Original Paper

Fetal Diagnosis and Therapy

Fetal Diagn Ther 2011;30:108–115
DOI: 10.1159/000324684

Received: December 21, 2010
Accepted after revision: January 26, 2011
Published online: April 1, 2011

Criteria for Screening and Diagnosis of Gestational Diabetes Mellitus in the First Trimester of Pregnancy

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Key Words
First trimester · Gestational diabetes mellitus · Glucose challenge test · Glucose tolerance test · Fetal macrosomia

Abstract
Objective: To propose new cutoffs in plasma glucose levels in screening and diagnosis of gestational diabetes mellitus (GDM) in the first trimester of pregnancy. ***Methods:*** A 50-gram oral glucose challenge test (GCT) was performed in 1,716 singleton pregnancies at 6–14 weeks' gestation. In those with a positive GCT, a 100-gram glucose tolerance test (GTT) was carried out. The GCT and as necessary the GTT were repeated at 20–30 weeks. The relation of the results of the GCT and GTT at 6–14 weeks to that at 20–30 weeks was examined. ***Results:*** The diagnosis of GDM was made in 85 cases. In the GCT, there was a significant association between 1-hour plasma glucose levels at 6–14 weeks and at 20–30 weeks ($r = 0.558$, $p < 0.0001$), and in all cases of GDM, the level was 130 mg/dl or more at 6–14 weeks and 140 mg/dl or more at 20–30 weeks. In the GTT, the plasma glucose 1, 2 and 3 h after the 100-gram glucose load at 6–14 weeks was, respectively, 18, 29 and 35% lower than at 20–30 weeks. ***Conclusion:*** Effective diagnosis of GDM in the first trimester can be achieved by lowering the GCT and GTT plasma glucose cutoffs.

Introduction

Gestational diabetes mellitus (GDM) is associated with increased risk of maternal and perinatal short- and long-term complications [1–8]. Screening and diagnosis of GDM is traditionally delayed until the late second or early third trimester of pregnancy with the rationale that the diabetogenic effects of pregnancy increase with gestation, and therefore, delayed testing would maximize the detection rate [9–12]. An alternative approach in screening for GDM would be to undertake earlier testing and adjust the traditional criteria of the tests. Effective early identification of the high-risk group for subsequent development of GDM is likely to improve pregnancy outcome because with appropriate dietary advice and pharmacological interventions the incidence of the disease and associated maternal and perinatal complications could potentially be reduced. Additionally, early testing would identify patients with undiagnosed preexisting diabetes.

The aim of this study is to examine the performance of the traditional cutoffs in the screening and diagnostic tests for GDM and propose new cutoffs for the first trimester of pregnancy.

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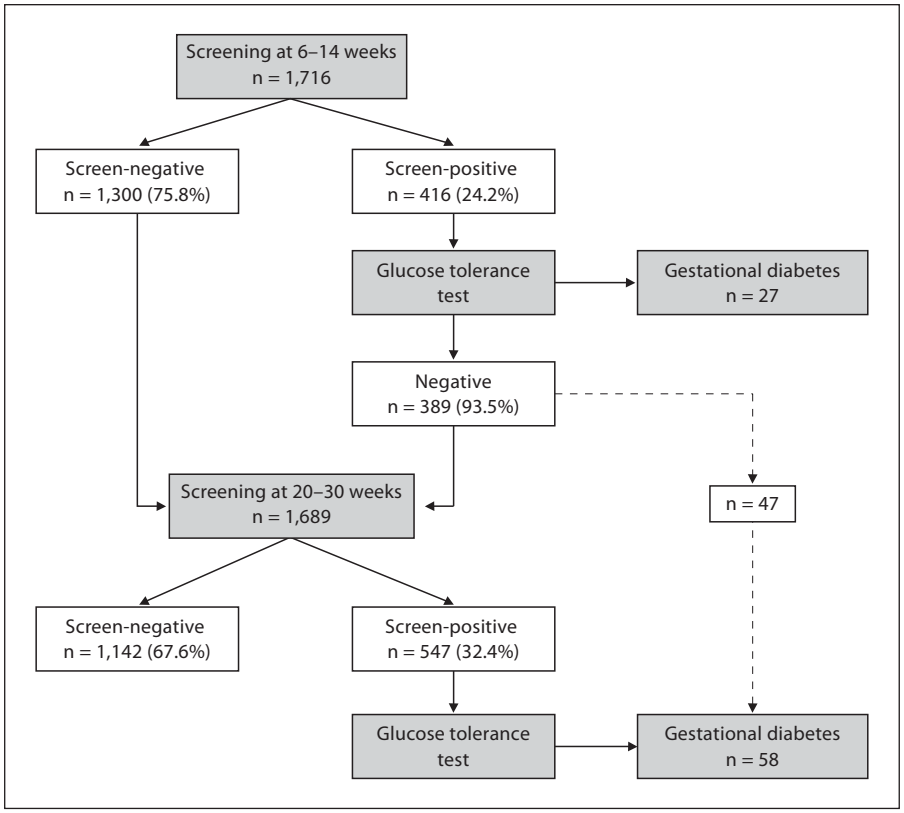

Fig. 1. Flow chart summarizing the pathway for screening and diagnosis of GDM at 6–14 and 20–30 weeks' gestation.

Methods

Screening for and diagnosis of GDM at the Hospital Universitario Materno-Infantil de Canarias, Las Palmas, Spain, is based on a two-stage approach. A screening test, involving the oral ingestion of a drink containing 50 g of glucose and the measurement of venous plasma glucose concentration 1 h later, is offered to all women at 6–14 weeks' gestation and again at 20–30 weeks. The screening test is considered to be positive if the plasma glucose is 140 mg/dl or higher [13]. When the screening test is positive an oral glucose tolerance test (GTT) is carried out and the diagnosis of GDM is made if the plasma glucose level is higher than the following cutoffs in at least two of the four results: fasting level of 105 g/dl and 1, 2 or 3 h after the oral administration of 100 g of glucose is 190, 165 and 145 mg/dl, respectively [14]. The first line in the management of GDM is dietary advice, and insulin therapy is reserved for women who despite dietary modifications, have fasting plasma glucose levels >95 mg/dl and/or 2-hour post-prandial glucose of 120 mg/dl or more.

We searched the computerized database of the biochemistry department of our hospital for the results of testing for GDM in singleton pregnancies examined between February 2008 and August 2009, and then obtained demographic characteristics and data on pregnancy outcome for these patients from the computerized database of obstetric care. On the basis of their results, the patients were subdivided into GDM and non-GDM groups.

Statistical Analysis

Comparison between variables was done by χ^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. Paired t test was used to examine the significance of difference between measurements of plasma glucose at 6–14 weeks with those at 20–30 weeks. Regression analysis was used to examine the association between pre-, post- and the difference between post- and pre-glucose levels. Logistic regression analysis was used to determine whether pre-, post- and post-/pre-glucose levels provided a significant independent contribution in the prediction of GDM. The detection and false-positive rates in the prediction of GDM were estimated using receiver operating characteristic (ROC) curves analysis and performance of screening was assessed by comparison of area under ROC (AUROC) curves.

The statistical software package SPSS 17.0 (SPSS Inc., Chicago, Ill., USA) was used for data analyses.

Results

During the study period, first-trimester screening for GDM was carried out in 1,765 singleton pregnancies (fig. 1). In 49 cases, the pregnancy resulted in miscarriage or termination and the patients did not have a second screening test (n = 31), or they were lost to follow-up (n =

Table 1. Maternal and pregnancy characteristics in the outcome groups

Maternal characteristics	Non-GDM (n = 1,631)	GDM (n = 85)
Maternal age, years, median (IQR)	30.7 (25.9–34.7)	33.8 (29.8–37.3)*
Maternal weight, kg, median (IQR)	65.3 (58.1–75.5)	71.4 (61.9–80.8)*
Maternal height, cm, median (IQR)	163 (158–167)	161 (157–165)*
Maternal body mass index, median (IQR)	24.6 (22.4–28.1)	26.8 (24.1–32.7)*
Gestation at sampling, first trimester, median (IQR)	8.5 (7.4–9.9)	8.9 (7.3–9.8)
Gestation at sampling, second-trimester, median (IQR)	24.3 (23.2–25.5)	24.6 (23.8–25.9)
Racial origin (%)		
Caucasian, n	1,614 (99.0)	83 (97.6)
African, n	13 (0.8)	2 (2.4)
South Asian, n	4 (0.2)	–
Parity (%)		
Nulliparous, n	925 (56.7)	47 (55.3)
Parous, n	706 (43.3)	38 (44.7)
Family history of diabetes, n (%)	248 (15.2)	35 (41.2)*
Cigarette smoker, n (%)	289 (17.7)	25 (29.4)*
Conception (%)		
Spontaneous, n	1,576 (96.6)	81 (95.3)
Assisted, n	55 (3.4)	4 (4.7)
Birth weight above the 90th percentile for gestation, n (%)	179 (11.0)	6 (7.1)

Comparisons between outcome groups (χ^2 test and Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables): * $p < 0.05$. IQR = Interquartile range.

18) and these cases were excluded from further analysis. In the 1,716 cases included in the study, the median gestation at screening for GDM was 9 (range 6–14) weeks. The screening test was positive in 416 (24.2%) cases and the subsequent GTT in the first trimester was positive in 27 cases. A second screening test at 20–30 (median 24) weeks was carried out in 1,689 cases, including the 1,300 with negative screening at 6–14 weeks and the 389 with negative GTT at 6–14 weeks. The second screening test was positive in 547 (32.4%) cases and the subsequent GTT was positive in 58 cases, including 47 with a positive screening test but negative GTT in the first trimester.

In total, the diagnosis of GDM was made in 85 cases. The maternal and pregnancy characteristics of the GDM and non-GDM groups are compared in table 1. In the GDM group compared to the non-GDM group, the median maternal age and weight was higher, the maternal height was lower, more women had a family history of diabetes and were cigarette smokers.

In 19 (22.4%) of the 85 cases of GDM, the patients were treated by insulin and in 66 (77.6%) by diet alone. Insulin treatment was given to 12 (44.4%) of the 27 cases diagnosed at 6–14 weeks, to 7 (14.9%) of the 47 cases diagnosed at 20–30 weeks but with a screen-positive result at 6–14 weeks, and to none of the 11 cases diagnosed at 20–30 weeks but with a screen-negative result at 6–14 weeks ($p = 0.011$).

Screening Test

In the 1,689 cases with screening at both 6–14 and 20–30 weeks, the median pre-glucose administration plasma glucose level at 6–14 weeks was significantly higher than the equivalent level at 20–30 weeks, whereas the median level after the administration of glucose was significantly lower at 6–14 weeks than at 20–30 weeks. The difference in the glucose levels before and after administration of a glucose load was significantly higher at 20–30 weeks than at 6–14 weeks (table 2).

In the 1,689 cases, there was a significant association between plasma glucose levels at 6–14 weeks and at 20–30 weeks before ($r = 0.390$, $p < 0.0001$) and after the administration of a glucose load ($r = 0.558$, $p < 0.0001$) and in the difference between post and pre values ($r = 0.514$, $p < 0.0001$; fig. 2a, b).

In 58 of the 1,689 cases, the diagnosis of GDM was made at 20–30 weeks. Logistic regression analysis demonstrated that in the prediction of GDM at 6–14 weeks there were significant contributions from pre- (AUROC

Table 2. Results of the screening test, which involved the measurement of the plasma glucose level before and 1 h after the oral administration of 50 g of glucose, at 6–14 and 20–30 weeks' gestation (IQR in parentheses)

	6–14 weeks	20–30 weeks	p value
Pre-glucose level, mg/dl			
Gestational diabetes, n = 58	91 (84–95)	87 (80–93)	0.008
No gestational diabetes, n = 1,631	85 (80–89)	79 (75–85)	<0.0001
Post-glucose level, mg/dl			
Gestational diabetes, n = 58	158 (144–175)	177 (168–197)	<0.0001
No gestational diabetes, n = 1,631	115 (96–135)	126 (107–145)	<0.0001
Post-pre-glucose level, mg/dl			
Gestational diabetes, n = 58	71 (56–86)	93 (80–113)	<0.0001
No gestational diabetes, n = 1,631	30 (12–50)	45 (28–65)	<0.0001

Table 3. Results of the glucose tolerance test, which involved the measurement of the plasma glucose level before and at 1, 2 and 3 h after the oral administration of 100 g of glucose, at 6–14 and 20–30 weeks' gestation (IQR in parentheses)

	6–14 weeks	20–30 weeks	p value
Pre-glucose level, mg/dl			
Gestational diabetes, n = 47	87 (81–92)	86 (79–98)	0.240
No gestational diabetes, n = 207	84 (79–89)	83 (77–88)	0.004
1 h post-glucose level, mg/dl			
Gestational diabetes, n = 47	166 (146–178)	198 (178–210)	<0.0001
No gestational diabetes, n = 207	146 (129–162)	158 (142–173)	<0.0001
2 h post-glucose level, mg/dl			
Gestational diabetes, n = 47	142 (120–153)	183 (170–194)	<0.0001
No gestational diabetes, n = 207	119 (103–136)	137 (122–150)	<0.0001
3 h post-glucose level, mg/dl			
Gestational diabetes, n = 47	105 (90–119)	150 (125–160)	<0.0001
No gestational diabetes, n = 207	96 (82–110)	112 (94–124)	<0.0001

0.701, 95% CI 0.639–0.762), post- (AUROC 0.912, 95% CI 0.892–0.932), and post-/pre-glucose levels (AUROC 0.890, 95% CI 0.864–0.916), but multiple regression analysis showed that significant independent contribution was provided only by post-glucose levels (fig. 3). Screening by the measurement of fasting plasma glucose level would detect 34 (58.6%) of the 58 cases of GDM at a false-positive rate of 30% with a glucose cutoff of 88.5 mg/dl.

In all 58 cases with GDM, the plasma glucose level after the administration of glucose was >130 mg/dl at 6–14 weeks and >140 mg/dl at 20–30 weeks. In the non-GDM group, 489 (30.0%) of the patients were classified as screen-positive at 20–30 weeks using the cutoff of 140 mg/dl, and at 6–14 weeks, 512 (31.4%) of patients would have been classified as screen-positive using the cutoff of 130 mg/dl (fig. 3).

Diagnostic Test

In the screening test at 20–30 weeks, the result was positive in 547 of 1,689 (32.4%) cases and in this screen-positive group, the GTT was positive in 58 and negative in 489. In 47 of the 58 cases with GDM, the screening test at 6–14 weeks was also positive but the GTT was negative. In 207 of the 489 cases without GDM, the screening test at 6–14 weeks was also positive and the GTT was negative. The pre-, 1, 2 and 3 h post-oral 100-gram glucose loads at 6–14 and 20–30 weeks in the 47 cases of GDM and the 207 cases without GDM are compared in table 3. The median pre-glucose levels at 6–14 compared to 20–30 weeks were higher in the non-GDM group and were not significantly different in the GDM group. The 1, 2 and 3 h post-glucose load at 6–14 weeks was significantly higher than at 20–30 weeks in both the GDM and non-GDM groups.

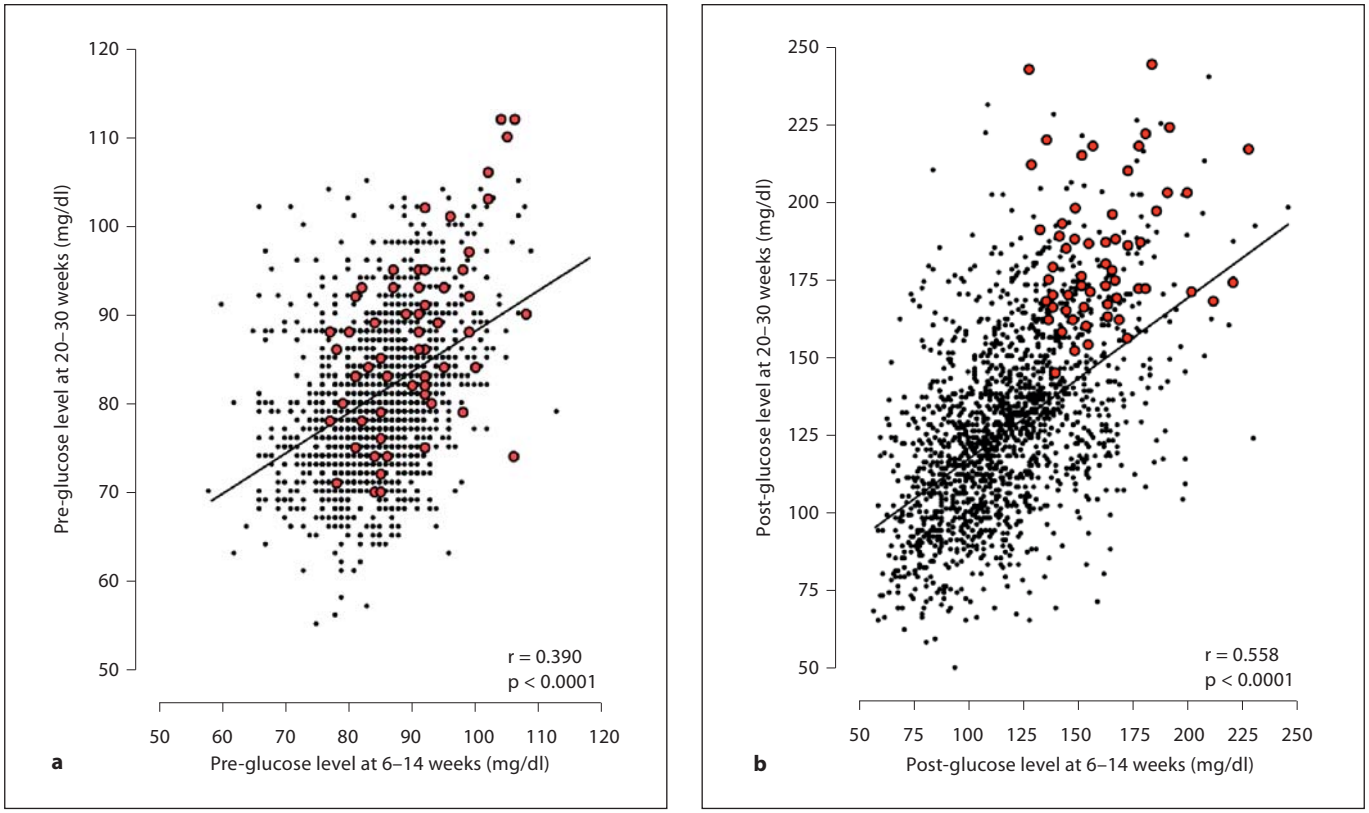

Fig. 2. Results of the 50-gram GCT for GDM. Association of plasma glucose levels at 6–14 and 20–30 weeks' gestation in patients with GDM (large circles) and those without GDM (black dots) in fasting (**a**) and 1-hour (**b**) plasma glucose level.

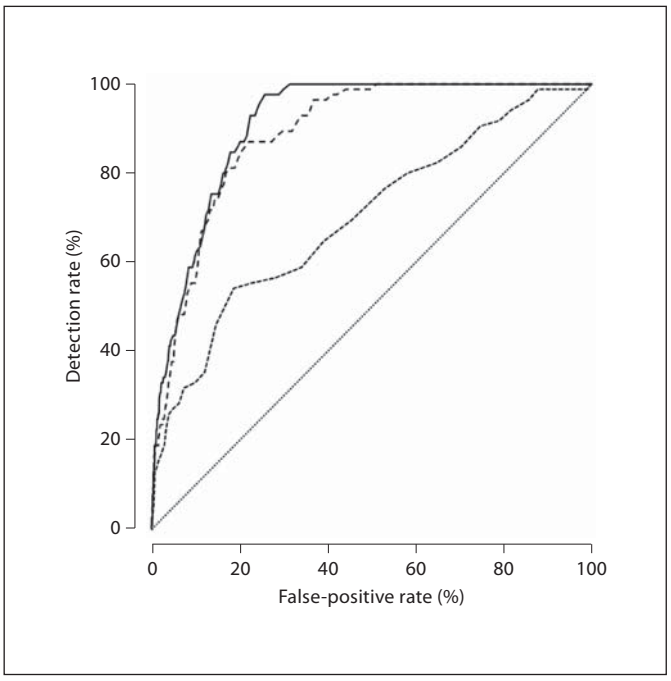

Fig. 3. ROC curves in the prediction of GDM by the 50-gram GCT at 6–13 weeks' gestation. Fasting plasma glucose level (· · · · ·), 1-hour glucose (——) and difference between the 1-hour and fasting glucose level (– – –).

The median ratios of glucose level at 20–30 weeks to that at 6–14 weeks at 1, 2 and 3 h post-glucose load in the GDM group were 1.18 (IQR 1.09–1.35), 1.29 (IQR 1.21–1.55) and 1.35 (IQR 1.12–1.52), respectively, and for the non-GDM group, they were 1.10 (IQR 0.95–1.23), 1.13 (IQR 0.99–1.29) and 1.14 (IQR 0.98–1.33), respectively, and each ratio was significantly higher in the GDM than in the non-GDM group ($p = 0.001$, $p < 0.0001$ and $p = 0.001$, respectively).

In the patients with a screen-positive result at 6–14 weeks ($n = 416$), we modified the cutoffs of the 1, 2 and 3 h post-glucose load by the median ratios of 1.18, 1.29 and 1.35, respectively, derived from the glucose level at 20–30 weeks to that at 6–14 weeks in the GDM group. The cutoffs for a positive GTT were reduced from 190 to 161 mg/dl for 1 h post-, from 165 to 128 mg/dl for 2 h post- and from 145 to 107 mg/dl for 3 h post-glucose load. On the basis of these cutoffs, the GTT was positive in 55 (74.3%) of 74 cases with GDM and in 92 (26.9%) of the 342 cases without GDM.

Discussion

The findings of this study demonstrate that, firstly, in the screening for GDM in the first trimester of pregnancy, the cutoff for the 1-hour plasma glucose level after the oral administration of 50 g of glucose should be 130 mg/dl rather than 140 mg/dl, and secondly, in the first-trimester diagnosis of GDM, the cutoffs for the 1-, 2-, and 3-hour blood glucose levels after the oral administration of 100 g of glucose should be 18–35% lower than the recommended cutoffs for the late second trimester of pregnancy. The study confirms that risk factors for the development of GDM include increased maternal age and BMI and family history of diabetes [15].

A limitation of this and most other studies on screening for GDM is the assumption that that the sensitivity of the 1-hour glucose challenge test (GCT) performed in the late second trimester of pregnancy is 100%, and therefore, a diagnostic test is performed only in the screen-positive group. Ideally, validation of screening results requires the performance of a diagnostic test in all cases, as was originally done by O'Sullivan and Mahan [16, 17]. We assumed that in all cases of GDM, the 1-hour glucose level after a challenge test at 20–30 weeks would have been 140 mg/dl or more. We found that there is a high association between the 1-hour plasma glucose level at 6–14 weeks and that at 20–30 weeks and demonstrated that if in the first trimester we had used a cutoff of 130 mg/dl, all cases of GDM would have been included in the screen-positive group. A previous study of 124 singleton pregnancies undergoing a 50-gram GCT in the first trimester and again at 26–32 weeks has also reported a high association between the 1-hour plasma glucose levels between the two measurements with an r value of 0.54 [18].

Our study has demonstrated that although in the GDM group the median fasting plasma glucose level was higher than in the non-GDM group, the performance of first-trimester screening for GDM by fasting plasma glucose is substantially lower than in screening by the GCT with a detection rate of 59 versus 100%, at a false-positive rate of about 30%. These results are similar to those of a screening study of 4,876 singleton pregnancies at 7–12 weeks, including 135 that were subsequently diagnosed with GDM, which reported that with fasting plasma glucose the detection rate of GDM was 61.5%, at a false-positive rate of 28.4% [19].

In both the GCT and GTT, the increment in plasma glucose concentration from before to after the ingestion of the glucose load in both the GDM and non-GDM groups was greater at 20–30 weeks than at 6–14 weeks. This finding confirms the well-described diabetogenic effect of pregnancy which increases with gestation [9–12]. The widely accepted gestation of 24–28 weeks for screening for GDM is based on an arbitrary recommendation which attempts to achieve a balance between two opposing factors [20]: (1) the need to maximize the detection rate of GDM by testing as late in pregnancy as possible, and (2) to maximize the duration of therapeutic intervention for reduction in the maternal and perinatal complications associated with GDM.

The desire to diagnose GDM in the first trimester of pregnancy could be achieved by lowering the currently used second-trimester cutoffs in plasma glucose levels both for screening and diagnosis of the condition. An alternative strategy would be to use only the 50-gram GCT and treat the 1-hour plasma glucose level as a continuous variable. This could then be combined with maternal factors and other biomarkers to estimate patient-specific risks not for GDM itself, whose definition and diagnostic criteria remain controversial, but rather for measurable adverse consequences or associations of GDM, such as incidence of neonatal macrosomia, or the development of type 2 diabetes in the mother or the neonate within a predefined period after delivery.

The proposal of merging the screening and diagnostic tests into one is compatible with the recent recommendation that the traditional two-stage approach for the diagnosis of GDM of using a 50-gram GCT followed by a

100-gram GTT should be replaced by a 75-gram single test [21, 22]. We selected 50 g rather than 75 g because the latter is likely to be more acceptable in the first trimester of pregnancy when the incidence of nausea and vomiting is at its highest. Similarly, the proposal that plasma glucose should be treated as a continuous rather than categorical variable is compatible with the results of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [23]. In this study, more than 25,000 non-diabetic pregnant women underwent a 75-gram, 2-hour oral GTT at 24–32 weeks and the doctors were blinded to the results, unless the fasting plasma glucose was >105 mg/dl or the 2-hour value was >200 mg/dl. The study demonstrated that there is a continuous rather than categorical relationship between maternal glycaemia and the incidence of neonatal macrosomia and other adverse outcomes. In this respect, we disagree with the recommendations that the gestation for carrying out the 75-gram glucose test should remain at 24–28 weeks and that plasma glucose cutoffs should be used to define a disease [21].

In our study, the diagnosis of GDM led to the management of affected pregnancies in specialist clinics for dietary advice, monitoring of glucose levels and ultimately the use of insulin therapy. Consequently, the incidence of neonatal macrosomia could not be used as an outcome measure for the development of prediction models based on a combination of maternal factors and plasma glucose levels. Indeed, the incidence of macrosomia in our GDM group was lower than in the non-GDM pregnancies. The alternative outcome measure was the need for insulin therapy which was carried out in 22% of our patients. Insulin treatment was given to about 45% of GDM cases diagnosed by the traditional criteria at 6–14 weeks, in 15% of those diagnosed at 20–30 weeks but with a screen-positive result at 6–14 weeks and in none of those diagnosed at 20–30 weeks but with a screen-negative result at 6–14 weeks. This finding demonstrates the inverse association between gestational age and severity of glucose intolerance and indirectly provides further support for, firstly, treating post-prandial plasma glucose level as a continuous rather than a categorical variable and, secondly, for the hypothesis that avoidance of at least some of the adverse consequences of glucose intolerance is more likely to be achieved by therapeutic interventions in earlier than later pregnancy.

Screening for GDM at 11–13 weeks' gestation can be provided by a combination of maternal characteristics and biomarkers. Algorithms derived from multiple regression analysis of maternal characteristics and obstetric history can potentially identify about 60% of pregnancies that will develop GDM, at a false-positive rate of 20% [15, 24]. The detection rate can be improved to about 75% by the addition of biomarkers, such as adiponectin and sex hormone-binding globulin [15]. It is likely that future non-intervention studies will attempt to combine maternal factors, biomarkers and the 1-hour plasma glucose level after the administration of a 50-gram glucose load at 11–13 weeks to estimate patient-specific and adverse outcome-specific risks rather than GDM per se.

Acknowledgement

The study was supported by a grant from The Fetal Medicine Foundation (UK Charity No. 1037116).

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