Is the evidence strong enough to change the diagnostic criteria for gestational diabetes now?

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The International Association of the Diabetes and Pregnancy Study Groups has proposed new thresholds for oral glucose tolerance tests that are based on the large observational Hyperglycemia and Adverse Pregnancy Outcomes study. By using these criteria about 18% of pregnant women will be diagnosed as having gestational diabetes mellitus. The question arises if we are ready for such an enormous increase in gestational diabetes mellitus patients, if outcome would really improve by using these criteria, and if additional studies are necessary before deciding on new diagnostic thresholds. In this clinical opinion, the pros and cons will be discussed.

Key words: adverse pregnancy outcome, diabetes mellitus, glucose intolerance, metabolic syndrome, oral glucose tolerance test

In 2008, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study group published the results of a large international observational study on the relationship between second-trimester oral glucose tolerance test (OGTT) values and outcome.[1] Unfortunately, but not surprisingly, there was a linear relationship among fasting, 1-hour and 2-hour glucose values, and the frequency of primary cesarean delivery, fetal macrosomia (birthweight >90th centile), clinical neonatal hypoglycemia, and cord blood C-peptide. The absence of clear cutoff values for normal or abnormal test results implies that threshold values will by definition be arbitrary. Based on the HAPO results new thresholds for OGTT have been proposed by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG). These are based on a 1.75-fold increase in incidence of fetal macrosomia.[2] By using these criteria, the frequency of gestational diabetes mellitus (GDM) may differ between countries from about 10% in Israel to 24% in areas in southeast Asia and from 17-25% in areas of the United States; overall mean incidence is 17.8%.[3] Following publication of these newly proposed thresholds, numerous articles have been published on their advantages and disadvantages, with an article by Ryan[4] as the most eloquent. Arguments in favor or against the IADPSG thresholds are summarized in Table 1 and will be discussed below.

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Arguments in favor

The diagnosis of GDM has traditionally been made by using OGTTs that were originally designed in such a way that about 2.5% of the pregnant population (>2 SD) had values exceeding the normal range or were simply based on criteria used in nonpregnant individuals.[5,6] GDM was therefore a laboratory-based diagnosis and not one that was related to perinatal outcome characteristics. The HAPO results provide data on the relation between OGTT values and perinatal outcome and are therefore better suited to identify abnormalities in metabolism than the previous criteria, although the exact cut-off levels remain uncertain.

A recent survey of prevalence of GDM by country showed a median incidence of GDM of about 5% in all world regions except southeast Asia (median 8%).[7] Obesity rates have doubled in the last 15 years in many countries, including the United States (presently about 30%[8]). The odds ratio (OR) for GDM in obese women with a body mass index (BMI) >30 is 3.5-4.[9,10] Therefore a higher incidence of GDM than the reported 5% seems likely.

Two randomized studies have shown that treatment of GDM improves outcome, by lowering the incidence of fetal macrosomia, mortality, birth trauma, and–in one study–cesarean deliveries.[11,12] These results make treatment and screening programs for GDM mandatory. However, criteria for GDM differed from the new proposed diagnostic criteria and were likely to include the more severe cases. Benefits for diagnosing and treating minor glucose abnormalities have, therefore, not yet been proven. In October 2012, Bodmer-Roy et al[13] published data indicating that women classified as nondiabetic by the Canadian Diabetes Association Criteria but considered to have GDM according to the IADPSG criteria (study group) had similar pregnancy outcomes as women without GDM. However, the data were not conclusive since there was a higher incidence of fetal macrosomia and preeclampsia in the study group, which was, however, not significant (the series reported only 186 cases and 372 controls).

Treatment of GDM is usually relatively easy, with insulin requirement in only 8-20% of women. This argument would favor identification of all women with minor hyperglycemia, but it does not take into account that overdiagnosis might result in other actions like labor inductions or cesarean deliveries without proven benefit (see below).

Thus far 2 studies have addressed cost-effectiveness of GDM screening according to the IADPSG criteria using decision analysis models. One study showed that

the IADPSG recommendations are cost-effective only when postdelivery care would reduce the frequency of diabetes in these women.[14] In a second study, the cost-effectiveness of the current US screening, 1-hour glucose challenge test followed by a 3-hour OGTT, was compared with the new IADPSG guidelines for the 2-hour OGTT. In the latter study, treatment according to the new guidelines would be effective if treatment would result in decreased preeclampsia >0.55% and decreased cesarean delivery >2.7%.[15]

The arguments against

The OGTT has poor reproducibility, with about 30% of patients having a negative test result after a previous positive result.[16,17] Reproducibility is even poorer with minor degrees of glucose elevations.[18,19] In other words, the stricter the threshold values the more patients will be diagnosed by chance as having GDM.

It is questionable if a birthweight >90th centile is an adequate endpoint for defining OGTT threshold values. Even with the strict IADPSG threshold criteria, only about 22% of all large-for-gestational-age pregnancies occur in patients with GDM.[4] It is unknown if this will be the subgroup of infants with an increased risk for obesity and metabolic syndrome later in life. Growth characteristic for type 1 diabetes, type 2 diabetes, and GDM is characterized by disproportionate fetal growth with a large abdominal circumference as compared to the head circumference, both in appropriate- and large-for-gestational-age infants.[20] A better description/definition of macrosomia will therefore be necessary.

Moreover and as has been pointed out before,[4] GDM is related to childhood obesity, but mainly in case of coexisting maternal obesity. A Finnish study has recently shown that overweight and abdominal obesity in 16-year-old adolescents was related to maternal obesity and especially to the combination of maternal obesity and GDM, but not to GDM alone.[21] In a systematic review on the association between GDM and childhood overweight and obesity it was found that there is currently inconsistent evidence of an association due to methodological limitations of existing studies.[22] In another recent metaanalysis it was found that there is an association between all types of diabetes in pregnancy with childhood obesity, but that this association disappeared after adjustment for maternal BMI in the 3 studies in which this was reported.[23] The Finnish study by Pirkola et al[21] had not yet been included in this analysis. So there is considerable doubt as to the independent effect of GDM on obesity in offspring, but data corrected for maternal BMI are limited. Absence of long-term risks of GDM for the offspring would weaken the need for diagnosing very mild cases.

From the HAPO data, we know that both obesity and GDM are independent risk factors with synergistic effects regarding preeclampsia, primary cesarean deliveries, macrosomia, increased cord C-peptide levels, and newborn body fat.[24] Follow-up studies of these infants will be important to assess the risk factors for metabolic syndrome during childhood and thereafter, ie, maternal obesity and/or GDM. Given the synergistic effects of GDM and obesity on direct and later outcome in the offspring, it might prove useful to use stricter threshold criteria for obese women than for nonobese women, instead of using the same thresholds for everyone.

Earlier this year Moynihan et al[25] addressed the problem of overmedicalization in an article entitled "Preventing overdiagnosis: how to stop harming the healthy." As drivers for overdiagnosis they mentioned: (1) technological changes detecting even smaller abnormalities; (2) commercial and professional vested interests; (3) conflicted panels producing expanded disease definitions and writing guidelines; (4) legal incentives that punish underdiagnosis but not overdiagnosis; (5) health system incentives favoring more tests and treatments; and (6) cultural beliefs that more is better, ie, faith in early detection unmodified by its risks. Many of these drivers may be present regarding GDM screening and GDM was indeed mentioned as an example. Quoting Moynihan et al[25] and an earlier article by Black[26]: "The ability to detect smaller abnormalities axiomatically tends to increase the prevalence of any given disease. In turn this leads to overestimation of the benefits of therapies, as milder forms of the disease are treated and improvements in health are

TABLE 1
Arguments in favor and against use of IADPSG threshold OGTT values for diagnosing GDM

Arguments in favor
- Previous OGTT thresholds were set in such a way that about 2.5% of population would classify as GDM, irrespective of relationship of glucose values with perinatal outcome
- Striking increase in obesity and type 2 diabetes in general population may well correspond to GDM incidence of about 20%
- Treatment of GDM improves perinatal outcome
- Treatment of GDM is generally easy with insulin treatment in only 8-20% of women
- Adequate diagnosis is cost-effective
Arguments against
- OGTT has poor reproducibility
- Even with very strict threshold values, only a minority of fetal macrosomia will be identified
- GDM is related to childhood obesity, but mainly in case of maternal obesity
- Overdiagnosis of GDM may well result in overtreatment
- Stricter OGTT criteria will result in increasing workload

GDM, gestational diabetes mellitus; *IADPSG,* International Association of Diabetes and Pregnancy Study Groups; *OGTT,* oral glucose tolerance test.

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