Editorial

Gestational Diabetes Mellitus Diagnosis—A Worldwide Controversy

There is continuous ongoing worldwide controversy relating to definition, screening, and diagnostic criteria for gestational diabetes mellitus (GDM). Even after several international workshops, criteria for diagnosis are still more controversial. The ongoing controversy is part of the several mysteries being scooped out to arrive at a hypothesis and essential changes in intrauterine milieu during pregnancy that may later on lead to DM II in women and/or in their offsprings.

"GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy."[1]

PATHOPHYSIOLOGY OF GDM

Pregnancy is diabetogenic due to insulin resistance due to the production of anti-insulin hormones like human chorionic somatomammotropin (HCS), cortisol, estriol, and progesterone. Another reason is increased insulin destruction by kidneys/plasma insulinases. Pancreatic beta cell dysfunction may be caused by genetics, autoimmune disorders, and chronic insulin resistance. In late pregnancy, maternal hepatic glucose production increases by 15–30% to meet fetal demand. Gluconeogenesis in fetus uses alanine and other amino acids depriving mother of major the glucogenic source. Combination of: glucose intolerance, hyperglycemia, and β-cell dysfunction lead to adverse maternal and neonatal outcomes.[2]

ADVERSE MATERNAL AND PERINATAL OUTCOMES

- Maternal risk factors—during pregnancy—preeclampsia, during labor—induction of labor, operative intervention, labor complications, postpartum and beyond—recurrent GDM, type II diabetes later on in life.
- Fetal risk factors—congenital—cardiac, central nervous system (CNS), fetal programming, large for gestational age, macrosomia. Neonatal complications—prematurity, perinatal asphyxia, respiratory distress, metabolic complications, polycythemia, hyperviscosity, hyperbilirubinemia, and cardiomyopathy. Long-term outcomes—obesity, DM I, DM II, and metabolic syndrome.[3]

There are various controversies regarding GDM:

- What is the definition of GDM?
- Whether to screen or not screen for GDM. Whether screening should be selective or universal.
- What is the best diagnostic criterion for GDM? What is the best screening technique—FBS, RBS, oral glucose tolerance test (OGTT), HbA1c?

DEFINITION OF GDM

The interesting take is while the diagnostic criterion for DM is clear, the criterion for diagnosis of GDM differs in different countries. Many proposed definitions with change of terminology have changed over the years, and its existence as a clinical entity has also been questioned by various authors, e.g., Hunter and Milner[4] stated that GDM is a diagnosis still looking for a disease. Its diagnosis is an ongoing controversy worldwide. The fact that the definition of GDM continues to be updated reflects the many uncertainties there are, with respect to GDM, being defined as a disease entity, and there is a high need for a uniform and standardized definition to diagnose GDM in a population that accurately reflects its associated risks in both mother and child.

SCREENING FOR GDM

National guidelines for Diagnosis and Management of Gestational Diabetes Mellitus 2010, under national health mission, Ministry of Health and Family Welfare, Govt. of India, states that between the ages of 25 and 39 years, there are 54 million prediabetic women, and 22 million diabetic with a prevalence of 10 to 14.3%.[5]

The incidence of GDM is expected to increase 20%, i.e., 1 in every 5 pregnant women is likely to have GDM. In a field study in Tamil Nadu performed under the Diabetes in Pregnancy—Awareness and Prevention project, of the

4,151, 3,960, and 3,945 pregnant women screened in urban, semi-urban, and rural areas, respectively, the prevalence of GDM was found to be 17.8%, 13.8%, and 9.9% in urban, semi-urban, and rural areas.[6]

If not managed on time, this can pose severe risk both to the mother and the neonate. Tamil Nadu is the only state which has implemented the universal screening and management of GDM for pregnant women and evidence clearly indicates its positive outcome. The prevalence of GDM has been observed across the country; however, a consistent understanding, standard operating procedures (SOP) for identification, and its management vary from state to state or even within the state. Tamil Nadu endorses universal screening of all pregnant women at 12 to 16 weeks gestation or at first antenatal visit. If the reports are normal, the next screening is done at 24 to 28 weeks gestation and later at 32 to 34 weeks.[4]

Ministry of China recommends using the fasting plasma glucose (FPG) test at first antenatal visit to rule out preexisting diabetes and OGTT between 24 and 28 weeks gestation for GDM diagnosis. Fasting glucose levels decline between early pregnancy and mid-trimester, therefore using the same cutoff value to diagnose GDM in early pregnancy and at 24 to 28 weeks may be inappropriate as shown in several studies in China.[7]

Screening is essential in all pregnant women as Indian women have 11-fold increased risk of developing glucose intolerance during pregnancy compared to Caucasian women.[8]

Screening for GDM is usually done at 24–28 weeks of gestation because insulin resistance increases during the second trimester and glucose levels rise in women who do not have the ability to produce enough insulin to adopt this resistance.

DIAGNOSTIC CRITERIA FOR GDM

There is no consensus on the diagnostic criteria for GDM. The three main criteria used worldwide and in India are given below in Table 1.

WHO 1999[9] and Diabetes in Pregnancy Study Group in India (DIPSI) 2010 criteria are almost similar, but while the former advocates for a fasting plasma glucose, the later advocates for FPG irrespective of the last meal as advocated by Seshiah et al.[10] Though studies have not recommended single test OGTT due to low sensitivity,[11] the advantage of a single test is that second visit is not necessary for diagnosis, it is more acceptable, it gives least disturbance to patients, and it is economical.

Thus, diagnosing GDM becomes important to prevent and manage/treat gestational diabetes. WHO 2013 criteria[12] based on HAPO study[13] were adopted internationally wherein the cutoffs used here were somewhat arbitrary as no infliction point in the curve of the relationship between glucose values and outcomes depicts it as a biological relationship rather than a disease.[12]

A recent study in North India also emphasized the need to screen all pregnant women for GDM. This study found out the prevalence of GDM in 5,000 North Indian pregnant women by using both WHO 1999 and WHO 2013 criteria (International Association of Diabetes and Pregnancy Study Groups (IADPSG)). The overall prevalence of GDM was 10.7% using the WHO 1999 diagnostic criteria. However, it increased to 32% when applying WHO 2013 criteria. The FPG measurements identified 94% of WHO 2013 GDM cases as opposed to 11% of WHO 1999 GDM cases. In contrast, 2 hour PG measurements identified only 13% of WHO 2013 GDM cases compared to 96% of the WHO 1999 GDM cases. Interestingly, this study saw a threefold increase in the prevalence of GDM using WHO/DIPSI vs IADPSG criteria. The relationship between FPG and PPG—not straightforward—defining GDM by the somewhat arbitrary WHO/modified Indian or IADPSG criteria identified different risk factors.[14]

GDM prevalence in North Indian women was found to be 32% using WHO 2013 criteria and appears to be inconsistent with the recently reported prevalence of 14.6% in South Indian women. Though the huge difference may be because of different genetic and cultural admixture of North vs South Indian women, this is unlikely to be the full explanation for the more than two-third difference in GDM prevalence between the studies.

Table 1: Diagnostic criteria for GDM using OGTT

	Glucose (g)	*FPG mmol/L (mg/dL)*	*1 hour PP mmol/L (mg/dL)*	*2 hour PP mmol/L (mg/dL)*
WHO Criteria 1999[9]	75	7.0 (126)	NR	>7.8 (140)
WHO Criteria 2013 (IADPSG)[12]	75	5.1 (92)	10.0 (180)	8.5 (153)
DIPSI 2010[5]	75	7.0 (126)	NR	>7.8 (140)

Defining GDM by somewhat arbitrary WHO 1999/DIPSI vs WHO 2013 criteria identified different distinct risk factors. Applying WHO 2013 criteria, GDM would affect more than one-third of all pregnant women in North India. The question arises whether these criteria can be endorsed uncritically in India. It is recommended to await further significant outcome data before introducing the proposed WHO 2013 criteria in India.

There are also different cutoff values in different countries and therefore it is very difficult to compare the data. The initial IADPSG recommendation was to use a single increased OGTT value, but 2013 National Institutes of Health (NIH) sponsored consensus development conference recommended a two-step approach. The diagnostic criteria differ in different countries because there is no definite inflection point for risk of pregnancy outcomes with increasing glucose. Organizations worldwide differ in the level of concern for a wide range of different pregnancy outcomes as examined by the HAPO study.

While association between plasma glucose levels and future risk of diabetes complications determines the diagnostic criteria in nonpregnant women, as many a large scale studies have shown. But, in GDM, immediate perinatal outcomes in hyperglycemic pregnancies are unclear and do not have a clear threshold. Maternal glucose concentration contributes significantly to low for gestational age (LGA) and macrosomia and other perinatal complications, but they are not solely dependent on maternal glucose levels.

In countries like India, where women are comparatively short statured, the LGA babies may produce significant adverse perinatal outcomes—a lower postload glucose threshold to diagnose GDM may be more appropriate.

GDM defines an unhealthy state of hyperglycemia that develops in response to an otherwise normal physiological adaptive insulin resistance state during pregnancy. However, the exact plasma glucose levels differentiating the unhealthy GDM state from a normal pregnancy is unknown, and relies on arbitrary cutoff criteria based on associations with adverse health outcomes in mother and child. The normal hormonal and physiological changes during pregnancy and difficulties in assessing long-term health outcomes associated with GDM in mother and child is a further complicating factor. Ethnic differences play a major role in defining GDM with Asian people developing diabetes including GDM at a lower degree of overweight compared with non-Asian people. There are a myriad of risk factors including family history of diabetes, age, BMI, diet, religion, illiteracy, and urban vs rural habitat influence risk of GDM, as well as impaired insulin secretion and action, in a hitherto unrecognized complex manner. Epidemiological data point toward Asia as the present and future capital of diabetes. Screening of women for gestational diabetes is a primary prevention tool for combating this diabetic epidemic hovering our nation.

Thus, different population-based study designs and results underscore the need for large prospective studies of GDM women and their offsprings in different ethnic groups to understand the quantitative and qualitative adverse health outcomes, diagnostic criteria, and ethnicity-based genetic risk factors as well as the need for tools and targets for prevention and treatment in a life-cycle perspective.

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