

# A perspective on testing for gestational diabetes mellitus

Sir,

Gestational diabetes mellitus (GDM) was until recently defined as any degree of carbohydrate intolerance with onset or first recognition during pregnancy.<sup>[1]</sup> Because this older definition includes women with diabetes who may not have been identified prior to pregnancy and because the line between morbidities associated with diabetes in pregnancy and gestational diabetes is blurred by this definition there have been fresh attempts at defining and classifying hyperglycemia during pregnancy. Recent consensus is that the term GDM should be restricted to hyperglycemia detected during routine testing in pregnancy (generally between 24 and 28 weeks) which does not meet the criteria of overt diabetes. Pregnant women with hyperglycemia meeting the criteria of diagnosis of diabetes in the nonpregnant state as per the WHO definition are classified as having diabetes in pregnancy.<sup>[2]</sup> Various diagnostic criteria and glucose cut-off values have been proposed by various organizations and professional groups to diagnose GDM.

Gestational diabetes mellitus represents a defect in pancreatic  $\beta$ -cell function both during and after pregnancy<sup>[3-5]</sup> and thus identifies a state of chronic  $\beta$  cell dysfunction, rather than the mere development of relative insulin deficiency in the face of rising insulin resistance during pregnancy.<sup>[6]</sup> The implication of this is that GDM is a stage in the evolution of type 2 diabetes mellitus (T2DM) in women and a harbinger of increasing prevalence of diabetes and obesity in the population.<sup>[7]</sup> Indeed, women with a history of GDM are at increased risk of future diabetes, predominantly type 2 diabetes, as are their offsprings,<sup>[8]</sup> resulting in trans-generation transmission of risks.<sup>[9]</sup>

Given the high rates of hyperglycemia in pregnancy in most venues and the fact that selective testing based on known risk factors has poor sensitivity for detection of GDM among all members of a given population, universal rather than risk factor-based testing seems most practical.<sup>[10,11]</sup> Universal testing is recommended by several organizations including International Association of Diabetes and Pregnancy study Group (IADPSG),<sup>[12]</sup> Australian Diabetes In Pregnancy Study,<sup>[13]</sup> Diabetes In

Pregnancy Study group India (DIPSI),<sup>[14]</sup> and United States task force.<sup>[15]</sup> Asian Indian women are considered to be at the highest risk of GDM and therefore anyway require universal testing. In India, approximately 27 million births occur annually requiring at least 27 million OGTTs annually; considering a 10% average prevalence of GDM, the number of GDM pregnancies would be around 2.7 million, a huge burden to deal with for any health system. Any recommendation for testing women for hyperglycemia during pregnancy must, therefore, be pragmatic, feasible, convenient and cost-effective.

There are certain practical problems in diagnosing GDM. All diagnostic criteria require women to be in the fasting state, but most of the time, pregnant women do not come for antenatal check up in the fasting state because of the belief that fasting for long hours during pregnancy is not good and also due to problems related to commuting. Attending the first antenatal visit in the fasting state is impractical or inconvenient in many settings.<sup>[12,16]</sup> The dropout rate is high when pregnant women are requested to come again for glucose tolerance test.<sup>[9,17,18]</sup> Even if women come in the fasting state it is often not feasible to collect samples early due to clinic timings, causing discomfort and inconvenience. A nonfasting test allows patients to be tested even when they attend clinics later in the day as is often the case with obstetrics and gynecology practices where they are likely to be operating in the morning and see routine cases later during the day. The need for a diagnostic test that can be performed irrespective of whether pregnant women are fasting or nonfasting is obvious. Petit *et al.*<sup>[19]</sup> in their path-breaking study on the long-term effects of abnormal glucose tolerance test during pregnancy on the offsprings of Pima Indian women used the nonfasting 2 h 75 g OGTT. In a prospective study comparing the performance of fasting and nonfasting 75 g OGTT, Anjalakshi *et al.*<sup>[20]</sup> reported that with a cut-off value of 2 h PG > 140 mg/dl (WHO criteria 2009) following a 75 g oral glucose load administered in the fasting or nonfasting state, without regard to the last meal time, was able to identify women with GDM equally. Performing this single test procedure in the fasting or nonfasting state irrespective of the last meal timing is rational as it helps clearly identify normal glucose tolerant women who are able to keep the glucose level within normal limits

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despite a nonfasting 75 g glucose load. DIPSI recommends this “Single step Procedure” to diagnose GDM.<sup>[14]</sup>

Mohan *et al.*<sup>[21]</sup> based on a large retrospective study comparing the IADPSG criteria and the WHO 2009 criteria concluded that, WHO 2hPG >140 mg/dl of  $\geq$ 140 mg/dl appears to be sufficient to diagnose GDM, as it picks up the majority of GDM cases diagnosed by IADPSG criteria as well. Since one blood sample of WHO criteria picks the same number of cases as the three samples of IADPSG criteria, the “Single WHO cut-point of 2h PG >140mg/dl appears to be suitable for large scale screening for GDM in India and other developing countries.

In another recent study comparing the WHO (2009), the DIPSI test (2 h non-fasting 75 g OGTT) and the IADPSG test, Mohan *et al.* reported a lower sensitivity of the DIPSI test.<sup>[22]</sup> In this study, women were first given the non-fasting DIPSI test and asked to come back in the fasting state for a repeat 75 g OGTT within 2-3 days of the first test. However, a large number of women (almost 23%) did not come back for the second (fasting) OGTT. The authors do not report data on women who did not come for the second test and make their conclusion based only on data of women who completed both the fasting and nonfasting test. To draw appropriate conclusions it is important to know that the incidence of GDM (according to DIPSI) was similar between the 2 groups that did and did not show up for the second test to rule out any detrimental effect of selection bias, especially due to the high dropout rate for the second test. While day to day variability in glucose challenge occurs, it is surprising that the same glucose load given in the fasting state identifies more women than when administered in the nonfasting state using the same 2 h cut-off value. Logically one would expect that in the nonfasting state the values would be higher because of a higher overall carbohydrate load when the test is done in the nonfasting state. It is however possible that in the fasting state elimination of any interaction between oral glucose and other foods present in the Gastro Intestinal tract (in the nonfasting state) that may slow down its absorption (mixed meal) may result in higher values. But one is unable to conclude this in the absence of full data. Another conclusion of this study was that there was no difference in rates of vomiting between women undergoing the test in the fasting and nonfasting state. Given that women that had vomited in the nonfasting state had already been eliminated and not subjected to the fasting test, this conclusion also seems subject to bias.

While one can discuss and debate sensitivity and specificity of the various tests-the key issue is if women will not come

for the test or not complete the test what value does it has in terms of applicability from a public health perspective? The study of Mohan *et al.*<sup>[21]</sup> is a classic example of this, wherein even under study conditions, almost 23% women failed to come back. One wonders what would happen in the real world?

The basis of DIPSI test is not that it is the most scientifically accurate and valid test but that it is the most feasible test and that a negative test to a great extent rules out GDM. In a large multicenter study across India as part of a Federation of Obstetrics and Gynecological Societies of India (FOGSI) initiative with a sample size of over 9000 women, DIPSI test identified 8% women with GDM<sup>[23]</sup> exactly the same rate as reported by Mohan *et al.*<sup>[22]</sup> with the WHO (2009) 2 h. criterion.

The significance of 2 h PG > 140 mg/dl during pregnancy has been established for both short-term and long-term outcomes. Treatment of GDM diagnosed by WHO 2009 criteria (2 h PG > 140 mg/dl) reduces serious perinatal morbidity and may also improve women’s health-related quality life.<sup>[24]</sup> When maternal 2-h PG was  $\geq$ 7.8 mmol/L (140 mg/dl), the cumulative risk of offspring developing T2DM was 30% at the age 24 years.<sup>[25]</sup> In addition, a number of studies have shown that diagnosing GDM with a cut-off of 2 h PG > 140 mg/dl and treating women with positive diagnosis is worthwhile, because of decreased macrosomia rate, fewer emergency cesarean sections and serious perinatal morbidity.<sup>[24,26-28]</sup>

Meanwhile, IADPSG came out with the guidelines,<sup>[12]</sup> based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study.<sup>[29]</sup> In this study, population from India, China, South Asian countries (except city of Bangkok, Hong Kong), Middle East and Sub-Saharan countries were not included. IADPSG recommended that GDM can be diagnosed, if any one value of fasting plasma glucose (FPG), 1-h and 2-h PG concentrations meet or exceed 5.1 mmol/L (92 mg/dl), 10.0 mmol/L (180 mg/dl) and 8.5 mmol/L (153 mg/d) respectively, with 75 g OGTT.<sup>[12]</sup>

The disadvantages of IADPSG criteria are (a) the center to center differences in GDM frequency and the relative diagnostic importance of fasting, 1-h and 2-h glucose levels. This may impact strategies used for the diagnosis of GDM.<sup>[30]</sup> The variations may influence the future development of optimal, cost-effective strategies for detection and treatment of GDM.<sup>[31]</sup> (b) A cost-utility analysis found that screening based on IADPSG criteria was not cost-effective.<sup>[32]</sup> (c) In Asian populations, FPG and

glycosylated hemoglobin concentrations have much lower sensitivity than the 2 h postglucose value.<sup>[33]</sup> In a study of 11 Asian cohorts more than half of the diabetic subjects had isolated postchallenge hyperglycemia.<sup>[34]</sup> (d) In a study in China 46.6% of the participants with undiagnosed diabetes (44.1% of the men and 50.2% of the women) had isolated increased 2-h plasma glucose levels after an oral glucose-tolerance test.<sup>[35]</sup> Therefore the need to identify postprandial hyperglycemia seems especially relevant in Asian populations. (e) In all women with GDM, FPG values do not reflect the 2-h post glucose value, which is the hallmark of GDM.<sup>[36]</sup> (f) There is no high-quality evidence that women and their fetuses benefit from treatment if only the fasting value is abnormal. (g) RCT shows benefit of treating GDM women identified primarily by post load values.<sup>[37]</sup> The WHO accepted the IADPSG criteria as the new WHO criteria (2013);<sup>[38]</sup> while endorsing the IADPSG criterion, WHO also accepts “a single step procedure” of DIPSI to diagnose GDM.<sup>[38]</sup> WHO has made a few important and pertinent observations with regard to GDM testing. OGTT is resource intensive and many health services, especially in low-resource settings, are not able to routinely perform OGTTs in pregnant women. In these circumstances, many health services do not test for hyperglycemia in pregnancy. For a pregnant woman, the request to attend fasting 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. Consequently, nonfasting testing may be the only practical option.<sup>[38]</sup> A 2-step procedure requiring attendance on two separate occasions is often not feasible in many low and middle-income countries. Laboratory glucose measurement is often not available, and testing with a portable blood glucose meter may be an option (DIPSI also recommends plasma glucose calibrated glucometers).

Only a pragmatic approach to testing and diagnosis of GDM has any chance of widespread acceptance and implementation. Recently, the single step procedure of DIPSI has been approved by the Ministry of health government of India (Ref - National Guidelines for diagnosis and Management of Gestational diabetes Mellitus, Maternal health Division, Ministry of Health and Family Welfare Government of India. [www.mohjw.gov.in](http://www.mohjw.gov.in) and [www.nhm.gov.in](http://www.nhm.gov.in)) National Institute of Clinical Excellence (NICE) also recommends 2h PG > 140 mg/dl to diagnose GDM. These guidelines, without compromising the clinical equipoise serves the purpose of implementing universal testing for GDM in public health programs. Importantly the recent National Institute of Clinical Excellence (NICE) also recommends 2hr PG > 140 mg/dl to diagnose GDM similar to DIPSI guidelines.<sup>[39]</sup>

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