment of diverse study populations to advance the understanding and management of GDM.

Gestational Diabetes Mellitus (GDM) poses significant risks to both mothers and babies, affecting a substantial number of pregnancies worldwide. Stemming from maternal insulin resistance during pregnancy, GDM leads to elevated glucose levels that surpass requirements for regular fetal growth. Beta-cell dysfunction (β-cells) primarily contributes to GDM, resulting in maternal hyperglycemia and elevated fetal glucose levels. Maternal complications range from preeclampsia to the development of type II diabetes later in life, while fetal complications can include macrosomia and preterm birth. Despite advancements in screening and treatment, GDM prevalence continues to rise globally, underscoring the need for effective management strategies. Recent research has focused on refining diagnostic criteria, exploring alternative markers, and assessing the impact of early interventions on outcomes. Studies have investigated novel β-cell sources and placental physiology in GDM, revealing insights into the complex cellular mechanisms underlying placental dysfunction. Additionally, there is a growing recognition of the importance of precise lifestyle interventions, although further research in this area is needed. Collectively, these efforts aim to mitigate the risks associated with GDM and improve maternal and neonatal health outcomes.

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