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Gestational Diabetes Mellitus: An Update

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Abstract

Background: Gestational Diabetes Mellitus (GDM) is a type of diabetes mellitus with hyperglycemia that appears in pregnant women without a prior history of the disease due to insulin resistance, obesity, insufficient insulin production, etc. Since there are no obvious signs of GDM in the mother, screening is crucial to ensure the health of child. Numerous studies have reported that those mothers had GDM are twice the amount likely to develop type 1 diabetes before the age of 22 as a child or adolescent whose mother did not have gestational diabetes. On the other hand, the risks of both type 2 diabetes, its late complication like cardiovascular disease and other difficulties at birth, are all enhanced with GDM. The child may be at increased risk for developing obesity, type 2 diabetes, and cardiovascular disease in the future. Several treatment or management procedures are available, such as insulin therapy and changes in lifestyle. This review article provides an update on the epidemiology, pathogenesis, diagnosis, and treatment of GDM based on the recent literature.

1. Introduction

Diabetes Mellitus is a disorder that necessitates steady medical consideration for their self-management to avoid chronic complications. Cho et al. (2018) estimated that there were 451 million persons (18–99) with diabetes globally in the year 2017[1] and this figure is expected to raise upto 693 million by the year 2045. Further, 49.7% of the population with diabetes are undiagnosed. In addition, it was predicted that 374 million people had Impaired Glucose Tolerance (IGT) and about 21.3 million live births to women were affected by hyperglycaemia in pregnancy. In the year 2017, globally 5 million deaths happened due to diabetes among people aged 20 to 99. In 2017, it was predicted that the global healthcare expenditures for people with diabetes totaled USD 850 billion. Gestational Diabetes Mellitus (GDM) is a condition with hyperglycemia that manifests among pregnant women without a previous history of the disease due to insulin resistance, obesity, inadequate insulin synthesis, etc. GDM is characterized as any degree of glucose intolerance developing during pregnancy[2].

2. Prevalence of GDM:

GDM complicate around 7% of all pregnancies, which in turn results over a 200,000 cases per annum. The incidence of GDM varies from 1 to 14% of all pregnancies, based on the population and their mode of diagnostic methods utilized[3].Bahl et al. (2022) analyzed data from the women and Infants Integrated Interventions for Growth Study (WINGS) intervention group, an individually randomized factorial design experiment. After pregnancy confirmation, an oral glucose tolerance test (OGTT) was conducted, and they reported that 19.2% of pregnant women had OGTT were later on diagnosed with GDM, and those

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mother with pre-diabetic condition during the first trimester had a significantly increased probability of acquiring GDM. In addition, Bahl et al. found that age and BMI were also risk factors independently related with GDM[4].

A major number of pregnant women from low to moderate socioeconomic status in Delhi developed gestational diabetes mellitus, with, higher BMI, longer age and pre-diabetes being significant threat factors. These findings underscore the necessity for preventative measures and adequate management of gestational diabetes in prenatal programs[4].

GDM was more prevalent among Asian immigrants than among non-Hispanic White (NHW) in the same country. South, East, and West Asian immigrants in the United Kingdom and Norway had odds for GDM that were twice as high as non-Hispanic whites[5,6,7]. Interestingly, length of immigration and country of origin appeared to have a correlation with GDM prevalence. For example, Danish-Chinese migrants were 62% more likely to develop GDM than those with lesser stay of 5 years[8]. In addition, foreign-born US-Indian migrants showed a greater prevalence of GDM than native-born US-Indian migrants[9]. GDM affects an estimated 4 million people in India, and its prevalence ranges from 3.8% to 41% across the country. In 2017, members of the International Diabetes Federation chose "women and diabetes" as the subject for the year, focusing on pregnant women and how the disease may affect their offspring[10,11].

3. Pathophysiology of GDM:

In a healthy pregnant mother, the immune system switches a sequence of physiological changes to aid the growing fetus' needs. Insulin sensitivity represents an important metabolic adaptation. Throughout pregnancy, there is a change in insulin sensitivity patterns in response to the demands of pregnancy[12].

As pregnancy progresses, placental lactogen, estrogen, cortisol, placental growth hormone, leptin and progesterone increases insulin resistance[13]. Thus, blood glucose is mildly elevated and effortlessly transported across the placenta to fuel fetal growth. This mild insulin resistance also increases endogenous glucose production and fat breakdown, raising free fatty acid (FFA) levels and blood glucose [14]. In animals, pancreatic β-cell hypertrophy and hyperplasia and increased glucose-stimulated insulin secretion (GSIS) help pregnant women maintain glucose homeostasis[15]. Post delivery, maternal insulin sensitivity goes back to pre-pregnancy levels, demonstrating the influence of placental hormones[16]. GDM occurs when the pregnancy-related metabolic changes do not take place normally[17].

The risk factors of GDM include being overweight or obese[18], having an abnormally large amount of pregnancy weight gain[19], being of a specific ethnicity[16], having a specific genetic polymorphism[20], being of advanced maternal age[21], having a low or high birthweight[22]in the womb[23], having a personal history for GDM[24], and/or having polycystic ovary syndrome[25].

4. Diagnosis of GDM

If only those at risk are screened for gestational diabetes, there is a chance that as many as 35-47% of pregnant women will not have their condition identified, which will undoubtedly have an impact on the outcomes of obstetric procedures[26].

The present criteria used for the diagnosis of GDM were introduced by The International Association of Diabetes and Pregnancy Study Groups (IADPSG). These were followed from the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. These criteria discovered a threefold elevation in the diagnosis of GDM, suggesting that earlier estimates were underestimated. The goal of the HAPO group was to establish new viewing standards that would improve the ability to identify GDM patients who were at an increased risk for perinatal complications. A positive linear relationship was found to exist among adverse perinatal outcomes and blood glucose values, as demonstrated by the HAPO study. In addition, the findings of the study discovered that the risk for perinatal began to raise among women with those glucose values that were formerly measured to be "normal"[27,28]. This was the finding that was made by the researchers. At the moment, gestational diabetes mellitus can be diagnosed in all pregnant women who have never been diagnosed with diabetes by giving them 75 grams of glucose between the 24th and 28th week of their pregnancies.

As shown by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the Maternal-Fetal Medicine Units Network, the treatment

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of even minimal amount of glucose intolerance in GDM can offer an supplementary benefit (MFMU). It has been demonstrated that both weight gain among pregnant women and hyperglycemia are responsible in lowering the incidence of obstetric complications. In the ACHOIS study, antihyperglycemic intervention resulted in a significant reduction of the composite endpoint, as well as a lower incidence of LGA and a lower weight gain (by an average of 1.7 kg). In the MFMU study, researchers did not find any significant shifts in the composite endpoint, but they did found a significant decline of both LGA and shoulder dystocia[29,30,31]. These findings indicated that the majority of scientific societies incorporate into their day-to-day operations the recommendations made by the IADPSG in 2010 and the WHO in 2013 respectively. The introduction of the IADPSG criteria in the screening of GDM resulted in a tripling of the disease's prevalence, despite the fact that there were no substantial improvements in GDM-related events for women who lacked risk factors[32], with the exception of lower risks for low birth weight infants, neonatal hypoglycemia, and premature birth. This resulted in additional research being conducted on a population of GDM patients. One-step screening, as opposed to two-step screening, was shown to double the frequency during GDM diagnosis in a large randomized trial conducted by Hillier et al. (2021)[33], but it had no effect on the risks of primary Caesarean section, LGA, gestational hypertension, adverse perinatal outcomes or pre-eclampsia..

5. Complications of GDM

Early miscarriage has been linked to insufficient control of blood sugar levels. As many as one-quarter of pregnancies carried by women with diabetes end in miscarriage. Birth defects are more common in infants born to women with type 1 diabetes, with the rate hovering around 11%. Heart and blood vessel abnormalities made upto half the amount of anomalies. The risk of having an isolated cardiac defect is five times elevated among type 1 diabetic women. Caudal regression sequence is an extremely unusual malformation, and maternal diabetes is a major risk factor[11].

HAPO study enrolled about 25,505 pregnant women who all underwent a 75g 2-hour oral glucose tolerance test (OGTT) between 24 and 32 weeks. Wherein 5.9% of pregnant women were diagnosed with hypertension during their pregnancy, 2.5% were found to have chronic hypertension, and 4.8% were found to be experiencing pre-eclampsia. Pre-eclampsia was more likely to develop in women whose glucose levels were high during the OGTT[34]. Five percent women with gestational hypertension and 6.3% percent with pre-eclampsia were identified in the Metformin versus Insulin for the Treatment of Gestational Diabetes (MiG) trial[35].

In women with GDM, preterm delivery is often the result of the presence of preeclampsia in addition to other conditions like placental abruption and intrauterine growth restriction. A stillbirth risk nearly four times as high was linked to untreated GDM. Stillbirth rates were lowered by insulin therapy and increased monitoring. The rate of stillbirth was approximately 1.4 per 1000 live births in a study which composed mostly women having GDM. A small percentage of women (0.56%) in the HAPO study actually had a perinatal death [36]. Clinical hypoglycemia was diagnosed in the HAPO study when blood sugar levels were 30.6 mg/dL or lower within 24 hours post delivery, or 45 mg/dL or lower after 24 hours. Only 480 out of the 23,316 mothers (2.1% of all births) had infants with clinical hypoglycemia. Despite treatment, physiological fluctuations in maternal glycemia in GDM women can cause neonatal hypoglycemia. Hyperplasia of adipose tissue and skeletal muscle, as well as hypoglycemia in neonates, have all been linked to prolonged exposure to glucose during pregnancy and hyperinsulinemia in the developing fetus[37]. Women with GDM are to be expected to have hyperbilirubinemia than those without GDM. It has been hypothesized that increased fetal oxygen uptake and fetal erythropoiesis, resultS in hyperbilirubinemia, are caused by maternal hyperglycemia, which in turn induces fetal hyperinsulinemia and reduces oxygenation. In HAPO study, approximately 8.3% of women were affected with hyperbilirubinemia.

Maternal diabetes is associated with an increase in the transport of glucose and other nutrients across the placenta, leading to macrosomia in the offspring. Macrosomia, wherein the infant has a birth weight greater than 4,000 grams, affects 12 percent of infants born to healthy mothers and 15 to 45 percent of those born to GDM mothers. Macrosomia is more common in babies born to mothers with GDM because of their increased insulin resistance. Macrosomia is the result

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of an excess of glucose being transported to the fetus and stored as fat due to the presence of GDM. Approximately 9.6% of infants in the HAPO study were born weighing more than the 90th percentile.

Researchers found a link between GDM and the development of postpartum diabetes in the mother. About 5–10% of GDM cases were considered to be newly diagnosed diabetes due to the increasing population occurrence for diabetes. Pregnancy-related metabolic stress and an impaired insulin secretory response account for the remaining and overwhelming majority of cases of GDM. Women with GDM may experience symptoms of their diminished beta-cell reserve as late as ten years after giving birth. It has been estimated that the risk of developing diabetes in women with a history of GDM is as much as seven times elevated than without such a history, even if the glucose tolerance test (GTT) performed after giving birth is normal. It is estimated that between 10% and 40% of patients with a history of GDM will develop T2DM within the first year following delivery. The prevalence of T2DM after delivery peaks within the first five years after giving birth and then gradually declines until it reaches a plateau by the tenth year. Chronic insulin resistance may worsen over time, as evidenced by studies of glucose regulation over the long term following GDM.

Bellamy et al. (2009) highlighted that Preventing or delaying the onset of diabetes and cardiovascular disease in women with a history of GDM is crucial, as their risk of developing these conditions is more than seven times that of women who had a normoglycaemic pregnancy[38].

The risk of cardiovascular disease in their offspring is greater in GDM compared with subjects having normal blood sugar levels during pregnancy[39]. Kim et al. (2002)[40] found a wide range in the recurrence of GDM in subsequent pregnancies. Recurrence of GDM was seen in about 45.0% of women in subsequent pregnancies[41]. Childhood obesity was linked to maternal type 2 diabetes in a study by Zhao et al. (2016)[42].

6. Treatment of GDM

Diet and exercise has a vital role in the management of GDM[43]. Those patients with uncontrolled glycemic index with a well-balanced diet must be considered for pharmacological treatment[30]. Studies have shown that insulin therapy is the preferred choice of treatment, and OAD (orally administered drugs) treatment must be opted only if the patient refuses insulin therapy or if it is unavailable[44]. Currently, both metformin and glibenclamide are administered orally. Although both Metformin and glibenclamide crosses the placenta, but their teratogenic effects are unlikely[45,46]). The trial on 751 GDM patients using Metformin (MiG) was a landmark study. Metformin alone or in combination with insulin was not associated with an increase in perinatal complications. This trial served as the foundation for numerous studies evaluating the safety and efficacy of metformin among GDM patients[47]. A study reported that the administration of metformin in GDM patients is associated with an increase in subcutaneous tissue, visceral fat and body weight[48]. Despite its efficacy, glibenclamide may increase the risk of fetal growth restriction, macrosomia, hypoglycemia and intrauterine deaths [49].

7. Conclusion

GDM being a common complications and poses threat to both mothers and their offspring. Observational data revealed a linear relationship between maternal glycemic parameters and risks for adverse pregnancy and fetal outcomes. GDM diagnostic criteria and treatment are still the subject of considerable debate. Insulin therapy is effective, but its use in clinical practice is limited by its expense and adverse patient reactions. The use of metformin as a first-line agent for the treatment of GDM is still debatable because the drug can cross the placental barrier and there is a lack of data on its effects over the long term. Additional clinical trials are required for the use of other oral hypoglycemic agents in the treatment of GDM. Future research in the field should examine clinical and implementation outcomes, as well as strategies to improve the quality of care provided to women with GDM. Due to the lack of data from large randomized controlled trials, the screening and treatment of GDM in early pregnancy are highly contentious. There is an urgent need for well-designed research that can inform decisions about the optimal screening and diagnosis practices for gestational diabetes mellitus.

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