Editorial

Classification of hyperglycemia in pregnancy

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Gestational Diabetes Mellitus (GDM) is defined as carbohydrate intolerance with onset or recognition during pregnancy.[1] To standardize the diagnosis of GDM, the World Health organization (WHO), in 1998, recommended using a 2 hr 75 gm oral glucose tolerance test (OGTT) with a threshold plasma glucose of ≥7.8 mmol/L (140 mg/dl) at 2 hrs similar to impaired glucose tolerance (IGT) outside pregnancy.[2] In 2009, Diabetes in Pregnancy Study group India (DIPSI) recommended a "single test procedure" for diagnosing GDM with 2 hr PG ≥7.8 mmol/L (140 mg/dl) after 75 gm oral glucose administered in the fasting and non-fasting states without regard to the last meal timing.[3] Ministry of Health, Govt of India has approved this DIPSI procedure;[4] WHO, in 2013, while recommending International Association of Diabetes Pregnancy Study Group (IADPSG) criteria also recommends the single step procedure of DISPI for diagnosing GDM. These landmark developments in the diagnosis of GDM are discussed in this article.

International Association of the Diabetes and Pregnancy Study Groups criteria

International Association of the Diabetes and Pregnancy Study Groups (IADPSG) suggested a set of guidelines to diagnose GDM based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. In this HAPO study, population from India, China, South Asian countries (except cities of Bangkok and Hong Kong), Middle East and Sub-Saharan countries were not included. Thus, essentially HAPO study was performed in Caucasian population. The IADPSG recommends that diagnosis of GDM can be made when any of the following plasma glucose values meet or exceed: Fasting: 5.1 mmol/L (92 mg/dL), 1-hour: 10.0 mmol/L (180 mg/dL) and 2-hour: 8.5 mmol/L (153 mg/dL) 7 with 75g OGTT. The IADPSG also suggests: fasting plasma glucose (FPG) >7.0 mmol/L (126 mg/dL)/ A1C >6.5% in the early weeks of pregnancy is diagnostic of overt diabetes. Fasting >5.1 mmol/L (92 mg/dL) and <7.0 mmol/L (126 mg/dl) is diagnosed as GDM.[5]

Limitations of using fasting plasma glucose

IADPSG diagnostic procedure requires pregnant women to be in the fasting state, but attending the first prenatal visit in the fasting state is impractical in many settings.[5] The dropout rate is very high when a pregnant woman is asked to come again for the glucose tolerance test.[6] In all GDM, FPG values do not reflect the 2-hr PG with 75g oral glucose load, which is the hallmark of GDM.[7] Ethnically, Asian Indians have high insulin resistance and as a consequence, their 2-hr PG is higher compared to Caucasians.[8] The insulin resistance during pregnancy escalates further[9] and hence FPG is not an appropriate option to diagnose GDM in Asian Indian women. In this population by following FPG >5.1 mmol/L (92 mg/dL) as cutoff value, 76% of pregnant women would have missed the diagnosis of GDM made by the WHO criterion.[10] Asian and South Asian ethnicity are both independently associated with increased insulin resistance in late pregnancy. A diagnostic FPG was present in only 24% of those with GDM in Bangkok and 26% in Hong Kong.[11] WHO also states that in some ethnic groups, FPG values may not be adequate

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to diagnose GDM.[12] Yet other drawbacks of IADPSG criteria are, center-to-center differences that occur in GDM frequency and relative diagnostic importance of fasting, 1-hr and 2-hr glucose levels. This may impact strategies used for the diagnosis of GDM.[11] A cost-utility analysis found that screening based on IADPSG criteria was not cost-effective.[13] As per GRADE rating, a high level of evidence is wanting for IADPSG criteria.[12]

Limitations of using HbA1c

Glycated hemoglobin has also been suggested as a screening tool for GDM. However, it is not possible to perform this test on a mass scale in resource-challenged countries, not only because it is expensive, but also due to lack of technically qualified staff. The cost and standardization of A1C testing are issues for consideration.[4]

Limitations of using OGTT

OGTT is resource intensive in many health services especially in low-resource settings are not able to routinely perform OGTT in pregnant women. In these circumstances, many health services do not test for hyperglycemia in pregnancy.[14]

Psychological impact of using imprecise test

A recent study by Anderson *et al.*,[15] found a single fasting glucose measurement is insufficient for reliably ruling out GDM. If the diagnosis of GDM is made with FPG ≥5.1 mmol/L (92 mg/dl), many women and their families do not accept the diagnosis due to the emotional disturbance that it creates in them. The diagnosis of GDM may have a negative psychologically impact as per women's perception of their own health, especially in countries with a pre-existing tradition of gender discrimination.[16-19] At the same time, we do not have conclusive evidence to prove that diagnosis and interventions, based only upon isolated impaired fasting glycemia, will help improve the lives of these women or their unborn offspring. In our attempt at "primum succurere" (first, hasten to help), we may actually be defeating our oath- bound purpose of "primum non-nocere" (first do no harm).

The pragmatic approach

An antenatal woman expects a test, which would definitely help her, and her treating obstetrician, to decide if addition of intervention for hyperglycemia in pregnancy is necessary. This test based on the currently available evidences is to estimate plasma glucose after oral administration of 75g glucose and to diagnose GDM with 2-hr PG ≥7.8 mmol/L (140 mg/dl). Intervention in pregnant women with 2-hr PG ≥7.8 mmol/L (140 mg/dl), with medical nutrition therapy, or with insulin, results in newborn birth weight similar to normal glucose tolerant women.[20-23] The impact of this approach is shown in Table 1. All 100% women with GDM will be detected of whom 18 will have (large for gestational age) LGA infants and 9 could be prevented by treatment. Overall there would be 76 cases of LGA infants in the women without GDM or without detected GDM.

Cost effectiveness and availability of resources must also be considered in decisions related to the selection of criteria for local implementation.[24] However, several options are available, which could be considered including measuring FPG alone to either diagnose or screen for GDM, using nonfasting glucose testing, or using a glucose- challenge test (GCT). But for a pregnant woman, the request to attend in fasting state for a blood test may not be realistic, because of the long travel distance to the clinic in many parts of the world, and increased tendency to nausea in the fasting state.[14] Consequently non-fasting testing may be the only practical option.[14] This is rationale, because

Table 1: Both WHO 2013 and DIPSI criteria have the same performance*

Test	Testing protocol	Number of women with GDM detected and requiring treatment	Number of women with GDM missed	Number of LGA infants in women with detected GDM	Number of LGA infants prevented in women with GDM with treatment	Number of LGA infants in women without GDM or without detected GDM	Number (%) of women requiring an OGTT
*2013 WHO criteria	75 g OGTT diagnostic	100	Nil	18	9	76	1000 (100)
FPG only	FPG Diagnostic	52	48	10	5	84	Nil
FPG to rule GDM in or out	Screening FPG±75 g OGTT	95	5	17	8	77	500 (50)
Random glucose test	Screening RGT±75 g OGTT	60	40	11	6	83	240* (24)
*Nonfasting 75 g OGTT^	Diagnostic Non-fasting 75 g OGTT	100	Nil	18	9	76	1000 (100)
Glucose challenge test	Screening 1-h 50 g GCT±75 g OGTT	75	25	14	7	78	220* (22)

^: DIPSI criteria (The Table 1 is adopted from Reference No- 14), OGTT: Oral glucose tolerance test, WHO: World health organization, FPG: Fasting plasma glucose, GDM: Gestational diabetes mellitus, GCT: Glucose- challenge test, DIPSI: Diabetes in pregnancy study group India, RGT: Random glucose testing

Table 2: Hyperglycemia in pregnancy assessed with 75 g oral glucose load

Plasma glucose	In pregnancy	Outside pregnancy
2 hour≥200 mg/dl	Diabetes	Diabetes
2 hour≥140 mg/dl and ≤199 mg/dl	GDM	IGT
2 hour≥120 mg/dl and ≤139 mg/dl	GGI	–
2 hour<120 mg/dl	Normal	Normal

GDM: Gestational diabetes mellitus, GGI: Gestational glucose intolerance, IGT: Impaired glucose tolerance

after a meal, a normal glucose tolerant woman would be able to maintain euglycemia despite glucose challenge due to brisk and adequate insulin response. Whereas, in a woman with GDM who has impaired insulin secretion, her glycemic level increases with a meal and with glucose challenge, the glycemic excursion exaggerates further.[25,26] This cascading effect is advantageous as this would not result in false positive diagnosis of GDM. The WHO also states that random control trials (RCT) show the benefit of treating women with GDM who were identified primarily by "Post load" values. Therefore, there is no high quality evidence that women and their fetuses, benefit from treatment if only the fasting value is abnormal.[14] In pregnancy, elevated postprandial plasma glucose levels may be more predictive of the potential for fetal macrosomia and morbidity compared with fasting or prepandial values. Therefore, fasting glucose values alone do not predict in the need for pharmacological therapy.[27]

Classification of hyperglycemia in pregnancy

"Hyperglycaemia in pregnancy", is defined as "Maternal hyperglycemia less severe than that in diabetes mellitus, but associated with increased risks of adverse pregnancy outcome". Increasing maternal carbohydrate intolerance in pregnant women without GDM is associated with a graded increase in adverse maternal and fetal outcomes[28] implying that the fetal morbidity starts at a lower maternal glycemic level of 7.8 mmol/L (<140 mg/dl). The occurrence of macrosomia was continuum as 2-h plasma glucose increased from 6.7 mmol/L (120 mg/dl)[29,30] Franks *et al*.,[31] on long-term follow-up documented that the cumulative risk of type 2 diabetes at 24 years in the offspring born to mothers who had third trimester plasma glucose, 120-139 mg/dl was 19%. In the same study,[31] the cumulative risk was found to be 30% in offspring born to women who had 2-h PG >140 mg/dl. Hence, it may be prudent to label 2-hr plasma glucose value ≥200 mg/dl as diabetes, between ≥140 and ≤199 mg/dl as GDM and between ≥120 and ≤139 mg/dl as gestational glucose intolerance (GGI) [Table 2].

Our responsibilities to our patients and their offspring demand that all women should be offered "A Single Step Diagnostic Procedure" which is feasible, economical and evidence based to assess glucose intolerance in every pregnancy.

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