Int J Diabetes Dev Ctries (January–March 2018) 38(1):20–25
DOI 10.1007/s13410-016-0545-y

ORIGINAL ARTICLE

Early diagnosis of gestational diabetes mellitus during the first trimester of pregnancy based on the one-step approach of the International Association of Diabetes and Pregnancy Study Groups

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Received: 17 September 2016 / Accepted: 21 December 2016 / Published online: 27 December 2016

Abstract To examine the utility of the 75 g oral glucose tolerance test (OGTT), conducted according to the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG), for the early diagnosis of gestational diabetes mellitus (GDM) and to propose new cut-off values. A total of 350 prospectively enrolled patients were admitted to Inonu University School of Medicine Obstetrics and Gynecology Outpatient Clinic between April 2012 and January 2015 for first-trimester screening. Gestational diabetes mellitus (GDM) during the first trimester of pregnancy (11–13 weeks) was diagnosed using the 75-g OGTT. In patients who tested negative, the OGTT was repeated at 24–28 weeks. GDM was diagnosed in 14.6% of the patients, of whom 80.3% were diagnosed during the first trimester. In these patients, there were no remarkable changes in fasting plasma glucose level when a fasting glucose cutoff of 92 mg/dl was used for the diagnosis of GDM. The sensitivity and specificity of the OGTT were 66.6% and 99.3%, respectively (area under the receiver operating characteristic curve [AUROC] 0.892, 95% CI 0.855–0.923, $p < 0.001$). The cutoff value for a positive 75-g OGTT result was reduced from 180 to 173 mg/dl for the 1-h post-glucose load (AUROC 0.908, 95% CI 0.873–0.936, $p < 0.001$) and from 153 to 129 mg/dl for the 2-h post-glucose load (AUROC 0.861, 95% CI 0.515–0.775, $p < 0.001$). The 75-g OGTT based on IADPSG criteria can be used to detect 80% of GDM cases as early as the first trimester. A modification of current cutoff values would improve the sensitivity of the test but lower its specificity.

Keywords Early diagnosis · Gestational diabetes · Hyperglycemia · Oral glucose tolerance test · Pregnancy

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Introduction

Gestational diabetes mellitus (GDM) is defined as a carbohydrate intolerance detected for the first time during pregnancy. Although the screening and diagnosis of GDM remain controversial, GDM is one of the most common complications of pregnancy [1]. It is also associated with an increased risk of maternal and perinatal complications, such as preterm delivery, gestational hypertension, preeclampsia, macrosomia, increased risk of cesarean delivery, shoulder dystocia, neonatal hyperbilirubinemia, and respiratory distress syndrome [2]. In 2010, based on the results of the Hyperglycemia and Adverse Pregnancy Outcome study, which specifically evaluated the relationship between maternal glucose levels and maternal, perinatal, and neonatal outcomes, the International Association of Diabetes and Pregnancy Study Group (IADPSG) recommended new criteria for the diagnosis of GDM based on a universal 75-g, 2-h oral glucose tolerance test (OGTT) performed during pregnancy. Patients in whom any single fasting, 1 h, or 2 h value exceeded a certain threshold value are considered positive for GDM [3].

The screening and diagnosis of GDM are traditionally performed at 24–28 weeks gestation, given the increased diabetogenic effect of pregnancy during the late second trimester [4]. Early GDM screening during pregnancy is recommended only for women with undiagnosed type 2 diabetes or with risk factors, including a prior history of GDM, known glucose metabolic impairment, and obesity [5]. Other authors have advocated an alternative GDM screening strategy for earlier testing, adjusting the established criteria of the test accordingly [6]. An effective definition of patients at high risk of GDM would allow early dietary advice and pharmacological interventions, thereby improving pregnancy outcomes and reducing GDM-related maternal and perinatal complications.

The aim of this study was to examine the utility of the 75-g OGTT for the early diagnosis of GDM. Based on the results, we propose new cutoff values for this test to allow an early diagnosis of GDM during the first trimester of pregnancy.

Materials and methods

The study was approved by the Ethics Committee of Inonu University Faculty of Medicine (no: 2012/4-1). Verbal and written information was provided to all study participants in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all patients prior to their enrollment. The study population consisted of 350 prospectively enrolled patients who were admitted to Inonu University School of Medicine Obstetrics and Gynecology Outpatient Clinic between April 2012 and January 2015 for first-trimester GDM screening. GDM was diagnosed during the first trimester of pregnancy (11–13 weeks) based on a positive 75-g OGTT result, as defined by the IADPSG one-step diagnostic approach. After fasting for 8–10 h, the patients were requested to drink a solution containing 75 g glucose, followed by measurement of the venous plasma glucose concentration 1 and 2 h after ingestion. The diagnosis of GDM was defined based on a single glucose concentration that met or exceeded the threshold value (fasting value, 92 mg/dl; 1-h value, 180 mg/dl; and 2-h value, 153 mg/dl). Patients with a negative test result during the first trimester were tested again during the second trimester (24–28 weeks). Patients with pregestational diabetes, multiple pregnancies, pregnancies with major fetal anomalies (fatal or requiring prenatal and postnatal surgery), fetal death, chromosomal abnormalities, or genetic syndromes were excluded from the study.

The data are presented as means and standard deviations or as medians and interquartile ranges. The Shapiro-Wilk test was used to analyze data with a normal distribution, and one-way analysis of variance was used to compare the three groups (GDM-negative group, GDM diagnosed during the first trimester, and GDM diagnosed during the second trimester). The Bonferroni test was used for multiple comparisons among the groups. The GDM-negative and late-onset (second trimester) GDM groups were compared using the Mann-Whitney *U* test. Area under the receiver operating characteristic curve (AUROC) analysis was performed to examine the performance of the accepted cutoff values proposed by the IADPSG during the first trimester and to determine new cutoff values predictive of first-trimester GDM. The optimum cutoff values were identified using the Youden index. A p value <0.05 was considered to indicate statistical significance. SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) was used for all data analyses.

Results

First-trimester GDM screening was performed in 350 patients. Of the 51 patients diagnosed with GDM, 41 (80.3%) had a positive OGTT result during the first trimester and 10 (19.7%) during the second trimester. Patient testing at 11–13 weeks resulted in an 11.7% positivity rate according to the IADPSG criteria. In the GDM-negative patients, the OGTT was repeated at 24–28 weeks, and 2.8% of these retested patients were positive for GDM. Thus, of the 350 patients who were screened, 14.6% had GDM, 80.3% of whom were diagnosed during the first trimester (Fig. 1).

The median age of the patients with early-onset (i.e., first trimester) GDM was 32.80 ± 6.98 years, which was significantly older than that of patients in the GDM-negative group ($p = 0.011$). Patients in the early-onset GDM group also had a significantly higher body mass index (26.90 ± 5.68) than that of GDM-negative patients ($p = 0.002$). Compared with patients in the early-onset GDM and GDM-negative groups, patients in the late-onset (second trimester) GDM group were not significantly different in terms of age or BMI. Table 1 summarizes the maternal and pregnancy characteristics of the three groups.

The fasting plasma glucose (FPG) level and the plasma glucose levels at 1 and 2 h after administration of the 75-g glucose load at 11–13 and 24–28 weeks gestation are shown in Table 2 for the 299 patients without GDM, the 41 patients with early-onset GDM, and the 10 patients with late-onset GDM. At 11–13 weeks, the median FPG level and the 1- and

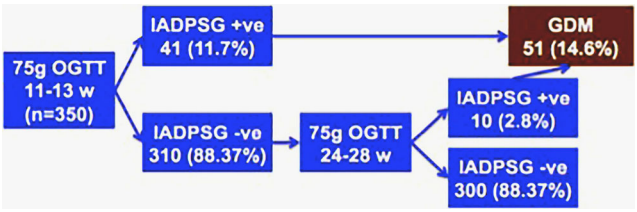

Fig. 1 A flow chart summarizing the diagnosis of GDM at 11–13 and 24–28 weeks gestation

Table 1 Maternal and pregnancy characteristics of groups

Maternal characteristics	Normal (n = 299)	Early-onset GDM (n = 41)	Late-onset GDM (n = 10)
Age	30.12 ± 5.39[a]	32.80 ± 6.98[b]	32.20 ± 5.53[ab]
Gravidy	2.42 ± 1.54[a]	3.24 ± 1.92[b]	3.50 ± 2.12[ab]
Parity	1.00 ± 1.06[a]	1.48 ± 1.59[b]	1.30 ± 1.05[ab]
Abortus	0.41 ± 0.92[a]	0.65 ± 0.96[ab]	1.20 ± 1.54[b]
BMI (kg/m^2)	24.25 ± 4.12[a]	26.90 ± 5.68[b]	24.50 ± 5.64[ab]
History of GDM	4 (1.3)[a]	3 (7.3)[a]	0 (0)[a]
DM in first degree relatives	1 (0.3)[a]	0 (0)[a]	0 (0)[a]
History of having macrosomic fetus	10 (3.3)[a]	3 (7.3)[a]	0(0)[a]
Mode of previous delivery			
Nulliparous	124 (41.5)[a]	11 (26.8)[a]	1(10)[a]
Vaginal	85 (28.4)[a]	15 (36.6)[a]	5(50)[a]
Cesarean	90 (30.1)[a]	15 (36.6)[a]	4 (40)[a]

Each subscript letter denotes a subset of group categories whose row proportions do not differ significantly from each other at the 0.05 level

2-h post-glucose load levels were significantly higher in the early-onset GDM group than in the GDM-negative and late-onset GDM groups. Also, during the first trimester, the median FPG and 2-h post-glucose load levels were similar between the GDM-negative and late-onset GDM groups, whereas the 1-h post-glucose load level was significantly higher in the late-onset GDM group than in the GDM-negative group.

Among the 51 patients diagnosed with GDM either in the first or second trimester, AUROC analysis was used to examine the performance of the IADPSG cutoff values in predicting first-trimester GDM and to determine new cutoff values predicting first-trimester GDM. The positivity rate, sensitivity, and specificity of the 75-g OGTT during the first trimester, according to the IADPSG cutoff values and the new cutoff values determined by AUROC analysis, are shown in Tables 3 and 4, respectively. There were no remarkable changes in terms of fasting plasma glucose level in the FPG cutoff value of 92 mg/dl [sensitivity 66.6%, specificity 99.3%; AUROC 0.892, 95% confidence interval (CI) 0.855–0.923, $p < 0.001$] for the diagnosis of GDM during the first trimester. The cutoff value for a positive 75-g OGTT result was reduced from 180 to 173 mg/dl for the 1-h post-glucose load (AUROC 0.908, 95% CI 0.873–0.936, $p < 0.001$) and from 153 to 129 mg/dl for the 2-h post-glucose load (AUROC 0.861, 95% CI 0.515–0.775, $p < 0.001$). Lowering the thresholds to 173 and 129 mg/dl for the 1- and 2-h post-glucose loads, respectively, improved the sensitivity from 60.7 to 70.4% and from 52.9 to 76.4%, respectively, but reduced the specificity of the test from 100 to 97.3% and from 99 to 91.3%, respectively. The AUROC values predicting GDM using the 75-g OGTT at 11–13 weeks gestation are shown in Fig. 2.

During the antenatal period, preeclampsia and preterm birth rates were similar among the three groups, as were gestational age at delivery and the frequency of cesarean delivery. Neonatal birth weight was significantly higher in the early-onset GDM group than in the other two groups. The macrosomia rate and 1- and 5-min Apgar scores were similar among the three groups, as were the rates of neonatal

Table 2 Results of the 75-g OGTT, which included the measurement of the plasma glucose level before and after 1 and 2 h oral administration of 75 g of glucose, at 11–13 and 24–28 weeks gestation (median and IQR in parentheses)

	Normal (n = 299)	Early-onset GDM (n = 41)	Late-onset GDM (n = 10)	p value
Fasting glucose levels (mg/dl)				
11–13 weeks	79 (76–84)[a]	99 (95–130)[b]	81 (78–85)[a]	<0.001
24–28 weeks	81 (77–87)[a]	–	93 (93–95)[b]	<0.001
1-h post-glucose level (mg/dl)				
11–13 weeks	134 (106–151)[a]	188 (180–202)[b]	152(135–177)[c]	<0.001
24–28 weeks	144 (131–156)[a]	–	186.5 (181–191)[b]	<0.001
2-h post-glucose level (mg/dl)				
11–13 weeks	101 (88–111)[a]	160 (148–166)[b]	105 (93–134)[a]	<0.001
24–28 weeks	106 (97–121)[a]	–	165.5 (151–166)[b]	<0.001

Each subscript letter denotes a subset of group categories whose row proportions do not differ significantly from each other at the 0.05 level

Table 3 The positive rate, sensitivity, and specificity of the IADPSG cutoff values of the 75-g OGTT in the first trimester GDM prediction after ROC curves analysis

	Cutoff point	Positive rate (%)	Sensitivity (95% CI)	Specificity (95% CI)
Fasting glucose (mg/dl)	92	9.4	66.6 (52.1–79.2)	99.3 (97.6–99.9)
1-h post-glucose level (mg/dl)	180	8.2	60.7 (46.1–74.2)	100 (98.8–100.0)
2-h post-glucose level (mg/dl)	153	7.4	52.9 (38.5–67.1)	99.0 (97.1–99.8)

hypoglycemia and requirement for the neonatal intensive care unit. There were no cases of perinatal mortality. The perinatal and neonatal outcomes of the patients are shown in Table 5.

Discussion

In this study, the 75-g OGTT was successful in detecting 80% of first-trimester GDM cases according to the IADPSG criteria. Our results showed that after oral administration of 75 g glucose, the cutoffs for 1- and 2-h blood glucose levels during first-trimester testing should be 4–15% lower than those during late second-trimester testing. Maegawa et al. [7] performed four screening tests in patients during their first trimester of pregnancy: a 50-g oral glucose challenge test, a casual plasma glucose measurement, measurement of glycosylated hemoglobin levels, and an FPG assay. After 2–4 weeks, they performed a 75-g OGTT as a diagnostic test in the same patients. Of the 749 pregnant women enrolled in the study, 22 (2.9%) were diagnosed with GDM. Consistent with the results of our study, the majority (14/22, 63.6%) of the GDM cases were detected during the first trimester. Dashora et al. [8] evaluated 564 patients during the first trimester of pregnancy for glucose intolerance using the 75-g OGTT. Patients with normal results were retested two or three times over 2-month intervals, with the last test conducted during the seventh month of gestation. Abnormal glucose tolerance was detected in 21.3% of pregnant women, 88% in whom GDM was detected before the seventh gestational month. In that study, 10% of the women required a second test, and 2.5% were not diagnosed until after the third test. The authors suggested that a significant percentage of cases can be detected early in pregnancy rather than waiting until 7 months gestation, as has been performed traditionally. They also concluded that early and multiple screenings for GDM can improve the detection of GDM and positively influence pregnancy outcomes. Our study further demonstrated that our three groups of patients did not differ significantly in terms of perinatal and neonatal outcomes. This is attributed, at least in part, to the implementation of preventative measures in the early-onset GDM group, enabling a reduction in the adverse effects of hyperglycemia during an earlier stage of pregnancy.

Several reports have suggested the utility of FPG measurements in GDM screening. Reichelt et al. [9] showed that in diabetes screening, a FPG level of 89 mg/dl maximizes both the sensitivity (88%) and specificity (78%) of the tolerance test, as 22% of the women in their study tested positive according to this criterion. Agarwal et al. [10] suggested that the variation in performance of FPG measurements observed among many studies may be due to the various diagnostic criteria used. They compared the effect of four different diagnostic criteria applied to the same 75-g OGTT values in a cohort of 4602 pregnant women and concluded that FPG was very useful in GDM screening based on the American Diabetes Association guidelines as the diagnostic criteria (as applied to the 75-g OGTT). The FPG measurements obtained in the present study afforded a sensitivity and specificity of 66.6 and 99.2%, respectively, during the first and second trimesters, using a FPG cutoff value of 92 mg/dl. In addition, AUROC analysis did not lead to remarkable changes in the FPG cutoff value used for the diagnosis of first-trimester GDM.

The increase in the plasma glucose concentration from before to after the 75-g OGTT was greater at 24–28 weeks than at 11–13 weeks, in both the GDM-negative and late-onset GDM groups. This finding confirms the well-described diabetogenic effect of pregnancy, which increases with gestation

Table 4 The positive rate, sensitivity, and specificity of the proposed cutoff values of the 75-g OGTT in the first trimester GDM prediction after ROC curves analysis

	AUC (95% CI)	Criterion (95% CI)	Positive rate	Sensitivity (95% CI)	Specificity (%95 CI)	*p*
Fasting glucose (mg/dl)	0.892 (0.855–0.923)	>92 (>81– > 94)	9.4	66.6 (52.1–79.2)	99.3 (97.6–99.9)	<0.0001
1-h post-glucose level (mg/dl)	0.908 (0.873–0.936)	>173 (>157– > 177)	12.2	76.4 (62.5–87.2)	97.3 (94.8–98.8)	<0.0001
2-h post-glucose level (mg/dl)	0.861 (0.820–0.895)	>129 (>123– > 149)	16.8	76.4 (62.5–87.2)	91.3 (87.5–94.2)	<0.0001

AUC area under curve, *CI* confidence interval, *h* hour

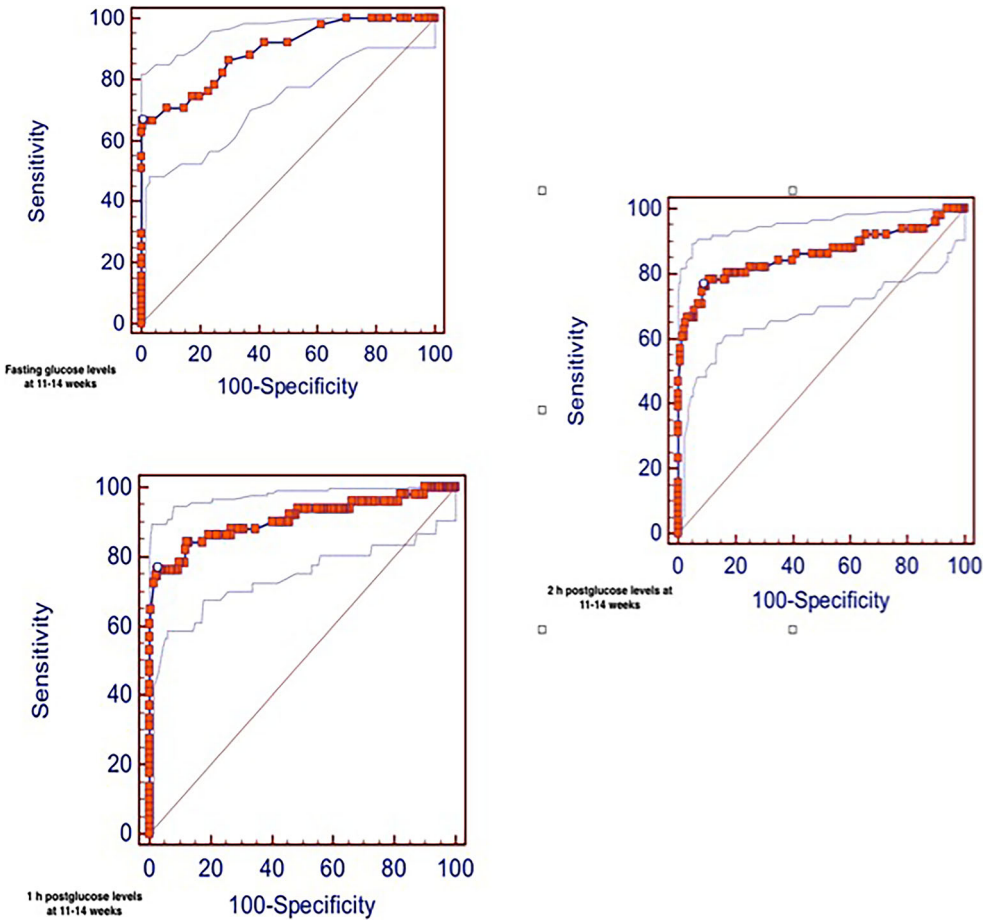

Fig. 2 ROC curves in the prediction of GDM by the 75-g OGTT at 11–14 weeks gestation

time. Consistent with the results of this study, Siegmund et al. [11] evaluated the daily blood glucose profiles of healthy, normal-weight pregnant women at different gestational stages and demonstrated a tendency towards increased blood glucose levels during gestation weeks 16, 22, and 30. The widely accepted timing for GDM screening of 24–28 weeks gestation is based on achieving the maximum GDM detection rate by testing as late in pregnancy as possible while still allowing for an optimal therapy duration to reduce or prevent GDM-associated maternal and perinatal complications.

Plasencia et al. [12] examined the performance of the cutoff values established for GDM screening and diagnostic tests in

Table 5 Perinatal and neonatal outcomes of the groups

	Normal (n = 299)	Early onset GDM (n = 41)	Late onset GDM (n = 10)
Preeclampsia	2 (0.6)[a]	0 (0)[a]	0 (0)[a]
Preterm birth <37 week	31 (10.3)[a]	3 (7.3)[a]	1 (10.0)[a]
Gestational age at delivery	39.1 (34.5–41.0)[a]	38.5 (33.1–41.2)[a]	39.3 (35.5–40.1)[a]
Delivery by cesarean section	123 (41.1)[a]	18 (43.9)[a]	5 (50.0)[a]
Birth weight (g)	3255 (1850–4650)[a]	3540 (2280–4750)[b]	3320 (2650–4560)[a]
Macrosomia (>4500 g)	8 (2.6)[a]	2 (4.8)[a]	1 (10)[a]
1-min Apgar score < 7 (n)	8 (2.6)[a]	2 (4.8)[a]	0 (0)[a]
5-min Apgar score < 7 (n)	7 (2.3)[a]	1 (2.4)[a]	0 (0)[a]
Neonatal hypoglycemia	7 (2.3)[a]	4 (9.7)[a]	1 (10)[a]
Neonatal intensive care unit requirement	10 (3.3)[a]	2 (4.8)[a]	0 (0)[a]

Each subscript letter denotes a subset of group categories whose row proportions do not differ significantly from each other at the 0.05 level

1765 patients with singleton pregnancies during their first trimester. Their results suggested that the 1-h plasma glucose cutoff level after a 50-g glucose load should be 130 mg/dl rather than 140 mg/dl. The authors recommended reducing the cutoff levels for a positive 100-g OGTT from 190 to 161 mg/dl, from 165 to 128 mg/dl, and from 145 to 107 mg/dl for the 1-, 2-, and 3-h post-challenge measurements, respectively. In our study, there were no remarkable changes in the FPG cutoff value for a first-trimester diagnosis of GDM. However, for the 1- and 2-h post-glucose loads following a 75-g OGTT, reductions in the cutoffs from 180 to 173 mg/dl and from 153 to 129 mg/dl, respectively, were recommended, as these new values would allow GDM diagnosis as early as the first, rather than the second, trimester of pregnancy. Lowering the cutoffs for both time points improved the sensitivity of the 75-g OGTT but at the expense of reducing the specificity.

In conclusion, in this study, we demonstrated that the 75-g OGTT based on the one-step approach of the IADPSG was successful in detecting 80.3% of GDM cases as early as the first trimester of pregnancy. To increase the diagnostic performance of the test during the first trimester, the currently used cutoffs should be lowered to enable early detection of GDM. The detection of GDM during the first trimester would help reduce the adverse effects of hyperglycemia by allowing preventative measures to be initiated at an earlier stage of pregnancy. A further benefit would be avoiding unnecessary testing during the second trimester of pregnancy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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