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Current Approaches To Screen And Diagnose Gestational Diabetes Mellitus

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Abstract

Gestational diabetes mellitus (GDM) is defined as a metabolic disorder that frequently occurs in pregnant women, with significant effects on the health of mothers and fetus, even years following delivery.GDM indicates the situation where serum glucose level is observed with the onset of gestation. Maternal diabetes has possible impacts on fetal development throughout gestation. At earlier stages of pregnancy, maternal diabetes might possibly result in congenital disorders with a higher miscarriage risk. The majority of congenital disorders exert adverse impacts on principal organs of the body such as the heart and brain. Throughout the second and third gestational trimesters, maternal diabetes might cause overfeeding along with exaggerated infantile growth. Moreover, GDM could rise the maternal risk of developing type 2 diabetes mellitus or possibly re-appearance of GDM later in life. In addition, mothers can be at higher risk of developing cardiovascular disease.

Early diagnosis of GDM is critical to avoid short term threats, such as those occurring during delivery, as well as long term influences, including cardiovascular and metabolic disorders in both mothers and infants. As a common practice, the oral glucose tolerance test (OGTT) has been accepted as a main parameter for the diagnosis of GDM. Current technological advances have made glycated hemoglobin (HbA1c) a more consistent and user-friendly test with accessibility for the diagnosis of GDM. Furthermore, this test does not need fasting and ensures higher level of comfort for pregnant women as compared to the OGTT. However, none of the recent guidelines related to GDM diagnosis have recommended this test so far.

Keywords: Gestational diabetes mellitus (GDM), oral glucose tolerance test (OGTT), glycated hemoglobin (HbA1c)

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is a prevalent compromise associated with pregnancy, characterized by the development of spontaneous hyperglycemia along the gestational period [1].This hyperglycemia is often caused by defects in glucose tolerance as a consequence of dysfunctional pancreatic β-cells associated with chronic insulin resistance [2]. In accordance with the most updated statistics of the International Diabetes Federation in 2017, GDM influences about 14% of global pregnancies, constituting about 18 million births each year [3].GDM is correlated with adverse effects in the mother and the newborn. Recent studies recognized a direct correlation between the stage of hyperglycemia in pregnant women and these adverse outcomes, where a linear association between glucose levels in mothers and different outcomes in neonates [4, 5]. Strict measures to control glycemia are necessary to decrease the gestational-associated and diabetes-complicated morbidity and mortality rates of mothers and fetuses [6]. Pregnant women influenced by GDM are at higher risk of developing several obstetric complications, including fetal growth abnormality, birth injury, shoulder dystocia, prematurity, and increased rate of Caesarean births. In addition, there is a high possibility for other implications for the health of mothers and infants in the future [7].

Pathophysiological aspects of GDM

Gestational diabetes mellitus is typically the consequence of impaired β-cell function associated with chronic insulin resistance throughout gestation. Consequently, both dysfunction of these pancreatic cells and insulin resistance in the tissues are among the significant contributions to the pathophysiology of GDM. In the majority of cases, these defects were obvious prior to pregnancy and growing with time—which indicates a possibly higher risk of T2DM development after pregnancy [8].Throughout healthy gestation, the maternal body is subjected to a sequence of physiological alterations to maintain fetal development. These involve modifications to the cardiovascular, hematologic, respiratory, renal, and metabolic systems. Insulin sensitivity is among the most vital adaptations in these metabolic systems. During the first and the early second trimester, elevated insulin sensitivity is observed because of comparatively elevated levels of estrogen, which stimulates glucose uptake within the fat tissues which, consequently, will secure fulfilling requirements for energy in later stages of pregnancy[9]. During the late second and early third trimesters, an efflux of local and placental hormones leads to raise resistance and reduce sensitivity to insulin, which collectively leads to raise the level of resistance within the maternal body. These hormones include estrogen, progesterone, cortisol, leptin, placental growth hormone, and placental lactogen. Consequently, a slight increase in the level of glucose in the blood occurs, which is transferred across the placenta to provide nutrients to the developing fetus. Diabetes develops when the function of the maternal pancreas is inadequate to handle this elevated resistance to insulin [10].
Previous reports propose that sustainable homeostasis of glucose is achieved in gestational women by compensation mechanisms against these alterations. These mechanisms involve hyperplasia and hypertrophy of pancreatic β-cells, as well as the elevated release of insulin which is stimulated byglucose[11]. The influences of the placental hormones in this process are clearly observed within few days post-delivery when sensitivity to insulin is restored to its pre-gestation level[12].

Risk factors of GDM
The key risk factors behind the development of GDM include the history of previous GDM, family history of diabetes, BMI $\geq$ 25 kg/m^2, previous macrosomia, history of congenital anomalies, multiparity, PCOS, history of stillbirth, history of preterm, history of abortion, Age $\geq$ 25, and pregnancy-induced hypertension [13].

Diagnosis of gestational diabetes mellitus
Upon the diagnosis of GDM, physicians must take into consideration that the patients might possibly suffer from other cases. These include: 1) undiagnosed type 2 diabetes mellitus, 2) pre-gestational moderate and aberrant tolerance to glucose which is exacerbated during pregnancy due to elevated insulin resistance, 3) ordinary tolerance to glucose prior to pregnancy that is changed into an abnormal tolerance with progress of gestation, or 4) rare undiagnosed type 1 diabetes mellitus associated with pregnancy [14].

Screening for GDM
In accordance with the American Diabetes Association, GDM is a type of diabetes, the first diagnosis of which occurs in the second or third gestational trimesters and can be utilized to prospect pre-existing type 1 or type 2 diabetes mellitus [1]. Predisposition of women to GDM and its associated complications is affected by factors that include elevated prevalence of DM and genetic predisposition to metabolic syndrome. Thus, there is a need for universal screening and diagnostic methods. Women diagnosed with GDM usually have a higher risk to develop diabetes, mainly Type II. Thus, diagnosis of GDM is a significant public health issue [15].
With the advance of gestational time, risk of developing GDM, caused by insulin resistance mediated by placental hormones, becomes higher. Therefore, performing the test in the first and early second trimesters is possibly not useful in certain patients. This is also true for testing in the third trimester, when metabolic interferences can be present. Therefore, it is recommended to perform the GDM test at (4-28 weeks) of gestation [16].

Measuring blood glucose and testing for hyperglycemia have been, consequently, considered as the only recommended diagnostic measurements for diabetes. Early diagnostic criteria depend on the results of the oral glucose test, while later analysis of glucose in the blood of fasting subjects has also become suitable [17]. Previous to 2010, glucose test was the adopted measurement of diabetes by almost all diabetes-related societies. Nevertheless, many clinical laboratories have been utilizing the HbA1c test during the recent years [18].

a- Glucose measurement

- Fasting blood glucose test

Measurement of blood glucose in fasting individuals is commonly accepted as one of the criteria of the diagnosis of diabetes. The test has advantageous features, as it is of low-cost and performed on automated equipment that are globally available in nearly all laboratories [19].

- Oral glucose tolerance test

The oral glucose tolerance test (OGTT) has been for years the classical analysis to estimate how effective is the body in metabolizing glucose. An elevation in glucose level after a meal typically occurs before that usually occurring after fasting. Consequently, postprandial glucose can sensitively predict the risk for the development of diabetes, and is also considered as an early sign of glucose homeostasis impairment [20]. The OGTT has been utilized as the test of choice for the diagnosis of DM. However, the earlier decades witnessed the utilization of controversial standards to diagnose GDM, while a variety guidelines have been suggested [1].

As of 2013, the World Health Organization stated the importance of GDM diagnosis in pregnant women at anytime upon the discovery of one or more of the cases listed below:

- Fasting blood glucose 92–125 mg/dl (5.1–6.9mmol/L)

- 1h blood glucose of 180 mg/dl (10.0mmol/L), following a 75 gm oral glucose load; 2-hour blood glucose of153–199 mg/dl(8.5–11.0mmol/L) following a 75 gm oral glucose load[21].The guidelines of the UK National Institute for Health and Care Excellence are dependent on these criteria; nevertheless, these guidelines included the recommendation that the cut-off value for fasting blood glucose should be lower [22]. The International Association of the Diabetes in Pregnancy Study Group (IADPSG), after publishing the outcomes of the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study which included approximately 25,000 pregnant women, advocated new criteria for the diagnosis of GDM. These criteria also depended on 2 h 75 gm OGTT; however lower thresholds of fasting blood glucose were adopted. GDM is considered as being existent when one or more outcome are changed [23]. In accordance with the American Diabetes Association, GDM can be diagnosed by utilizing the one-step 2 h, 75 gm OGTT and applying the similar threshold diagnostic guidelines of IADPSG. Alternatively, the two-step strategy (1 h, 50 gm OGTT) can be adopted, then a 3 h, 100 gm OGTT is performed for subjects with positive test results [1].

b- Glycated hemoglobin (HbA1c) measurement

Hemoglobin A1C is produced when glucose non-enzymatically binds to the *N*-terminal valine moiety of the β-chain of hemoglobin. Erythrocytes can live for up to120 days. Therefore, HbA1C indicates long-term glycemic contact, which represents the normal glucose level along the previous 8–12 weeks [24].HbA1c is a single, non-fasting test which is known by its simplicity and might provide insight into gestational diabetes [25].

American diabetes association has consented glycated hemoglobin (HbA1c) as a test for diagnosing DM [26]. Currently, there are many certified methods/instruments that are accessible for HbA1c measurement. These approaches are mostly dependent on four types of tests: enzymatic assays, affinity chromatography, ion-exchange chromatography, and immunoassays. The International Federation of Clinical Chemistry Working Group on HbA1c Standardization developed a reference system for HbA1c [27]. In spite of all these global efforts, several situations may affect HbA1c values, including the existence of a variant Hb values, in addition to anemia and uremia [28]. In recent times, an increased association between

race/ethnicity and HbA1c results was increased. The values were found to be elevated in Blacks, Latinos and Asians in comparison with those in White persons. Such considerations added reasons for the restriction of the utilization of HbA1c in certain cases [29].
Results from the HAPO study demonstrated that the outcomes of HbA1c test, such as those of glycemia levels, were frequently associated with adverse effects. In addition, elevated values of maternal HbA1c were found to be associated with higher incidence of these adverse effects [30].
Throughout gestational time, hemoglobin level varies in order to adapt to the elevated blood volume in mothers and the iron requirements of the fetus. In addition, this period is characterized by a decline in the concentration of fasting blood glucose [21]. As a result, HbA1c concentration is higher during pregnancy. Because of these factors, various reference values HbA1c are adopted during pregnancy and the interpretation these values must take these factors into consideration [31]. Furthermore, significantly reduced values of HbA1c are recorded during the first trimesters. Also, the determination of trimester-specific reference values of HbA1c throughout pregnancy is of great importance [32]. HbA1c levels were demonstrated to differ from 20 mmol/mol to 42 mmol/mol in gestational women depending on the studied populations [33].
HbA1c level in gestational women with GDM was demonstrated to be significantly elevated as compared to that in gestational women without GDM [25]. The pathophysiology of GDM is different from that of DM. Nevertheless, GDM can be employed as an indicator of elevated risk of type 2 DM in the infant life. Pregnancy is described as a situation of resistance to insulin. Hormones released by the placenta, including corticotropin-releasing hormone, growth hormone, progesterone, and placental lactogen, collectively cooperate to raise insulin resistance in pregnant women. This will assist to maintain sufficient provision of nutrients necessary for fetal development. Where the pregnant women have insufficient pancreatic function to manage with this rising insulin resistance, diabetes follow [10].
Before pregnancy, the process of metabolic control in diabetic women aims at keeping HbA1c levels around the standard range [34]. The elevated HbA1c levels in the third-trimester are correlated to the higher risks of macrosomia, preeclampsia, and stillbirth. These factors resulted in the postulation that a lower level of HbA1c during pregnancy should be targeted as compared to the value in non-pregnant women, in order to avoid the adverse effects [35, 36, 6].
Even though the global institutes recognize OGTT as the diagnostic tool to assess GDM, the participant must be fasting for minimum 8h. In addition, the test requires the provision of health care providers, it lacks reproducibility, and needs a minimum of 2 h for sampling where at least two blood samples are collected [30]. In contrast, HbA1c can be performed without fasting and could be of more relief for pregnant women as compared to OGTT. It also has higher reproducibility lower biological variance, and higher analytical stability in comparison with glucose tests [18]. However, because of some analytical and physiological factors that may overlap with HbA1c values, it has so far not been adopted as a diagnostic measurement for GDM [1].

Complications for mother and fetus

Being diagnosed with GDM poses several essential implications for both the mother and her baby. As for the complications in the fetus, GDM is related with a higher risk of macrosomia, hypoglycemia, respiratory distress syndrome [37], polycythemia, hypertrophic cardiomyopathy, and hyperbilirubinemia. Such complications have been demonstrated to occur with different frequencies [38].

As for the complications in the mother, higher possibility of the development of hypertension and preeclampsia are the main concerns of antepartum morbidity related to women with GDM (39). Nevertheless, GDM is considered as a substantial risk factor for the development of permanent diabetes in the future (40% in 10 subsequent years)[40]and GDM in the following pregnancies (35%). These risks become higher with the increase in maternal age and weight (41).

2. CONCLUSIONS

Pregnancy is a condition that is characterized by elevated rates of metabolism, during which it is extremely important to maintain glucose homeostasis. When a pregnant woman is diagnosed with hyperglycemia, this condition is as GDM. Diagnosis of GDM is necessary for both maternal and fetal health. The remarkable development related to the fields of medical and midwifery care has caused improvement in the pregnancy complications However, other factors such as efficient screening, diagnosis, and treatment of GDM would not merely avoid adverse effects to mothers and fetuses, but also avoid their development of diabetes mellitus later in life. A post-partum follows up and monitoring must be performed for mothers who have history of GDM in order to test for risks of having type 2 diabetes mellitus. This measure would assist in reducing the complications of diabetes and preventing conception of the successive pregnancies in the presence of uncontrolled hyperglycemia.

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