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Abstract

Background: Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance with onset during the second or third trimester of pregnancy.

Aims: The purpose of this study was to investigate the prevalence of pregnant women who were not screened for gestational diabetes mellitus and compare the maternal and fetal outcomes.

Methods: Women who refused to attend gestational diabetes screening test (n=162) at a maternity hospital in Ankara, Turkey, between October 2014 and January 2015 were included in this prospective cohort study. Control group was recruited from age-parity and BMI matched women who have accepted gestational diabetes screening test (n=194).

Results: The prevalence of pregnant women who did not attend gestational diabetes screening test was 12%. Women who did not attend gestational diabetes screening test were at higher risk for idiopathic polyhydramnios (p=0.026). Prevalence of GDM was 8.8% (n=17) and 30.9% (n=50) respectively. The maternal and fetal outcomes of GDM patients were similar in both groups. Women who did not attend GDM screening test had increased risk for mild idiopathic polyhydramnios in late gestation.

Conclusions: Fasting and postprandial plasma glucose screening can replace gestational diabetes mellitus screening in women who refuse glucose load.
Introduction

Gestational diabetes mellitus (GDM) is defined as impaired glucose tolerance with onset during the second or third trimester of pregnancy (1). The prevalence of GDM is as high as 9.2%, according to a 2014 analysis by the Centers for Diseases Control and Prevention (2). Risk factors for GDM include advanced maternal age (> 25 years), multiparity, multiple pregnancy, family history of diabetes, and pregnancy losses at second or third trimester, history of fetal macrosomia childbirth, GDM history in previous pregnancy, and overweight and obesity (3).

Pregnancies with complicated GDM are faced with abortion, large for gestational age (LGA), intrauterine growth restriction, polyhydramnios, and intrauterine fetal death, preeclampsia, and delivery complications including caesarean section, birth trauma, neonatal hypoglycemia, hyperbilirubinemia, polycythemia, and requirement for neonatal intensive care unit (NICU). Therefore, early diagnosis and treatment of GDM may reduce fetal exposure to maternal hyperglycemia and decrease maternal and fetal complications (4,5).

Screening for GDM is recommended as a single or two-stage oral glucose tolerance test (OGTT) between 24 and 28 weeks of pregnancy (6). In this study, we aimed to determine the prevalence of pregnant women who refused to attend a gestational diabetes screening test and compared their maternal and fetal outcomes with those who accepted a gestational diabetes screening test. Our second aim is whether fasting and postprandial plasma glucose screening can replace gestational diabetes mellitus screening in women who refuse glucose load.
Methods

This prospective, cohort study was conducted among 1450 patients admitted for routine antenatal follow-up between 24 and 28 weeks of gestation at a maternity hospital in Ankara, Turkey, between October 2014 and January 2015. The hospital is a maternity care hospital and a tertiary referral center that has 18 000 births annually. This study was conducted according to the Declaration of Helsinki (7). The institutional review board (# 18/2014) approved the study. Exclusion criteria included multiple gestation, clinical evidence or historical pre-gestational of diabetes, fasting plasma glucose exceeding 126 mg/dl or the two-hour postprandial or GCT (Glucose Challenge Test) value exceeding 200 mg/dl, history of a positive glucose tolerance test in the first trimester, and women with known diseases of the kidney, liver or thyroid gland. Maternal age, gravidity, parity, body mass index, family history of diabetes, history of gestational diabetes and macrosomia (>4000 g) in their previous pregnancy were recorded. All patients were informed about gestational diabetes mellitus and screening of GDM. Women who refused to attend gestational diabetes screening test were followed with fasting and postprandial 2nd hour plasma glucose levels, initially at screening time and at 32 weeks of gestational age. Abnormal glucose test was defined as fasting venous plasma glucose level > 92 mg/dl and / or postprandial two-hour venous plasma glucose level >120 mg/dl.

The control group was selected by simple random sampling method and 194 age-parity matched women who had accepted the gestational diabetes screening test were recruited in the study. Women in the control group underwent a two stage GCT. A positive 50-g GCT is defined as glucose level one hour after glucose challenge of at least 140 mg/dl. Women who had a positive 50-g GCT were advised to follow a normal diet three days before the 100-g OGTT. The standard protocol for the OGTT was used; after an eight-hour overnight fast, venous plasma samples were collected when fasting one, two and three hours after the receipt of the oral 100-g glucose load. Women who had a positive OGTT test according to the criteria identified by Carpenter and Coustan were labeled as having GDM. GDM was diagnosed if the two diagnostic criteria were found (8).

Diagnosis for polyhydramnios was made measuring either amnion fluid index (AFI) and/or single deepest pocket (SDP) (9,10). Polyhydramnios was defined and categorized into three groups according to severity: mild polyhydramnios (AFI of 24–30 cm and/or SDP 8–11.9 cm), moderate polyhydramnios (AFI 30.1–35 cm and/or SDP 12–15.9 cm) and severe polyhydramnios (≥ 35 cm and/or SDP ≥ 16 cm) (10). Macrosomia defined as fetal birth weight exceed 4000 g. Deliveries occurring prior to 37 weeks of gestation were recorded as preterm deliveries.

Patients with abnormal plasma glucose level (FPG >92 mg/dl and or PPG >120 mg/dl) or
positive OGTT were followed by a qualified dietitian and initially received an 1800–2200 calorie diet with the meal composition of 40–45% carbohydrates, 20% protein, and 40% fat, individualized due to pre-pregnancy weight, activity level, dietary intake, and weight gain. FPG and PPG tests two hours after a standard breakfast were performed 10 days after nutritional counseling. Treatment targets to maintain maternal capillary glucose concentration were at <92 mg/dl in the fasting state, and <120 mg/dl two hours after starting the meal. If levels were still above the mentioned objectives despite repeated FPG and PPG measurements, the patient was treated by insulin if necessary.

Clinical patient characteristics such as age, gravity, body mass index (BMI), gestational age, socio-economic and education level, family history of diabetes, previous pregnancy GDM and macrosomia history were evaluated. Weight gain, labor, delivery, birth outcomes, obstetrics complications included hypertension, diabetes, oligohydramnios, polyhydramnios, premature rupture of membrane, and neonatal outcomes including first and fifth minute Apgar scores, birth weight, fetal sex, and NICU admission were obtained from medical records.

An enzymatic method using Roche automated clinical chemistry analyzer (Hitachi 912 analyzer, Roche Diagnostics GmbH, Germany) was used for quantitative determinations of blood glucose. Glucose was measured using a commercial glucose oxidase kit (Glucose GOD-PAP, Roche Diagnostics GmbH, Germany). Detection range was 2–450 mg/dl (0.11–25 mmol/l) and intra- and inter-assay coefficient of variation (CV) values was 0.9 and 1.8%, respectively.

Distribution of the data was analyzed with Kolmogorov–Smirnov and Shapiro–Wilks test. The data were presented as mean with standard deviation (SD) or median with a range for continuous variables, and as a number with percentage for categorical variables. The Mann–Whitney U test was used to analyze non-normally distributed data. An independent sample t-test was used to compare the continuous variables with normal distribution. The Chi-Square and Fisher-Exact tests were used to compare categorical variables. Data were evaluated using SPSS for Windows 23.0 (SPSS Inc., Chicago, IL, USA). The significance boundary was given as 0.05.

For the power calculation, we assumed a GDM prevalence of 5–10% and an effect size of 0.3 (11–13). The sample size calculation for the entire study population of 1450 women involved a two sample comparison with a 5% level of significance (alpha) and power of 0.95 and gave a study population of 220 patients in each group. This sample size was able to detect a 0.5 standard deviation difference in continuous variables given the same power and significance level. However, during the study period only 162 patient refused to be screened by 50 gr GCT and the actual power of this study was therefore 0.91 with alpha and beta error probabilities of
Results

In the present study there were 1450 pregnant women admitted at the hospital for routine follow-up at 24–28 weeks between October 2014 and January 2015. Sixty-two patients were excluded from this study due after quitting antenatal follow-up or having any chronic disease before pregnancy. Five of 62 women were excluded from this study due to the fasting plasma glucose exceeding 126 mg/dl or the two-hour postprandial value exceeding 200 mg/dl and were referred to an endocrinology specialist. Among the 1388 pregnant women, 162 women (12%) refused to attend screening test and 1226 women (82%) accepted gestational diabetes screening test. The control group recruited 194 age-parity matched women who had accepted gestational diabetes screening test.

Mean maternal age of all women included in this study was 27 (17–43 years) years and median parity was one (0–6). In the study group, median FPG was 81 (61–124) mg/dl, postprandial plasma glucose (PPPG) was 102 (74–198) mg/dl. Fifty women (30.8%) in this group had abnormal glucose levels. Twenty-three women (14%) had FPG ≥92 mg/dl and five women had complicated polyhydramnios and macrosomia. Thirty-seven women (10.4%) had PPPG ≥120 mg/dl and five women had complicated polyhydramnios and macrosomia. Out of the 147 patients (90.7%) who refused to attend GDM screening test and the 177 patients (91.2%) in the control group, at least one risk factor for GDM was indicated. Prevalence of GDM in the control group was 8.8% (n=17) whereas it was 30.9% (n=50) in the GCT refusing group. There were no statistically significant differences between groups in terms of maternal age, gravity, parity, body mass index, socio-economic level, education level, family history of diabetes, history of gestational diabetes in their previous pregnancy, whether they delivered a macrosomic baby (> 4000 g), or number of risk factors for gestational diabetes (P > 0.05). Demographic characteristics of patients are shown in Table 1.

All the patients recruited in the study had only diet treatment. No insulin or oral antidiabetic drugs are needed. Pregnant women who refused to attend gestational diabetes screening test had higher rates of polyhydramnios compared to control group (p=0.026). All of polyhydramnios cases were mild. There were no significant differences between control and study group for neonatal outcomes. Obstetric complications and neonatal outcomes in two groups are shown in Table 2 and 3. There are three cases of neonatal hypoglycemia and hyperbilirubinemia in the study population without statistical significance (three (1.9%) and zero (0%) p=0.093). When two groups were reanalyzed according to gestational diabetes diagnosis, the maternal and fetal
outcomes were similar in both groups of those with and without diabetes diagnosis (Table 4 and Table 5).

Discussion

In the present study, we evaluated the prevalence of pregnant women who refused to attend gestational diabetes screening, and compared their maternal and fetal outcomes with the women screened by two-step GCT. The prevalence of women who refused to attend GDM screening was 12%. We also found that idiopathic polyhydramnios is higher in women who refused to attend gestational diabetes screening test compared with the control group.

Although the current evidence is controversial and insufficient to interpret the benefits and harm of GDM screening, there are studies showing that treating GDM allows for a significant reduction in macrosomia, neonatal fat mass, shoulder dystocia, preeclampsia, and caesarean section (5,12). Therefore, the American Diabetes Association recommended that all pregnant women should undergo risk assessment for GDM at the first antenatal visit and if necessary, this group should undergo glucose testing as soon as possible (1). Women with abnormal glucose levels in the first trimester should be classified as type 2 diabetes (1). Patients not known to have prior diabetes or normal glucose values at the initial screening should go for repeat testing between 24 and 28 weeks of gestation (1). In addition, the American College of Obstetricians and Gynecologists suggested that all pregnant women should be tested between 24 and 28 weeks of gestation (13). The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study found that there were also associations between increased maternal hyperglycemia and preterm delivery, shoulder dystocia, preeclampsia, and hyperbilirubinemia (14). Adverse obstetrics outcomes and perinatal mortality rates decrease because of better glycemic control (15).

However, although the debate is ongoing about a cut-off value in the screening, the GCT can be performed as a 100-g three-hour test and a 75-g two-hour test (16–18). Although the 100-g three-hour GTT is generally applied as the second stage of the two-stage approach while the 75-gm two-hour test is applied as the only test in the one-stage approach, this is optional. For example, the Canadian Diabetes Association (CDA) clinical guidelines suggest the 75-gm two-hour GTT (18). Even if carbohydrate loading is recommended for three days before the screening test, it is not necessary in patients who do not want to follow a low-carbohydrate diet (19,20).
GDM prevalence has been steadily increasing with the rise of obesity and type 2 diabetes. The prevalence of GDM reported by studies worldwide has ranged from 1–14% (16). For our control group, prevalence of GDM was estimated at 8.8%. This rate is somewhat lower than the GDM prevalence reported by Yeral et al. (11.2%) using two-step methods in the Turkish population (17). Majority of women (90%) in our study population had one or more risk factors of GDM.

Glucose solutions used for oral glucose tolerance test (OGTT) and GTT have a hyperosmolar content at high concentration and can cause gastric irritation, delayed emptying, and gastrointestinal osmotic imbalance, leading to nausea and, in a small percentage of women, vomiting ((21). Therefore, some pregnant women could not succeed in completing the OGTT because of rejecting to undergo the test, vomiting, eating during the test, or other reasons. For this purpose, some alternatives to the oral screening and GTTs have been described in the literature and are better tolerated. These methods include offering the hyperosmolar glucose drink on ice, using candy, a predefined meal, or commercial soft drinks instead of a standard glucose monomer or polymer solution, and intravenous GGT. But these options seem to be less sensitive and have not been affirmed in prospective randomized studies ((22–27). None of them have been confirmed by ADA or ACOG. Agarwal et al. reported that 5% (n=242) of 4844 women who underwent the OGTT at 24–28 weeks of gestation were not able to complete this test (28). To the best of our knowledge, this is the first study determining the prevalence of pregnant women who refused to attend gestational diabetes screening test and evaluating maternal and neonatal outcomes in the Turkish population, and was found to be as high as 12%. This can be explained by patients having lower socio-economic levels (85%) and education levels (78%) and the popularity for high protein / low carbohydrate diets resulting in refusal of GDM screening test.

A number of studies have focused on the association between fasting plasma glucose (FPG) and adverse perinatal outcomes. HAPO study demonstrated that FPG ≥95 mg/dl was correlated with fetal macrosomia in the second half of pregnancy at the time of screening at 24–28 weeks (14). A review of FPG as a screening test for GDM demonstrated that when the ADA diagnosed criteria used with 75-g or 100-g OGTT, it appears to be a good test for the screening of GDM. If used with WHO criteria (FPG ≥109 mg/dl), it could limit the usefulness of FPG as a screening of GDM due to poor specificity and high false–positive rates (29). Tam et al. recommended that the FPG (threshold of 88 mg/dl (4.9 mmol/l) is a better test rather than using GCT or postprandial glucose for universal screening (30).

Previous studies had focused on postprandial two-hour glucose screening (30–35) mostly with accompanying FPG (31–34) for the diagnosis of GDM. Bhattacharya et al. (34) and Rust et al. reported against the use of PPPG, but Bhattacharya determined FPG cutoff value as 105 mg/dl (higher than the conventional threshold of 92/mg/dl) and Rust et al. did not evaluated FPG (34,35). While Senanayake et al. found FPG superior to PPPG when screening for GDM (33),
Huddleston et al. reported that if FPG is normal then a two-hour postprandial glucose test is not needed (31). Agarwal et al. (32) pointed to the high false-positive rates of FPG and PPPG testing, whereas we found that GDM prevalence turned out to be 31% with FPG and PPPG screening when compared to 9% of regular 50 gr GCT.

There are some limitations to the present study. Initially HbA1c levels were not evaluated. However, screening with HbA1c is not routinely performed and recommended (36). The study population was less than we have predicted. Lastly, all the patients recruited in the study had only diet treatment. No insulin or oral antidiabetic drugs were needed, which shows that all the cases were mild.

Polyhydramnios is a condition associated with an excess volume of amniotic fluid. The incidence of polyhydramnios ranges from 1–2% in general obstetric practice and most cases display mild severity. The most common causes of mild polyhydramnios are maternal diabetes, multiple gestation, fetal infection, fetal structural anomalies, and idiopathic factors (40). In our study, only idiopathic polyhydramnios was found to be higher in women who did not attend GDM screening test compared with those in the control group \( n=7 \ (3.7\%) \ vs \ n=1 \ (0.5\%) \). All cases had mild severity and were diagnosed in the third trimester. Six out of seven patients were correlated with high levels of plasma glucose. The remaining one case was accepted as idiopathic polyhydramnios because of evaluation of fetal infection including toxoplasma, rubella and cytomegalovirus was negative in the first trimester, and mid-trimester the fetal ultrasound was normal. Some of these idiopathic cases may be constituted by impaired glucose metabolism that had not been diagnosed with FPG and PPG. In the follow-up women who did not attend GDM screening test, shortening the interval of visit, use of different cut-off levels on FPG/PPG or additional parameters, and adequate counselling before pregnancy can be useful in prevention of polyhydramnios.

**Conclusion**

As GDM is linked to many serious fetal and maternal complications, screening, diagnosis, treatment, and follow-up of GDM is recommended for all pregnant women. Although pregnant women were screened by FPG and PPPG in the second trimester, 40% of fetal macrosomia and 28.6% polyhydramnios were missed out, and other adverse perinatal outcomes were not increased. Therefore fasting and post-prandial plasma glucose screening could be a good individual screening for gestational diabetes mellitus in women who refuse glucose load.

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