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ANALYSIS

TOO MUCH MEDICINE

Gestational diabetes: new criteria may triple the prevalence but effect on outcomes is unclear

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This article is part of a series on overdiagnosis looking at the risks and harms to patients of expanding definitions of disease and increasing use of new diagnostic technologies.

Maternal obesity, excess maternal weight gain during pregnancy, and gestational diabetes are all associated with large for gestational age infants and other adverse outcomes. With obesity being a major risk factor for gestational diabetes (diabetes first recognised in pregnancy), the increasing incidence of the condition is unsurprising. Treatment of obesity during pregnancy has disappointingly little effect on the numbers of babies born large for gestational age, but treatment of gestational diabetes is more successful. This has led to an emphasis on diagnosing and treating gestational diabetes, but do the recently proposed diagnostic criteria[1] that triple its prevalence make sense? Is it good clinical care, or yet another example of overdiagnosis?

A label of gestational diabetes brings with it an intervention package that includes glucose monitoring; extra clinic visits; more obstetric monitoring with greater likelihood of labour induction, operative delivery, and admission of the baby to special care; and, finally, for the mother, a label of high risk for diabetes. We argue that the diagnostic changes are unjustified because they are based on the results of an observational study and use a test that has poor reproducibility. Furthermore, there is no evidence of any treatment benefit from interventional studies.

Background

The term gestational diabetes was introduced to describe women with a poor obstetric history who, during a subsequent pregnancy, had high glucose levels on oral glucose tolerance tests.[2] In 1979 the National Diabetes Data Group (NDDG) in the United States recommended that gestational diabetes be recognised as a distinct entity with its own criteria for which all high risk pregnant women should be screened.[3] The following year the American Diabetes Association suggested using a two step procedure: a 50 g glucose challenge test followed, if the result was positive, by an oral glucose tolerance test for all pregnant women (table⇓).[4] Gestational diabetes was recognised to be associated with macrosomia, neonatal hypoglycaemia, and maternal pre-eclampsia, but the diagnostic criteria were based on the ability of a positive test result to predict future diabetes, not pregnancy outcomes. The proposals were widely adopted, although many countries developed individual diagnostic criteria. All were decided by expert opinion[5] and resulted in rates of gestational diabetes of 2-6%.[6]

Established management

The main concern associated with diabetes in early pregnancy is the increased risk of congenital malformation, hence the emphasis on good glycaemic control before conception in women with established diabetes. Unrecognised type 2 diabetes (now common in obese young women) puts the baby at risk of malformation.[7] Any pregnant woman who is at high risk of diabetes should be screened at the first prenatal visit.

Gestational diabetes is typically asymptomatic and selective screening misses nearly half of cases, hence universal screening is suggested at 24-32 weeks.[8] Most centres use a 50 g glucose challenge, administered at any time of the day, with plasma glucose measured one hour later. A value of ≥7.8 mmol/L prompts a 75 g or 100 g oral glucose tolerance test with one or two raised values needed for diagnosis. Women who have gestational diabetes are referred to a diabetes pregnancy clinic, receive instruction on diet and lifestyle changes, and are taught how to check their glucose levels (fasting and after meals). For the 30-40% of women whose glucose values remain above strict glycaemic targets, insulin or oral hypoglycaemic drugs are introduced and adjusted up to delivery.[9] Women also receive more intensive fetal surveillance, and delivery before 40 weeks' gestation is routine. The baby is monitored for hypoglycaemia and may be admitted to the special care unit. The mother is

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Summary box

Clinical context—Mild gestational diabetes is associated with perinatal morbidity

Diagnostic change—International recommendation to move from dual step testing to reliance on a single abnormal glucose value in an oral glucose tolerance test with reduced thresholds

Rationale for change—An observational study showed that any degree of impaired glucose regulation in pregnancy is associated with adverse outcomes

Leap of faith—Reducing mildly raised blood glucose concentrations will improve outcomes for mother and baby

Effect on prevalence—Nearly 1 in 5 pregnancies will be identified as being affected by gestational diabetes: a 2-3-fold increase over existing levels of 2-6%

Evidence of overdiagnosis—Despite increased diagnosis there is no evidence from randomised controlled clinical trials that outcomes are improved

Harms from overdiagnosis—Many more women will experience medicalisation of their pregnancy with increased intervention

Limitations—Maternal obesity and excess weight gain in pregnancy are associated with gestational diabetes; both affect birth weight and other more serious pregnancy outcomes. The importance of mild hyperglycaemia is unknown

Conclusion—We need to understand better how to identify high risk pregnancies, incorporating other important factors in addition to glucose concentration

screened for diabetes postpartum and at intervals for the rest of her life.

Where did new recommendations for diagnosis come from?

In order to determine definitive international diagnostic criteria for gestational diabetes, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[10] examined the effect of varying degrees of maternal glycaemia on pregnancy outcomes. A total of 23 316 women had a 75 g oral glucose tolerance test at 24–32 weeks' gestation. The study found continuous associations between maternal glucose levels and birth weight and one surrogate outcome (cord blood C peptide levels, which reflect fetal insulin secretion),[10] even below glucose levels that are diagnostic of diabetes. However, no inflection point for diagnosis was evident.

The International Association of Diabetes Pregnancy Study Groups (IADPSG) met in 2008 to determine the glucose thresholds for diagnosing gestational diabetes. The group mainly comprised hospital physicians with little or no input from primary care providers, midwives, public health experts, or patient representatives. The group made four important recommendations[1]:

- Diabetes diagnosed in early pregnancy at the first prenatal visit based on a fasting plasma glucose ≥7.0 mmol/L or glycated haemoglobin (HbA_{1c}) level ≥6.5% (48 mmol/mol) would be identified as overt diabetes
- Glucose levels associated with an arbitrary 1.75-fold increase risk above the mean (from HAPO results) for birth weight, cord C peptide concentration, and percentage body fat being above the 90th centile would constitute a diagnosis of gestational diabetes
- Only one abnormal value would be needed for diagnosis since fasting, one hour, and two hour glucose values were all associated with the defined adverse outcomes
- Two step testing could be abandoned in favour of a single oral glucose tolerance test.

The American Diabetes Association promptly endorsed the IADPSG recommendations, and they were subsequently adopted by diabetes associations in several countries, including Australia, France, and China. The Endocrine Society and World Health Organization adopted similar guidelines, although WHO rated the quality of evidence for the position as "very low."[11] The result is that 18% of pregnant women will have gestational diabetes diagnosed, based on an odds ratio of harm below 3 for all but the highest glucose categories.[10] The reliability of such low odds ratios derived from observational data is poor, and this problem is compounded by the requirement for only one abnormal value.[12]

Drivers for change in criteria for diagnosis

The IADPSG guidelines aimed to standardise the diagnostic criteria for gestational diabetes, relating them to pregnancy outcomes and putting them on a more scientific footing. It says that the resulting dramatic rise in prevalence of gestational diabetes simply reflects the substantial increase in the community prevalence of obesity and type 2 diabetes. The current intense interest in the developmental origins of adult disease has emphasised the putative (but unproved) link with later obesity and diabetes in the offspring.

How effective is treatment of gestational diabetes?

There have been two major randomised controlled trials of treatment, both of which used two step testing to identify gestational diabetes.[13 14] Their results and those of meta-analyses suggest modest benefits on the intermediate endpoint of birth weight, fewer cases of pre-eclampsia, and a small reduction in the relatively infrequent complication of shoulder dystocia.[15 16]

Positive outcomes from the suggested changes

The NDDG's definition of gestational diabetes as any degree of glucose intolerance first detected in pregnancy conflated into a single entity a spectrum ranging from mildly but transiently raised blood sugar concentrations in late pregnancy through to previously unrecognised diabetes. The presence of notable hyperglycaemia in early pregnancy is not typical gestational diabetes but probably unrecognised type 2 diabetes. The IADPSG was right to suggest a diagnosis of overt diabetes if the fasting plasma glucose or HbA_{1c} concentration is clearly raised in early pregnancy, and these women need the same attention as those with known diabetes. In addition, most women with gestational diabetes are overweight so diagnosis gives them the opportunity to access professional dietary advice that could be beneficial in the short or long term.

Why the concern about the new diagnostic criteria?

Poor screening test

The main reason that cases of gestational diabetes have trebled using IADPSG criteria is the reliance on a single raised blood sugar result for diagnosis. Blood glucose values after a glucose load are notoriously variable, which is why the oral glucose tolerance test is being used less commonly to diagnose diabetes outside pregnancy. Forty per cent of pregnant women who had a second test shortly after an abnormal result had a normal result the second time.[17] A systematic review of the tolerance test concluded that "caution should be exercised when interpreting a single test result."[18]

One advantage of the two step test (non-fasting 50 g glucose challenge, followed, if positive, by a tolerance test) is that women have to fail two tests before gestational diabetes is diagnosed, increasing confidence in the diagnosis. Although a single oral glucose tolerance test might seem attractive, the test requires fasting, takes two hours, and presents real logistical difficulties, particularly in low and middle income countries.

Disease or risk factor?

Rather than a disease, maternal hyperglycaemia is primarily a risk factor for adverse maternal and infant outcomes. Large babies may be more difficult to deliver, experience birth trauma, and be at risk of neonatal hypoglycaemia. The mother is at risk of pre-eclampsia. In the long term the mother is at risk of diabetes and child is at risk of being overweight and developing glucose intolerance. But all of these unwelcome outcomes have other risk factors, most notably maternal obesity and gestational weight gain.[19-21]

Separating out the role of gestational diabetes is difficult—the randomised controlled trials that showed benefit from treating gestational diabetes also ameliorated weight gain in the mothers;[13 14] the risks of obesity and glucose intolerance in the offspring associated with gestational diabetes are lost when maternal body mass index is factored into the analysis.[22] Overall, 78% of large for gestational age babies in HAPO were born to women with normal glucose tolerance.[23]

We need to understand better how these factors interact to increase risks and to manage them, and not assume that lowering minimally raised blood sugar values is of paramount importance. The main effect of treatment of mild gestational diabetes is to reduce birth weight,[13 14] but this is a crude measure: a long thin baby can weigh the same as a short fat one, but the metabolic risks may be greater for fatter babies.

Resource implications

Two studies have modelled the cost effectiveness of the IADPSG proposals. One concluded that they would be cost effective (defined as <$100 000 (£60 000; €73 000) per quality adjusted life year) only if detection of gestational diabetes reduced the rate at which type 2 diabetes subsequently developed.[24] The long term risk of type 2 diabetes in women identified by the IADPSG criteria is unknown but will certainly be less than in women with greater degrees of hyperglycaemia. The second study concluded that the IADPSG proposals would be cost effective only if they reduced the rate of caesarean section.[25] Although one intervention trial reported a lower caesarean delivery rate (27% *v* 34%),[14] the reduction was not significant in systematic reviews.[15 16] In practice, the 100-140 g reduction in birth weight achieved by treating mild gestational diabetes is unlikely to reduce the number of caesarean sections. Diagnosis of gestational diabetes is associated with an increase in caesarean section rate even if birth weight is normalised by treatment.[26]

Managing pregnancy successfully in women with established diabetes is demanding and complex, requiring the full support of a multidisciplinary team. Diagnosis of gestational diabetes increases the number of clinic visits and interventions,[13 14] and a large increase in women with low risk gestational diabetes attending the clinics will divert resources from women with pre-existing diabetes, who benefit most from these services.

Absence of evidence on harms and benefits

Preventive medical interventions in asymptomatic pregnant women must be based on the highest level of evidence not on observational data. Treating women identified by the IADPSG criteria might improve maternal and fetal outcomes, but there is no evidence from randomised controlled trials to support such a position. Pregnancy is a time when women are particularly sensitive to their health and receptive to changes but also vulnerable to stress, anxiety, and guilt. In the case of the IADPSG proposals, a large number of hitherto healthy pregnant women will become labelled as diseased.

Conclusions

Established diabetes is an important risk factor for several serious adverse pregnancy outcomes and the risk is greater if glycaemic control is poor. Screening high risk women for undiagnosed type 2 diabetes at the first prenatal visit is wise.

Mild glycaemia does not carry anything like the same degree of risk. The IADPSG proposals seem a striking example of overdiagnosis. If adopted, they will double or treble the rates of diagnosis of gestational diabetes, largely on the basis of one raised blood sugar measurement. Interventions and costs will increase with no clear evidence that benefit will accrue. Although the American Diabetes Association and some other national diabetes associations have adopted the IADPSG proposals, the US College of Obstetricians and Gynecologists has not endorsed the change, and the 2013 National Institutes of Health consensus conference was concerned about the adoption of new criteria without clear evidence of clinically important benefit.[27] For general practitioners, midwives, and pregnant women the conflicting advice from professional bodies is bewildering and unhelpful.

We suggest that all overweight pregnant women receive basic dietary counselling[28] and that until further evidence is available the best compromise position is to follow the advice on screening from the Canadian Diabetes Association. This advocates a 50 g one hour glucose challenge test followed, if needed, by a 75 g oral glucose tolerance test for women at a twofold increased risk of large baby from HAPO data (table⇓).[29]

Contributors and sources: TC and EAR have attended at specialist diabetes in pregnancy clinics for many years and have independently studied and reported on many aspects of diabetes and pregnancy. Both have published about their concerns around the IADPSG criteria for GDM. EA spent many years as a GP in a remote area of Australia delivering about 300 babies a year and more recently in urban areas has been involved with share care arrangements of pregnant women. All three are concerned about the medicalisation of pregnancy. All authors contributed to the article.

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Table

Table 1| Evolving concepts around the diagnosis of gestational diabetes

Date	Observations	Recommended test	Diagnostic criteria for oral glucose challenge test (mmol/L)				Prevalence (%)
			Fasting blood glucose	1 hour	2 hour	3 hour	
1930-40s	Women who later developed (type 2) diabetes had high incidence of large babies and fetal loss	Not yet developed	—	—	—	—	NA
1950s	The term "gestational diabetes" introduced for women with poor obstetric histories who during a subsequent pregnancy had high glucose levels on an OGTT	OGTT 100 g in high risk patients	—	—	> 9.4	—	NA
1960s	Women with high risk pregnancies followed postpartum with annual OGTT—a high proportion subsequently developed type 2 diabetes	OGTT 100 g in high risk patients (need 2 abnormal values) Whole blood glucose levels	≥ 5.0	≥ 9.2	≥ 8.1	≥ 6.9	2
1979-80	Missed cases lead American Diabetes Association to recommend universal screening using criteria suggested by National Diabetes Data Group	50 g glucose challenge followed by OGTT 100 g (need 2 abnormal values)	≥ 5.8	≥ 10.6	≥ 9.2	≥ 8.1	5
1990s	Modification for using plasma not whole blood	OGTT 100 g (need 2 abnormal values)	≥ 5.3	≥ 10.0	≥ 8.6	≥ 7.8	6
2005-9	Randomised controlled trials in women with mild gestational diabetes identified by two step testing show modest benefit of treatment, predominantly on birth weight	—	—	—	—	—	—
2008-10	HAPO study shows continuous relation between untreated maternal blood glucose and some primary endpoints but no threshold for markedly increased risk	OGTT 75 g, no screening and 1 abnormal value*	≥ 5.1	≥ 10.0	≥ 8.5	—	18
2013	Individual countries struggle to come up with guidelines for diagnosis. Shown is the Canadian Diabetes Association preferred approach	50 g glucose challenge followed by OGTT 75 g (1 abnormal value)†	≥ 5.3	≥ 10.6	≥ 9.0	—	9

OGTT=oral glucose tolerance test, HAPO=Hyperglycemia and Pregnancy Outcome Study.

*International Association of Diabetes in Pregnancy Study Group recommendation based on HAPO.

†Based on data from HAPO but levels associated with a twofold increased risk of birth weight, fetal adiposity, and cord C peptide concentrations being over the 90th centile.