# Reply to letter to the editor on "A perspective on testing for gestational diabetes mellitus" by Seshiah V *et al*.

Sir,

Gestational diabetes mellitus (GDM) is an area of intense clinical research paralleling the dramatic rise in its prevalence all across the globe. India is experiencing a similar rise in prevalence of GDM, which is a disturbing trend. A scientifically robust, well-validated approach to screening, diagnosing and management of GDM is hence clearly the need of the hour. The logistics of adopting and applying such an approach becomes the responsibility of clinicians and the healthcare system.

Unfortunately, the field of GDM is deeply mired in controversies. After decades of debate and consensus gatherings, workshops, expert meetings, opinions, and global research, we (at least in India) have moved toward universal screening, but have not yet arrived at a consensus for screening and diagnosis of GDM.

The "Letter to the Editor" in the July-August issue of the IJEM from Seshiah *et al*.,[1] all of whom are highly regarded clinicians and researchers, is a welcome step as it helps address some of the challenges in GDM management in India. We concur with several of the issues raised by the authors and agree that solutions have to be found for these challenges. This response is meant to provide explanations, raise relevant counter arguments and open the door to further scientific dialog. We are grateful for this opportunity to express our views.

First, we would like to explain the premise for our paper in Acta Diabetologica[2] which the authors repeatedly refer to in their letter. Our aim is to find a screening strategy that can be applied in India and many other resource-limited settings and is part of an International Diabetes Federation supported initiative, called Women in India with GDM Strategy (WINGS) project. One of the many aims of WINGS, was to validate the existing practice in India, of the nonfasting oral glucose tolerance test (OGTT) (The Diabetes in Pregnancy Study group India [DIPSI] guidelines) against the global practice of doing a fasting OGTT.

We have noted the various points raised in the letter and offer appropriate explanations.

- Changing to the new WHO guidelines for GDM: The 2 h value of 140 mg/dl used by many organizations (including DIPSI) was based on the original 1999 WHO recommendations for GDM.[3] The WHO 1999 recommendation and cut off was based on a fasting OGTT. Moreover, this was not outcome based, but based on an arbitrary cut point. Finally, without a fasting value, it cannot differentiate overt diabetes from GDM in early pregnancy. This criteria has since been categorically removed by the WHO with new recommendations[4] based on the large Hyperglycemia and Adverse Pregnancy Outcome (HAPO) data – the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria.[5] The new guidelines also emphasize the need for diagnosing overt diabetes early in pregnancy with a fasting glucose test. Indeed, when we submitted one of our papers to an international journal recently, based on the WHO 1999 criteria for GDM, it was rejected on the grounds that we had used obsolete GDM criteria! This underscores the need for internationally accepted criteria for GDM
- NICE guidelines 2015: The new NICE guidelines 2015 recommend using the 2 h post 75 g value of 140 mg/dl.[6] However, NICE recommends doing a fasting OGTT. Furthermore, they have now included an alternative fasting value of 100 mg/dl as well, emphasizing the fact that NICE felt that the fasting glucose cut point is equally important
- India and HAPO: India's inclusion into the HAPO study could have been helpful. However, from Asia, Singapore, Hongkong (China) and Thailand were included. Furthermore, many landmark trials such as DCCT, UKPDS, ACCORD, etc., did not include India, but are adopted by us. This is largely because of the enormous cost and effort involved in replicating such studies. More importantly, the robustness of the scientific data is the reason why it need not be replicated in each population unless we have a different question to answer
- Need for combining pragmatism with scientific validity: Our study comparing nonfasting and fasting OGTT was done to identify the most feasible test that will also help other countries that have limitations like us in India. The low sensitivity of the nonfasting test[2] and the inability to replicate the perfect performance (100% sensitivity and 100% specificity) of the nonfasting test reported earlier,[7] has been a challenge to recommend its use as a diagnostic test. An independent study done in North India by Vij *et al*.[8] also reported a low sensitivity of the DIPSI nonfasting test leading the authors to conclude "Since the DIPSI criteria would miss a substantial number of patients, we suggest that the IADPSG criteria are better for screening of GDM in India." Finally, a recent study from Sri Lanka confirms the low sensitivity of the nonfasting test.[9] The authors show that nonfasting test will miss as many as 60% of true GDMs. Worse, it will misdiagnose 33% of normal women as GDM who will be undergoing unnecessary monitoring through the rest of the pregnancy. Thus, at best in situations where a fasting test cannot be done, the nonfasting test can be used as an initial screening test, provided lower cut points are used to maximize the sensitivity. This must then be followed by a definitive diagnostic OGTT done in the fasting state
- Percentage of dropouts in our study: We agree that 23% of the women in our study did not return for the fasting test after having undergone a 75 g test in the nonfasted state, 2–3 days earlier. This is probably because they did not want another OGTT so soon. We would argue that if the women had instead been asked to come just for one fasting OGTT, in a real life situation, the compliance may have been better than 80% and not less as suggested in the letter. In our opinion, pregnant women are a most highly motivated group and they will come if proper facilities are provided

- Moreover, there was no significant differences between the small number of nonresponders ($n$ = 284) and responders ($n$ = 1071) in our study with respect to age, body mass index, family history of diabetes or any of the other clinical characteristics. Hence, it is very unlikely that this small dropout rate affected the results of our study
- Cost effectiveness of IADPSG: The cost effectiveness of applying the IADPSG criteria has been validated by a large study from Spain. Though the IADPSG criteria have been shown to increase the number of women classified as GDM, it has been shown to improve outcomes, both maternal and fetal. Cost effectiveness cannot be considered just as the cost of screening, but as the cost to health care from adverse outcomes of women who go undetected with GDM. Duran *et al*.[10] have shown in their study a reduction in rate of C section, prematurity, large-for-gestational-age (LGA) babies and neonatal care resulting in an estimated cost savings of €14,358 per 100 women evaluated using the IADPSG criteria, compared to the group diagnosed using the two-step Carpenter and Couston criteria. If we can work to strengthen our postpartum care and reduce the development of type 2 diabetes in these women, the cost effectiveness will be even more[11]
- Sensitivity of nonfasting OGTT: Seshiah *et al*. argue that the blood sugars (and hence the sensitivity) should have increased after a double carbohydrate load was given, that is, the usual food followed by the glucose. If one looks at the simple physiology, the answer becomes very clear. When the lady consumes a carbohydrate load, her glucose levels begin to rise even in normal situations which are why postprandial blood sugar cut points are set higher than fasting in the first place! When the blood sugars begin to increase, this stimulates insulin release. In this situation, when one now gives the glucose load, this blunts the rise in blood glucose levels because the insulin levels are not at the basal state, but in a stimulated state. When the blood glucose levels are blunted, the sensitivity of the test drops dramatically. This is why all associations recommend an overnight fast (or at least no calories for at least 8–10 h) as one of the essential quality control checks when any OGTT is done and this has been followed for decades worldwide. This was also shown in GDM by Coustan *et al*.,[12] many years ago using the 50 g OGTT
- Why the IADPSG (new WHO) criteria are important: There is no argument at all that a pragmatic approach is very much needed from a public health point of view. However, combining pragmatism with evidence and robust science is possible, which is why the WHO adopted the IADPSG guidelines.[4] A recent study by Meek *et al*.[13] has shown that the IADPSG criteria identifies women at substantial risk of complications who would not be identified by the NICE 2015 criteria which uses the old WHO 1999 (and DIPSI) cut points. They show that these women who "fell through the net," that is, testing NICE-negative but IADPSG-positive ($n$ = 387), had a higher risk of having a LGA infant (birthweight >90$^{th}$ percentile for gestational age; adjusted odds ratio [95% confidence interval] 3.12 [2.44, 3.98]), caesarean delivery (1.44 [1.15, 1.81]) and polyhydramnios (6.90 [3.94, 12.08]) compared with women with a negative screening test. The LGA risk was also highest among women with fasting plasma glucose in the range of 5.1–5.5 mmol/l again showing the importance of estimating fasting plasma glucose as part of screening for GDM.

Gestational diabetes affects several million women across the globe and in India. Women who develop GDM are at increased risk of developing diabetes in the future. Identifying them in pregnancy, gives a huge opportunity for prevention of type 2 diabetes. We completely agree that we need a test that has to be implementable in parts of India where there are challenges of manpower and technology. In many such places, it may well be impossible to do a blood sugar test, be it fasting or nonfasting. While we try to find means of screening pregnant women and identifying GDM in these areas, we also have to look at ways of implementing a test (OGTT) and criteria (IADPSG) that has been scientifically validated and accepted worldwide and proven to impact outcomes, both maternal and fetal. To say that we can use a test that is not very scientifically accurate, simply because it is feasible, is not an acceptable argument. We have outlined an alternative approach to the screening and diagnosis of GDM in India in a recent editorial[14] and this is reproduced in Figure 1.

A review of GDM published in IJEM also makes a strong place for IADPSG criteria for India and says that the DIPSI criteria to be only considered where IADPSG criteria is not feasible.[15] The Sri Lanka study also rejects the nonfasting test and strongly recommends the IADPSG criteria.[9]

Providing cost effective and ethical care, while adhering to standards of care to all these women is a great challenge. The health system needs strengthening and capacity building, to handle this burden. A good example of

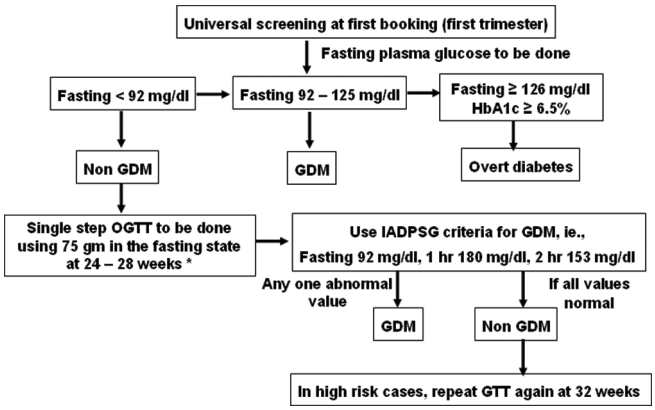


**Figure 1:** Proposed guidelines for screening for gestational diabetes mellitus in India. *(1) When a single step fasting oral glucose tolerance test is not possible, do a 2 step procedure, that is, 50 g glucose challenge test in the nonfasting state followed by 3 h oral glucose tolerance test in the fasting state using 100 g Carpenter and Coustan criteria in those who screened positive in the glucose challenge test. (2) Where the Diabetes in Pregnancy Study group India nonfasting test is already in vogue, this can be continued as an initial screening test using lower cut points to maximize sensitivity and those who screen positive can be referred for a definitive diagnostic oral glucose tolerance test done in the fasting state. Source: Modified from Mohan V, *et al.* J Postgrad Med 2015;61:151-4. (Reprinted with copyright permission)

what can be done if there is the political will to support it is the example of Tamil Nadu. Until a few years ago, institutional deliveries were uncommon in Tamil Nadu. Thanks to the incentive scheme and support provided by the Government of Tamil Nadu, irrespective of which party is in power, the institutional deliveries have gone up to 99% in Tamil Nadu.[16] In fact 67% of all deliveries take place in government institutions compared to 33% in private institutions. If similar steps are taken to promote screening for GDM in the fasting state and incentives are provided both for pregnant women, as well as to the health-care teams, nothing is impossible for a country which has successfully sent its own spacecraft to the moon!

We salute the pioneering work and the untiring efforts of Seshiah *et al.* in the field of GDM and share several of their concerns which are indeed true. However, we also recognize the need for research that involves multiple centers across the country that will evaluate the merits and demerits of all the available strategies. This will help arrive at a consensus for screening and diagnosis of GDM in our country that is feasible, and yet scientifically valid and internationally acceptable. We owe this to the millions of pregnant women in India to ensure that both maternal and fetal outcomes are improved in our country.

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## Conflicts of interest

There are no conflicts of interest.

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