Classifications of Diabetes in pregnancy

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Abstract.

Any degree of glucose intolerance that begins or is first noticed during pregnancy is known as gestational diabetes mellitus (GDM). GDM is usually occur due to advanced mother age, higher body mass index (BMI), type 2 diabetes in the family, and prior GDM. As well as, high parity, short stature, low birth weight, the thalassemia trait, polycystic ovarian condition, and previous delivery of a macrocosmic child, consuming a lot of saturated fat, Caesarean section, pregnancy-related high blood pressure, stillbirth, smoking, and many pregnancies. Macrosomia and the pathophysiological effects of foetal hyperglycemia and hyperinsulinism are the main causes of foetal problems, which may arise e.g. (birth injuries, hypoglycemia, hypertrophic cardiomyopathy, polycythemia and hyperbilirubinemia, infant respiratory distress, premature birth, and congenital deformities). GDM maternal complications include (Pre-eclampsia, Pre-term labor, Polyhydramnios, labour dystocia, traumatic vaginal delivery, caesarean delivery, postpartum hemorrhage, and infections). Although GDM is worldwide issue, the exact pathophysiology of the condition is still unclear.

Keywords: Diabetes; Pregnancy; Macrosomia; GDM; Complications

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List of abbreviations:

ADA: American diabetes mellitus.

GDM: gestational diabetes mellitus.

ACOG: the American College of Obstetricians and Gynecologists.

DM: diabetes mellitus.

FBG: fasting blood glucose.

WHO: world health organization.

HAPO: The Hyperglycemia and Adverse Pregnancy Outcomes.

OGTT: oral glucose tolerance test.

IADPSG: International Association of the Diabetes and Pregnancy Study Groups.

BMI: body mass index.

GLT: glucose load test.

1. Introduction

A set of metabolic conditions known as diabetes mellitus are defined by hyperglycemia brought on by deficiencies in insulin secretion, action, or both. Long-term harm, dysfunction, and failure of numerous organs, including the eyes, renal system, nervous system, cardiac muscle, and vessels, are linked to the long-lasting hyperglycemia of diabetes.[1]

The development of diabetes is influenced by a number of pathogenic mechanisms. These can range from defects that lead to resistance to insulin action to autoimmune destruction of the beta cellsin the pancreas with subsequent insulin insufficiency.[2,3]

Insulin secretion and action deficiencies sometimes occur in the same patient, and it is frequently difficult to determine which aberration, if either alone, is the main

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contributor to the hyperglycemia. Frequent micturition, polydipsia, weight loss, occasionally coupled with polyphagia, and hazy vision are signs of severe hyperglycemia. Along with prolonged hyperglycemia, growth impairment and susceptibility to specific infections are possible side effects.[1]

2. Classifications of Diabetes Mellitus[1,4]

1. Type one diabetes: (related to autoimmune -cell damage, typically resulting in total insulin insufficiency, including adult-onset latent autoimmune diabetes).
2. Type two diabetes: (varying from largely an insulin secretory malfunction with insulin resistance to predominantly insulin resistance with relative insulin insufficiency).
3. Other specific types of diabetes e.g.,genetic dysfunction of beta cells, genetic issues that affect insulin action, Endocrinopathies, exocrine pancreatic diseases, induced by drugs, chemicals, or infections.
4. Gestational diabetes mellitus: pregnancy-related diabetes discovered in the second or third trimester but not before becoming pregnant.

2.1. Diabetes diagnostic criteria:[5,6]

- HbA1C is ≥6.5 % or
- Fasting blood glucosemore than 126 mg/dl (7.0 mmol/l). In order to fast, one must refrain from eating for at least 8 hours. or
- During an oral glucose tolerance test, with blood glucose level after 2 hoursmore than 200 mg/dl (11.1 mmol/l). The World Health Organization (WHO) recommends carrying out the test using a glucose load that is equivalent to 75 g of anhydrous glucose dissolved in water. or
- A random plasma glucose reading of more than 200 mg/dl (11.1 mmol/l) in a patient with the typical signs and symptoms of elevated blood glucose levels or hyperglycemic crises.

In presence of equivocal hyperglycemia, the first three criteria should be verified by retesting.

2.2. Diagnosis of GDM

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study, which encountered about (23,000 pregnant women) is a global epidemiologic research, showed that even within ranges formerly thought to be ordinary for pregnancy, the hazard of adverse maternal, foetal, and neonatal outcomes constantly become higher as a function of maternal glycaemia at 24-28 weeks. There was typically no risk threshold for problems. The diagnostic cutoff for GDM have undergone comprehensive review because of these findings. Table1[5,7]

One-step strategy:

The revised guidelines for diagnosing GDM were created by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG), an international panel comprising representatives from several obstetrical and diabetes organizations, including the American Diabetes Association. All women who are not known to bediabetic should complete a 75-g OGTT between 24 and 28 weeks of pregnancy, the association advised. Furthermore, the association established diagnostic cut values for fasting, 1-, and 2-hour plasma glucose readings that represented odds ratios for unfavorable outcomes of at least 1.75 in comparison to women in the

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HAPO study who had mean glucose levels.[8]

Due in large part to the fact that only one aberrant number, rather than two, is required to diagnose GDM, these revised criteria will considerably increase the prevalence of the disease. The goal of these adjustments to the diagnostic criteria is to improve the gestational outcomes for women and their unborn children in light of the alarming global rise in the prevalence of obesity and diabetes.[9,10]

Two-step strategy:

A meeting on consensus formation was held by the NIH in 2013 to discuss diagnostic standards for the diagnosis of GDM. Representatives from obstetrics and gynecology, pediatrics, feto-maternal medicine, biostatistics, diabetes research, and other interconnected professions were included on the 15-member panel. The panel advised a two-step screening process consisting of a 1-h 50-g GLT and a 3-h 100-g OGTT for individuals who tested positive. The American College of Obstetricians and Gynecologists (ACOG) suggests that 1-h 50-g GLT be performed at any of the standard cutoffs of 130, 135, or 140 mg/dL. A systematic review for GLT cutoffs of 130 mg/dL (7.2 mmol/L) and 140 mg/dL (7.8 mmol/L) were compared by the United States Preventive Services Task Force. The lower cutoff produced sensitivity of 88-99% and specificity of 66-77%, while elevated cutoff produced 70-88% and 69-89%.sensitivity and specificity respectively. There are few data on a 135 mg/dL cutoff.

Clinical trial data absence that demonstrating the advantages of the strategy of one step and the potential drawbacks of identifying a sizable population of women with GDM, including the pregnancy medicalization with increased health care use and expenses, were important considerations for the NIH panel. Furthermore, screening using a 50-g GLT does not necessitate fasting, making it simpler for many women to complete. Shoulder dystocia, large-for-gestational-age births, and newborn macrosomia rates are all decreased when higher-threshold maternal hyperglycemia is treated, but small-for-gestational-age birth rates are not increased. The two-step technique is currently supported by ACOG; however, one high value, rather than two, may be utilized for the diagnosis of GDM, which undoubtedly increases the incidence of GDM.11

Table 1Diagnosis of GDM

One-step strategy
Perform a 75-g OGTT with plasma glucose measurements while the patient is fasting, at 1 and 2 hours, and between weeks 24-28 of pregnancy in women who have never been given a diabetes diagnosis.
The OGTT needs to be done in the morning following a fast of at least 8 hours.
When any of the following plasma glucose readings are met or surpassed, GDM is diagnosed:
• Fasting: 92 mg/dL (5.1 mmol/L)
• first hour: 180 mg/dL (10.0 mmol/L)
• at second hour: 153 mg/dL (8.5 mmol/L)
Two-step strategy
Step 1: Conduct a 50-g GLT (non-fasting) at 24-28 weeks of gestation in women who have never

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been given a diabetes diagnosis, with a 1-hour plasma glucose measurement.
If the measured blood glucose atone hour after the load is ≥130, 135, or 140 mg/dL (7.2, 7.5, or 7.8 mmol/L, respectively), advance to a 100-g OGTT.
Step 2: The patient should be fasting during the 100-g OGTT.
When at least 2 of the following 4blood glucose levels (measured fasting and at 1, 2, and 3 h during OGTT) are happened or surpassed, it is determined that the patient has GDM. (Carpenter-Coustan criteria)
• Fasting: 95 mg/dL (5.3 mmol/L)
• first hour: 180 mg/dL (10.0 mmol/L)
•second hour: 155 mg/dL (8.6 mmol/L)
• third hour: 140 mg/dL (7.8 mmol/L)

3. Complications of GDM

3.1. Maternal complications

There are many complications of GDM e.g. (preeclampsia, pre-term labor, polyhydramnios, shoulder dystocia, and infections) mostly related to hyperglycemia and complications of macrosomia.[7]

1. Preeclampsia as women with uncontrolled hyperglycemia are two times more likely to develop preeclampsia and gestational hypertension. The risk of preeclampsia increases by about 8 fold from the lowest to the highest category of maternal BMI, and higher BMI is also linked to greater risk. In addition, preeclampsia frequency rises as OGTT plasma glucose levels rise (fasting, 1-hr and 2-hr).[12–14]
2. Pre-term labor:About 20% of diabetic women experience spontaneous preterm birth. Preterm birth risk is higher in women with type-1 diabetes. Polyhydramnios, infections, and iatrogenic factors, such as in patients with vasculopathies and pre-eclampsia, are likely causes.[15]
3. Polyhydramnios: is more likely to occur in femaleswith gestational diabetes as well as pregestational diabetes. Rather, the patient's glycemic condition needs to be reviewed if polyhydramnios appears in the third trimester. Numerous factors, including as excessive amniotic fluid osmotic pressure, fetal hyperglycemia, fetal polyuria, and related congenital abnormalities, have been linked to its incidence in diabetes. Postpartum hemorrhage is a well known complication due to polyhydramnios.[12]
4. Labor dystocia and caesarian delivery: Obstructed labour, perineal tears, vaginal abrasions, and protracted labour are among risks associated with vaginal delivery of a macroscopic baby. Due to macrosomia, the chance of a caesarean section is much higher in people with diabetes.[13,15,16]
5. Infections: Women with diabetes should undergo a per-speculum examination, a urine microscopic examination, and a urine culture because they are more likely to acquire a urinary tract infection and

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a vaginal fungal infection. This is especially important when blood glucose levels are not under control. Infection of the post-Caesarean wound is another possibility.[12]

3.2. *Fetal complications*

The dangers of maternal GDM to the fetus and newborn are associated with macrosomia as well as additional pathophysiological effects of foetal increased glucose and insulin levels that have been hypothesized.[13,16,17]

1. Preterm birth: The HAPO study discovered a constant linear association between preeclampsia, a condition that increases the risk of preterm birth, and the results of glucose tolerance testing.[18]
2. Polycythemia, and hyperviscosity: A venous hematocrit of more than 65% indicates polycythemia, which is caused by foetal hypoxia, which also triggers erythropoiesis.[19]
3. Neonatal respiratory distress: that is mostly occur due to risk of premature birth.
4. Birth injuries: Even in the absence of maternal GDM, macrosomia poses a risk for shoulder dystocia and the birth injury it causes; the most frequent injuries are Erb's paralysis, clavicle fractures, and humerus fractures. The likelihood of suffering a birth injury rises with birth weight, according to a sizable cohort study conducted in the United States: odds ratio (OR) =2.4.[20,21]
5. Hypoglycemia: Temporary hyperinsulinism that inhibits the typical counter regulatory responses (gluconeogenesis, lipolysis, glycogenolysis, and fatty acids beta-oxidation) to loss of glucose supply from the placenta and rises glucose useperipherally, is the mechanism for hypoglycemia in neonates born to GDM mothers. Prefeed blood glucose monitoring, early, and multiple enteral feeding are the cornerstones of the prevention and treatment of hypoglycemia (preferably breast-feeding). About 5% of newborns will experience hypoglycemia that requires intravenous glucose therapy since it cannot be treated with enteral feeding alone.[22]
6. Hypertrophic cardiomyopathy: The hypertrophy andproliferation of cardiac myocytes can be caused by foetal increased insulin levels in conjunction with the naturally higher expression and affinity of foetal insulin receptors[23]. Together with the naturally greater expression and affinity of foetal insulin receptors, foetal hyperinsulinism can lead to the mulitplication and hypertrophy of cardiac muscle cells.[24]
7. Congenital malformations: Diabetic embryopathy is well recognized complications in early pregnancy that may lead to congenital cardiac diseases e.g. (tricuspid atresia, transposition of great vessels, patent ductus arteriosus, ventricle septal defect, truncus arteriosus, and dextrocardia. Caudal regression syndrome, neural tube defect, vertebral anomalies, duodenal atresia, cleft palate, and renal agenesis. On the other hand, hyperglycemia in second and third

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trimester may lead to diabetic fetopathy that leads to polycythemia, hypoglycemia, hypoxia, respiratory distress, hypertrophic cardiomyopathy and macrosomia.25,26

4. Pathophysiology of GDM:

A diabetogenic condition characterizes pregnancy. While 95% of pregnant women are able to maintain normal glucose tolerance, 1-6% of them may likely acquire gestational diabetes. In fact, normal pregnancy is accompanied by temporary increases in insulin resistance that are offset by an increase in insulin secretion. The best illustration of physiological insulin resistance is pregnancy. Roles of various tissues, Functional anomalies of insulin secretion, and environmental effects and nutrition are all part of the pathophysiology of GDM, however, the complete GDM pathogenesis is not wellunderstood.[27,28]

4.1. Roles of tissues:

1. Role of adipose tissue: adipocytokines were produced by adipose tissue. These adipocytokines function as hormones and have been linked to the control of gestational resistance of insulin and maternal metabolism[29,30]. The intrauterine environment is also known to create adipocytokines, including as adiponectin, leptin, interleukin six (IL-6) tumor necrosis factor alpha (TNF-α)[31], as well as visfatin[32], resistin,ANGPTL-8, nestatin-1, afamin, adropin, and apelin.[33–38]There is evidence that one or more of these adipokines[39], such as leptin and TNF-α, may disrupt signaling of insulin and result in resistance of insulin. Particularly TNF-α has the ability to reduce sensitivity of insulin.[40]
2. Genotyping: The presence of a first-degree relative who currently has GDM or another form of diabetes suggests that both hereditary and (non-genetic) environmental factors contribute to the familial aggregation of GDM. The polygenic risk for GDM may be influenced by genetic polymorphism at or close to the genes for insulin receptor substrate one, hepatocyte nuclear factor one*alpha*, mannose-binding lectin, *β*3-adrenergic receptor, plasminogen activator inhibitor 1 insulin receptor, insulin receptor substrate 1[41], tRNALeu mitochondrial, and sulfonylurea receptor 1.[42–44]
3. Subcellular studies: The regulation of intracellular and blood glucose levels depends on signaling of insulin. Binding of insulin to the insulin receptors (IR) triggers cytoplasmic tyrosine phosphorylation of the receptors and tyrosine phosphorylation of IR substrates, activating the insulin-signaling cascade.This enables IRS to interact with later-stage effectors like phosphatidylinositol-3-kinase (PI3-K). Through the induction of end point events like the translocation of the glucose transporter (GLUT)-4, they have the capacity to control uptake of glucose.[41] Therefore, they play a crucial role in the intracellular glucoselevels regulation. A crucial stage in preserving euglycemia in people is the glucose uptake through cells as a result of the

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insulin signaling cascade. In order for the cell to absorb glucose, GLUTs must move from the cytoplasm to the cell membrane. While GLUT-4, which is present in a lesser degree in the placenta, is sensitive to insulin- GLUTs, its expression is inversely correlated with the extracellular glucose content there. In peripheral tissues, poor glucose absorption causes resistance of insulin and is typically associated with a decline in GLUT-4 transporter in diabetes conditions. It is possible to speculate that GLUT-1 is the primary GLUT used in GDM patients when insulin signaling is compromised. [45,46]

4. Autoimmunity: GDM has recently been associated with the inflammatory cytokines up-regulation like TNF-*α,* IL-10,IL-6, and leptin in comparison to control women, as well as the down-regulation of Th1 (pro-inflammatory T-helper cells) cytokines like adiponectin, interferon-*γ* (IF-*γ*), and IL-2. The immune-metabolic network that exists in pregnant people is further complicated by the placenta's ability to generate a wide range of cytokines. This suggests that the development of a low-grade inflammatory response during the third trimester of pregnancy may be influenced by placental cytokine production.[47,48]
5. The feto-placental unit role: Progesterone and pregnenolone are produced by the placenta from cholesterol. A portion of the progesterone enters the foetal circulation and serves as a substrate for the adrenal glands' production of corticosterone and cortisol. As the pregnancy progresses, these hormones gradually rise due to the anti-insulin impact of the pregnancy. It has been demonstrated that the main hormone thought to be responsible for the decline in glucose tolerance in a typical pregnancy is an increase in cortisol levels. The level of human placental lactogen (HPL) increases by about ten folds during the second part of pregnancy. In order to give the mother a different source of fuel so that the fetus's supply of amino acids and glucose can be preserved, it increases lipolysis, which results in elevated free fatty acids amount that are circulated. As a result, the insulin-directed entry of glucose into cells is directly hampered by the rise in free fatty acid levels. As a result, HPL is regarded as a powerful antagonist to the effect of insulin during pregnancy. Pituitary growth hormone and placenta growth hormone are distinct by 13 amino acids.[49,50]

4.2. Functional abnormalities of insulin secretion:

1. Abnormalities of Fasting Insulinemia: The first functional abnormality is the increase in fasting insulin. Indeed, fasting insulin levels increase progressively during pregnancy. In general, the rates are doubled between the first and the last trimester of gestation. Some researchers have shown that plasma insulin fasting were

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identical among normal-tolerant pregnant females and in gestational diabetes women. Others noted that patients with plasma insulin were higher gestational diabetes. These differences are partly explained by the fact that the populations studied were not comparable on the Body Mass index (BMI).[51]

2. Dynamic abnormalities of insulin secretion: Hyperinsulinism is reactionary, predominant in a postprandial situation and it is reversible. After oral hyperglycemia (OGTT), insulin levels in pregnant women are also higher. However, the insulin response in glycemic stimulus unit (insulin index) was significantly higher in euglycemic women than gestational diabetic women. Other researches have shown that the insulin secretion in second phase is increased similarly in both groups. It had been shown that despite the increase in Insulinemia, the sensitivity of **β**-cells to glucose (allowing the early peak of insulin secretion) is decreased.[52]

4.3. *Environment and diet effect:*

It has been established that the body mass index (BMI) before pregnancy has a bigger role in the development of GDM. Additionally, maternal obesity increases the risk of developing maternal GDM and significantly increases the likelihood that future generations of kids would have glucose intolerance, insulin resistance, and obesity. The majority of the weight acquired during pregnancy is made up of fat tissue. Starting in the middle of pregnancy, adipose tissue proliferation is frequently accompanied by a state of relative insulin resistance. Regimenspoor in carbohydrates and rich in fat may worsen maternal insulin resistance and newborn obesity, contributing to the pathogenesis of GDM.[53]

5. Conclusion:

GDM is a metabolic disease that is relatedto increase mortality and morbidity for both women and the baby due to macrosomia, birth injuries, pre-eclampsia, postpartum hemorrhage, and infections. Risk factors for developing GDM include previous GDM history, elevated BMI, increased maternal age, history of diabetes in the family, and a history of macrosomicneonates.The absence of universal screening criteria leads to different screening criteria with different diagnostic cut points that leads to widely difference in incidence.The full pathophysiology of GDM should be completely recognized as well for better diagnosis and treatment.

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