Complications of Gestational Diabetes: An Overview

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In a healthy progressing pregnancy, the mother's body undergoes various physiological changes to support the needs of the growing fetus. These changes include cardiovascular, renal, hematological, and metabolic adaptations. Among the metabolic adaptations, changes in insulin sensitivity can be mentioned. Insulin sensitivity varies throughout different pregnancy stages according to the gestation requirements.[1]

During pregnancy, the blood glucose levels in a healthy individual tend to be lower. This can be attributed to several factors, including increased glycogen formation, enhanced peripheral glucose utilization, increased hepatic glucose production, and elevated glucose provided by the fetus. The primary reason for the rise in blood glucose levels is associated with the broader distribution of maternal glucose to both the mother and the fetus during pregnancy.[2] Moreover, during the second and third trimesters of pregnancy, there is an increase in hormones that antagonize the action of insulin, which physiologically predisposes to the development of insulin resistance. The primary purpose of these mechanisms is to provide glucose to the fetus.[3] As pregnancy progresses, increases in local and

ABSTRACT

Gestational diabetes mellitus (GDM) is characterized by glucose intolerance first identified during pregnancy. During pregnancy, various physiological changes occur to support the growing fetus, including alterations in insulin sensitivity. Insulin resistance develops due to increased hormones antagonizing insulin action, facilitating glucose supply to the fetus. Gestational diabetes mellitus results from beta-cell (β-cell) dysfunction and insulin resistance, with β-cell dysfunction exacerbated by insulin resistance. Risk factors contributing to GDM include obesity, advanced maternal age, and dietary factors. Diagnosis involves glucose tolerance tests, with lifestyle modifications as the primary treatment. Pharmacological intervention, such as insulin or oral agents like metformin and glyburide, may be required if lifestyle changes are insufficient. Complications of GDM include adverse pregnancy outcomes increased risks of perinatal death and long-term metabolic issues in offspring. Postpartum management involves breastfeeding encouragement, glucose monitoring, and screening for diabetes. Awareness of GDM's lifelong implications and associated risks is essential for comprehensive postpartum care. This review provides an overview of the physiological changes, pathophysiology, diagnosis, treatment, and complications associated with GDM.

Keywords: Beta cell, gestational diabetes mellitus, glucose intolerance, insulin resistance, postpartum management, pregnancy complications.

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placental hormones such as estrogen, progesterone, leptin, cortisol, placental lactogen, and placental growth hormone support the development of insulin resistance.[4]

The susceptibility to insulin resistance during pregnancy is the increase in insulin levels due to the elevated glucose levels in maternal blood. Insulin resistance can be described as a decrease in the response of the target organ where insulin is expected to act.[5,6]

The emergence of this effect may involve diabetogenic hormones such as growth hormone, corticotropin-releasing hormone, and placental lactogen.[7]

Even in healthy pregnancies, the target tissues of the mother gradually become less sensitive to insulin over time. Therefore, in women without gestational diabetes mellitus (GDM), as well as in women with pregestational or gestational diabetes, there is typically a decrease in insulin sensitivity of approximately 50-60%.[8]

Gestational diabetes mellitus is a form of glucose intolerance that develops or is first recognized during pregnancy in women without a prior diagnosis of overt diabetes.[9-11]

According to the American Diabetes Association, GDM is diabetes that first appears during the second or third trimester of pregnancy and has not been previously diagnosed as Type 1 or Type 2 diabetes.[12]

The International Association of Diabetes and Pregnancy Study Groups recommends the diagnosis of overt diabetes for women diagnosed during the prenatal period, while the diagnosis of GDM is suggested for diabetes that arises during the second and third trimesters of pregnancy.[9]

Pathophysiology

Gestational diabetes mellitus often results from beta-cell (β-cell) dysfunction on the background of pre-existing chronic insulin resistance during pregnancy. Therefore, the critical components of GDM can be represented as both β-cell dysfunction and tissue insulin resistance. In the majority of GDM patients, these abnormalities may exist before pregnancy and can progress over time.[13-16]

The primary function of β-cells is to store and release insulin in response to glucose levels. When β-cells lose their ability to respond appropriately to the glucose load and secrete insulin, a condition known as β-cell dysfunction occurs.[17]

Additionally, the underlying causes of β-cell dysfunction can vary or emerge through complex mechanisms.[18,19]

Beta-cell dysfunction is exacerbated in the presence of insulin resistance. Decreased insulin levels stimulate glucose uptake. However, β-cells must increase their insulin production to cope with the increased demand. This situation contributes to hyperglycemia. Glucotoxicity refers to the direct contribution of glucose to β-cell dysfunction. This creates a vicious cycle, where once β-cell dysfunction begins, it leads to dysfunction in other β-cells. Moreover, a decrease in β-cell hyperplasia may contribute to GDM, based on animal studies and postmortem human studies. Additionally, evaluations of the pancreas in patients with Type 2 diabetes mellitus have shown a decrease in β-cell mass by 40-60%.[20-22]

In the development of insulin resistance, cells fail to generate an adequate response to insulin. The molecular basis of this insulin resistance is the failure in insulin-dependent signaling. This results in inadequate translocation of glucose transporter 4 (GLUT-4) to the plasma membrane. Insulin resistance can also develop through decreased tyrosine phosphorylation or increased serine/threonine phosphorylation of the insulin receptor. Additionally, alterations in the expression or phosphorylation of regulators of insulin signaling, such as insulin receptor substrate, phosphatidylinositol 3-kinase, and GLUT-4, have been described in GDM. These molecular-level changes often persist beyond the end of pregnancy.[8,23,24]

Many of the risk factors thought to be influential in the development of GDM are believed to exert their effects by interfering with insulin signaling mechanisms. In particular, it has been observed that saturated fats directly interfere with insulin signaling mechanisms.[25]

Neurohormonal dysfunction also plays a role in insulin resistance disorders. The neurohormonal network consists of central and peripheral signals that regulate activities such as appetite, metabolic rate, and energy expenditure.[26,27]

Neurohormones contribute to the development of GDM by influencing fat cells and glucose utilization.[28,29]

As shown in some animal studies, neural networks that are effective in controlling body weight are believed to develop in early life. For example, it has been observed that inadequate or excessive nutrition in early life leads to epigenetic changes in the regulatory points of hypothalamic neurons. This contributes to the suggestion that susceptibility to GDM may develop in the womb.[30,31]

THE PREVALENCE AND RISK FACTORS

Gestational diabetes mellitus affects approximately 5-20% of pregnancies worldwide. The main reasons contributing to the increasing incidence include rising rates of obesity, sedentary lifestyles, and advanced maternal age in women.[32,33]

Although epidemiological studies aiming to identify risk factors for GDM are limited, they are

influenced by various factors.[34,35] Additionally, inconsistencies in diagnostic criteria for GDM and the presence of risk factors make it difficult to compare findings across studies. Despite these variations, certain risk factors consistently emerge. These include excessive gestational weight gain, a Western-style diet, ethnicity, polymorphisms, advanced maternal age, low or high birth weight, family history, and other insulin resistance disorders such as polycystic ovary syndrome (PCOS).[36-43]

The mentioned risk factors directly or indirectly contribute to impairment in β-cell function or a decrease in insulin resistance. For example, excessive weight gain is associated with insulin production from β-cells and is linked to insulin signaling pathways. Additionally, dietary patterns and content play a role in the development of GDM. Saturated fat, refined sugar, and processed meat are associated with an increased risk of GDM.[25,44,45] Another mechanism of action of saturated fats is to induce inflammation and endothelial dysfunction, making them a pathogenic factor for GDM.[46]

On the other hand, consumption of fish and seafood or intake of unsaturated fatty acids derived from these products has anti-inflammatory properties.[47]

There is evidence suggesting a strong association between processed meat consumption and the development of GDM, even after adjustments for changes in fatty acids, cholesterol, hemoglobin, and protein content.[48]

Interestingly, high-protein diets are associated with GDM independently of meat consumption.[49-51]

One theory proposed in this regard is related to the role of amino acids in serving as substrates for hepatic glucose production.[52]

Low or high birth weight is also a potential risk factor believed to be associated with insulin resistance. Low birth weight typically occurs due to inadequate maternal nutrition or placental insufficiency resulting in fetal malnutrition. Studies suggest that the fetus tries to compensate for inadequate nutrition by epigenetically altering the expression of genes involved in energy utilization and metabolic processes. Additionally, results from animal experiments indicate that inadequate nutrition in the womb is associated with a decrease in β-cell count.[53]

According to a phenomenon referred to as "developmental programming," the changes experienced by the fetus in the womb can be beneficial during prolonged periods of fasting. However, when there is a mismatch compared to the nutrition in the womb after birth, it can contribute to the development of obesity or metabolic disease.[54-56]

On the opposite end of the spectrum, fetuses exposed to excessive nutrition in the womb experience excessive growth. These individuals are more likely to experience hyperglycemia and β-cell exhaustion even before birth. This condition also predisposes them to hyperglycemia during metabolic stress periods, similar to during pregnancy.[57]

Apart from the identified and aforementioned risk factors, some scientists in the United States conducted a prospective cohort study to evaluate the relationship between maternal plasma 25-hydroxy vitamin D levels in early pregnancy and the risk of developing GDM with typical features.[58] The study revealed a negative correlation between plasma 25-hydroxy vitamin D concentration and the frequency of GDM development. In the cohort, approximately 33% of women showed a nearly 20% decrease in mean maternal plasma 25-hydroxy vitamin D concentration around the 16th week of pregnancy. Additionally, it was demonstrated that this group of women had a significantly higher likelihood of developing GDM. After controlling for well-known and prominent risk factors, significant differences were observed between the remaining diagnostic groups and these women.[59-61]

Diagnosis, Detection, and Screening

Various organizations have attempted to establish protocols for diagnosing GDM in populations.[62]

There is a general consensus on the feasibility of conducting undiagnosed diabetes testing using standard diagnostic criteria during pre-pregnancy examinations for women at risk of Type 2 diabetes mellitus.[63]

Pregnant women confirmed to have a high-risk factor for GDM should undergo diabetes screening as soon as possible. Conditions, where pregnancy screening should be conducted earlier, include obesity with body mass index ≥30 kg/m2, a history of previous GDM, hemoglobin A1c (HbA1c) ≥5.7%, a family history of diabetes in first-degree relatives, being from an ethnic group identified as high risk, a history of PCOS, a history of hypertension or cardiovascular disease, and a history of a macrosomic baby.[11,64-66]

Gestational diabetes mellitus screening can be implemented using either a one-step or two-step

approach. Since 2010, the American Diabetes Association has recommended a one-step approach for GDM screening instead of the two-step approach.

According to the one-step approach for GDM diagnosis, a 75-gram oral glucose tolerance test (OGTT) is conducted after at least eight hours of fasting. Gestational diabetes mellitus diagnosis can be made if at least one of the following values is met: fasting plasma glucose ≥92 mg/dL, plasma glucose at one hour ≥180 mg/dL, or plasma glucose at two hours ≥153 mg/dL.[67,68]

According to the American College of Obstetricians and Gynecologists 2018 approach for two-step GDM screening, if the plasma glucose level is <140 mg/dL one hour after a 50-gram oral glucose challenge test, it is considered normal. However, if it is >140 mg/dL, the individual proceeds to a 100-gram glucose challenge test. The 100-gram glucose challenge test is conducted after at least 8 hours of fasting. Gestational diabetes mellitus diagnosis can be made if at least two of the following criteria are met: fasting plasma glucose ≥95 mg/dL, plasma glucose at one hour ≥180 mg/dL, plasma glucose at two hours ≥155 mg/dL, or plasma glucose at three hours ≥140 mg/dL.[11,62,63,67,68]

Alongside measuring blood glucose levels, another parameter that can assist in the diagnosis of GDM is HbA1c measurement. Hemoglobin A1C assessment aids in evaluating glycemic control. A result of HbA1C above 6.5% supports overt diabetes. However, if the value is below 6.5%, it is not fully known how beneficial it is to routinely monitor HbA1c levels in pregnant women.[69-71]

TREATMENT OF GESTATIONAL DIABETES MELLITUS

The main goal in the treatment of GDM is to prevent the occurrence of hyperglycemia and reduce the risk of adverse pregnancy outcomes associated with it. The potential positive impact of medical treatment on fetal and maternal morbidity in GDM was first demonstrated in the Australian Carbohydrate Intolerance in Study in Pregnant Women.[72]

Dietary regulation, blood sugar monitoring, and insulin intervention when necessary have been associated with a 67% reduction in infant mortality, shoulder dystocia, bone fractures, and nerve paralysis compared to routine care.[73]

Lifestyle Modification

Lifestyle modification, including dietary adjustments, physical activity, and weight management, is a cornerstone of GDM management. It is estimated that achieving this component may be sufficient for 70-85% of women diagnosed according to the American Diabetes Association criteria to reach the targeted blood sugar goal.[74]

A recent meta-analysis of randomized controlled trials has indicated that dietary intervention is associated with improvements in maternal fasting and postprandial glucose levels. As a result, the need for pharmacological treatment has decreased.[75]

Furthermore, a decrease in average birth rates and rates of macrosomia has also been observed.[76]

Other positive outcomes resulting from intervention include an increase in the mother's success in reaching her postpartum target weight and a decrease in neonatal adiposity. According to a Cochrane review evaluating the role of diet and exercise combined intervention in preventing GDM, a reduction in the risk of GDM was also reported.[77]

Pharmacological Treatment

If the target range for blood sugar cannot be achieved through lifestyle changes, pharmacological treatment is added. While insulin is considered the first-line pharmacological treatment in the United States and Canada, in the United Kingdom, the first-line pharmacological treatment is oral therapy. While continuous subcutaneous insulin infusion, which provides continuous insulin delivery, is considered a potential alternative in the United States, insulin is generally administered in the form of multiple daily injections.[74,78-80]

Evidence supporting insulin analogs as a safe alternative to insulin during pregnancy is increasing.[81]

In the treatment of GDM, metformin and glyburide are the preferred single oral agents. In a randomized study investigating cases where metformin was used for GDM, it was found that there were no significant risks in terms of perinatal complications between the treatment groups using metformin and insulin.[82]

Additionally, in patients undergoing metformin therapy, insulin treatment had to be added to achieve the target blood glucose level in 46% of cases.[83]

In approximately 4% of women using glibenclamide, insulin had to be added to maintain the target blood sugar level. According to the results of a randomized study, in women with GDM who did

not achieve the target glycemic value with metformin and where monotherapy was unsuccessful, insulin was found to be superior to glibenclamide as an additional treatment.[84]

It has been found that insulin provides better glycemic control than glibenclamide and is less associated with hypoglycemic episodes. However, analyses comparing the safety and efficacy of metformin and glibenclamide have yielded different results. In an analysis conducted in 2015 comparing metformin and glibenclamide, results suggesting the superiority of metformin were put forward, including reductions in maternal weight gain, decreased risk of low birth weight, and reduced risk of macrosomia.[85]

However, it should be noted that these results are based on only two randomized trials. According to a Cochrane review, oral treatment for GDM was examined in 11 studies, and there was insufficient evidence to reach a conscious conclusion that any oral treatment was more beneficial than another.[86]

The effects of long-term intrauterine exposure to metformin and glibenclamide are not fully understood. It is believed that glibenclamide passes through the placenta at low concentrations. This has raised concerns about reducing the expression of glucose transporters in the placenta. It is possible that fetal insulin production may increase and β-cell fatigue may occur in the long term.[87]

Metformin easily crosses the placenta and has been observed to be present in fetal and maternal blood at similar concentrations.[88]

In a controlled study incorporating data from 11 European congenital anomaly databases, first-trimester exposure to metformin was reported not to increase the risk of non-genetic congenital anomalies.[89]

An increased risk of pulmonary valve atresia has been reported following exposure to metformin. However, the authors acknowledge that this risk could be considered as a chance finding within the context of multiple statistical tests.[90]

The Postnatal Management and Postpartum Follow-Up of GDM

Breastfeeding is encouraged because it is associated with faster postpartum weight loss in mothers and lower obesity and diabetes risk in their babies.[91]

In breastfeeding mothers receiving insulin supplementation, consuming additional carbohydrate snacks may prevent hypoglycemia and may require lower insulin doses. According to a comprehensive clinical review, the use of metformin during breastfeeding is considered safe. However, there is insufficient data regarding the safety of other glucose-lowering agents. The American Diabetes Association also recommends the use of metformin.[92]

The 6-week period following childbirth is crucial for maternal pregnancy planning. During this time, recommending long-acting reversible contraception to the mother is ideal. It's important to remember that the risk of an unplanned pregnancy may be higher than the risk associated with the preferred contraceptive option.[93]

In women who have experienced GDM during pregnancy, an OGTT should be performed within 4-12 weeks after delivery to rule out pre-existing diabetes. When investigating for diabetes, HbA1c, fasting blood glucose measurement, and a 75g OGTT can be utilized and repeated every 1-3 years based on the patient's risk factors.[94] However, HbA1c may not provide reliable results because it can be affected by changes in blood glucose levels during pregnancy. Despite the importance of OGTT administration, participation rates for this test are low postpartum. Communicating with mothers who have complaints related to postpartum GDM can increase participation rates.[95] Women with GDM should be reminded that they have a lifelong risk of elevated blood glucose levels and an increased risk of cardiovascular diseases.[96]

COMPLICATIONS

Hyperglycemia has been documented to have adverse effects on both the mother and the baby. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) studies have shown that even less severe dysglycemic conditions, which are not as pronounced as overt diabetes mellitus, are associated with adverse outcomes during pregnancy. Following this study, evidence supporting the HAPO findings has been put forward.[97]

Babies born to mothers with GDM are at risk for many acute complications such as macrosomia, preterm birth, birth trauma, shoulder dystocia, neonatal hypoglycemia, neonatal admission, and respiratory distress.[98-103]

The relationship between GDM and the increased risk of perinatal death is still uncertain. A cohort study conducted in France in 2012 aimed to investigate this issue, including all births, including 57,629 mothers

with GDM. In births occurring at or after 37 weeks, babies born to mothers with GDM were shown to have a 30% increased likelihood of perinatal death compared to babies born to non-diabetic mothers.[104]

The effects on offspring exposed to GDM intrauterine for a prolonged period remain an issue that is still uncertain. According to a study on children, compared to children without diabetic parents, they are more predisposed to adiposity, insulin resistance, increased systolic blood pressure, and an increased risk of cardiovascular-related diseases.[105,106]

According to a study on adult offspring, compared to the previous generation, there is a decreased susceptibility to insulin resistance, diabetes, metabolic syndrome, and an increased risk of obesity.[107,108]

According to a meta-analysis of 18 studies, the likelihood of recurrence in the next pregnancy for women with GDM is estimated to be 48%.[109]

It has been observed that women with GDM also have an increased risk of developing Type 2 diabetes mellitus.[110]

It is estimated that approximately one-third of cases of Type 2 diabetes mellitus diagnosed in postpartum women are attributed to a history of GDM.[111,112]

In conclusion, GDM during pregnancy poses potential risks to both maternal and fetal health. The management of women diagnosed with GDM is crucial for controlling diabetes and preventing possible complications. Dietary regulation, physical activity, and pharmacological interventions when necessary are essential components of GDM management. Additionally, postpartum follow-up and assessment of diabetes risk are important.

Declaration of conflicting interests

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