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ORIGINAL ARTICLE

One-step versus two-step diagnostic testing for gestational diabetes: a randomized controlled trial

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ABSTRACT

Objective: To evaluate the incidence of gestational diabetes mellitus (GDM) using the one-step as compared with the two-step approach.

Study design: This was a parallel group nonblinded randomized trial conducted at Thomas Jefferson University Hospital (TJUH) in Philadelphia, Pennsylvania from June 2016 to December 2016. The primary outcome was GDM incidence in the one-step compared to the two-approach. Pregnant women without a history of pregestational diabetes were offered screening for GDM at gestational age 24–28 weeks. Obese women, defined as having a BMI $\geq$30 kg/m^2, as well as those with a history of a pregnancy complicated by GDM, a history of a macrosomic baby (>4000 g), or with polycystic ovarian syndrome (PCOS), were offered early screening at their initial prenatal visit, and screening was repeated at 24–28 weeks if initially normal. Women were excluded if they had pre-existing diabetes or had a history of bariatric surgery. Women who were eligible were randomized in a 1:1 ratio to either the one-step or two-step approaches. A sample size of 142 women was planned per group. Women randomized to the one-step approach, after an overnight fast, were given a 2-h glucose tolerance test, which consisted of a 75-g glucose load. Blood glucose levels were measured fasting, at 1 h and 2 h after the glucose load. Diagnostic cutoffs for GDM diagnosis were one value of either fasting $\geq$92 mg/dL, 1 h $\geq$180 mg/dL, or 2 h $\geq$153 mg/dL, respectively. Women randomized to the two-step approach were given a nonfasting 50-g glucose load, and the blood glucose level was measured an hour after the glucose load. If that value was $\geq$135 mg/dL, the patient had a 3-h glucose tolerance test consisting of a 100-g glucose load. Diagnostic cutoffs for GDM diagnosis for this 3-h test were $\geq$2 abnormal values of fasting $\geq$95 mg/dL, 1 h $\geq$180 mg/dL, 2 h $\geq$155 mg/dL and 3 h $\geq$140 mg/dL, respectively. All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated.

Results: Two hundred eighty-four women agreed to take part in the study and underwent randomization from June 2015 to December 2015. Of them, 249 completed the screening and were followed up for the primary endpoint. Out of the 249 women who completed the screening, 123 were assigned to the one-step group and 126 to the two-step group. GDM occurred in 10 women (8.1%) in the one-step group, and 7 women (5.6%) in the two-step group ($p = .42$). Preeclampsia, preterm birth (PTB), induction of labor, mode of delivery and incidence of gestational age (OASIS) were not significantly different. Perinatal outcomes were similar as well.

Conclusions: Screening for GDM with one-step, compared with the two-step approach, resulted in a similar incidence of GDM.

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Diabetes mellitus; diet; hyperglycemia; obese; stillbirth

Introduction

Gestational diabetes mellitus (GDM) is associated with significant maternal and neonatal morbidity [1–5]. Screening for GDM has been the subject of much debate. The American College of Obstetricians & Gynecologists (ACOG) currently recommends screening with the two-step approach, starting with an initial 50-g glucose challenge test (GCT) followed, if the GCT is abnormal, by a 100 g oral glucose tolerance test (OGTT) [6].

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In 2008, the Hyperglycemia and Pregnancy Outcome (HAPO) study demonstrated a linear relationship between maternal glycemic control and adverse pregnancy outcomes, screening with a one-step approach using a 75 g OGTT [7]. In 2010, in an effort to promote a more unified global guideline for screening and diagnosing GDM, the International Association of Diabetes in Pregnancy Study Group (IADPSG) adopted GDM screening based on the results of the HAPO study [8].

However, this decision has not been without controversy. Specifically, the one-step approach using a 75 g OGTT leads to a considerably lower threshold for GDM diagnosis than the two-step approach. The one-step approach has resulted in an increased GDM incidence, up to 18% [8], as compared to approximately 6% using the two-step approach [6]. The incidence, however, varies widely in different populations and carries possible clinical implications on obstetrical practice [9–15]. As a result, national and international organizations have set differing guidelines for screening and diagnosing GDM, some recommending the two-step approach (e.g. ACOG) [6] while others the one-step approach (e.g. IADPSG, WHO, FIGO, American Endocrine Society) [7,8,16–18]. Moreover, the randomized controlled trials comparing the incidence of GDM using the one-step versus the two-step approach have shown differing results [11,12,19].

The aim of our study was to evaluate the incidence of GDM using the one-step as compared with the two-step approach in randomized controlled trial (RCT).

Materials and methods

This was a parallel group nonblinded RCT conducted at Thomas Jefferson University Hospital (TJUH) in Philadelphia, Pennsylvania. Institutional Review Board (IRB) approval was obtained before active patient recruitment.

All pregnant women without a history of pregestational diabetes were offered screening for GDM at gestational age 24–28 weeks. Obese women, defined as having a BMI $\geq$30 kg/m^2, as well as those with a history of a pregnancy complicated by GDM, a history of a macrosomic baby (>4000 g), or with polycystic ovarian syndrome (PCOS), were offered early screening at their initial prenatal visit, and screening was repeated at 24–28 weeks if initially normal. Women were excluded if they had pre-existing diabetes or had a history of bariatric surgery. Women meeting these criteria were consented and then randomized to GDM screening with either the one-step or two-step approaches.

Randomization was based on a 1:1 computer-generated schema in random-sized blocks (size 4, 6 and 8). Sequentially numbered opaque envelopes were used to mask the allocation until patient's consent was given to participate in the study, at which time randomization and allocation was performed. Patients and clinicians were unblinded to the screening test they were assigned to.

For the women randomized to the one-step approach, after an overnight fast, they were given a 2-hour glucose tolerance test, which consisted of a 75-g glucose load as recommended by IADPSG [8]. Blood glucose levels were measured fasting, at 1 and 2 h after the glucose load. Diagnostic cutoffs for GDM diagnosis were one value of either fasting $\geq$92 mg/dL, 1 h $\geq$ 180 mg/dL, or 2 h $\geq$ 153 mg/dL, respectively.

For women randomized to the two-step approach, they were given a nonfasting 50-g glucose load as recommended by ACOG [6], and the blood glucose level was measured an hour after the glucose load. If that value was $\geq$135 mg/dL, the patient had a 3-h glucose tolerance test consisting of a 100-g glucose load. Diagnostic cutoffs for GDM diagnosis for this 3-h test were $\geq$2 abnormal values of fasting $\geq$95 mg/dL, 1 h $\geq$180 mg/dL, 2 h $\geq$155 mg/dL and 3 h $\geq$140 mg/dL, respectively.

Gestational age was confirmed on all women prior to their 24–28 weeks GDM screening. Once GDM diagnosis was made, all women met with a dietician and a diabetic educator. Subsequently, blood-glucose selfmonitoring was initiated four times per day (fasting, and 2-h postprandial) using a portable glucometer. Medical treatment was started initially with an oral hypoglycemic agent usually if >30% of blood glucose values were elevated (fasting glucose level >95 mg/dL and 2-h postprandial >120 mg/dL). If treatment with an oral agent, either metformin or glyburide, was maximized and blood glucose control remained suboptimal (>30% of blood glucose values still elevated, i.e. fasting glucose level >95 mg/dL 2-h postprandial >120 mg/dL), insulin treatment was recommended.

Diet-controlled GDM patients did not have any extra antenatal surveillance. For women requiring medical treatment for GDM, nonstress testing was performed weekly starting at 32 weeks and then twice weekly starting at 36 weeks, along with serial growth scans every 4 weeks. Delivery at 39 0/7 to 39 6/7 week was recommended to all women with GDM on medical treatment.

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated. The primary outcome was the incidence of GDM. Maternal secondary outcomes included preeclampsia, preterm birth (PTB) < 37 weeks, induction of labor, mode of delivery and obstetric anal sphincter injuries (OASIS). Perinatal secondary outcomes included birth weight, large for gestational age (LGA) (defined as estimated fetal weight on antenatal ultrasound >90th percentile), intrauterine growth restriction (IUGR) (defined as estimated fetal weight on antenatal ultrasound <10th percentile), polyhydramnios (defined as maximum vertical pocket >8 cm, or amniotic fluid index >24 cm), macrosomia (defined as birth weight >4000 g), shoulder dystocia, 5 min Apgar score <7, neonatal hypoglycemia (defined as glucose <40 mg/dL), neonatal hyperbilirubinemia requiring phototherapy, stillbirth (defined as intrauterine fetal demise >20 weeks), neonatal death (defined as death of a live-born infant within the first 28 days of live) and perinatal death (defined as either stillbirth or neonatal death).

Our sample size calculation was based on a GDM incidence increase from 6% as an average background rate of GDM in the USA to an 18% GDM rate as anticipated according to the HAPO trial [9]. We calculated that with a sample size of 284 (142 in each group), the study would have at least 80% power with an alpha of 0.05.

Data analyses for this study were generated using Statistical Package for Social Sciences (SPSS) v 19.0 (IBM Inc, Armonk, NY). Data are shown as mean ± SD, or as number (percentage). Univariate comparisons of dichotomous data were performed with the use of the chi-square test with continuity correction. Comparisons between groups were performed with the use of the T-test to test group means by assuming equal within-group variances. No adjustment for multiple comparisons was made, so the findings of the secondary outcomes should be considered exploratory. A 2-sided *p* value less than 0.05 was considered significant. This trial was registered at ClinicalTrials.gov (identifier NCT03073330).

Results

Two hundred eighty-four women consented to take part in the study and underwent randomization. Of them, 249 completed the screening and were followed up for the primary endpoint, while 35 never performed any GDM screening. Out of the 249 women who completed the GDM screening, 123 were assigned to the one-step group and 126 to the two-step group (Figure 1).

Overall, 26.9% (67/249) of the women were obese and 11.6% (29/249) were smokers. The mean age was about 29 years. Four women (3.3%) in the one-step, and 3 women (2.4%) in the two-step group had history of GDM in a prior pregnancy (Table 1).

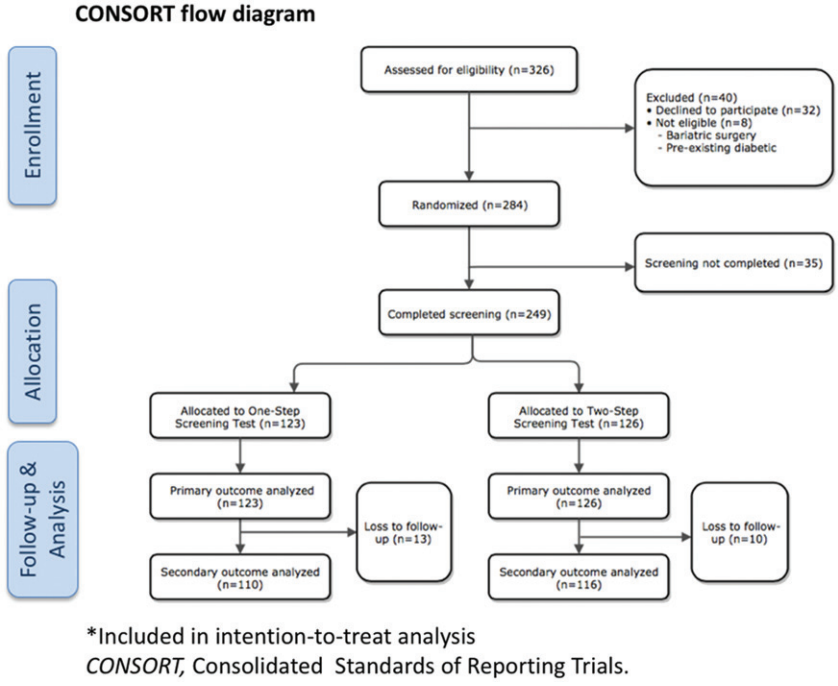

Figure 1. Study flow chart [25].

Table 1. Characteristics of the included women.

	One-step ($n = 123$)	Two-step ($n = 126$)
Age (years)	29.5 ± 5.9	29.5 ± 5.3
Ethnicity		
White	40 (32.5%)	47 (37.3%)
Black	64 (52.0%)	61 (48.4%)
Hispanic	6 (4.9%)	3 (2.4%)
Asian	11 (9.0%)	10 (7.9%)
Other/declined to answer	2 (1.6%)	5 (4.0%)
BMI ≥30	33 (26.8%)	34 (27.0%)
Smoking	8 (6.5%)	21 (16.7%)
Prior GDM	4 (3.3%)	3 (2.4%)
Prior macrosomia	12 (9.8%)	4 (3.2%)
Family history of GDM	42 (34.2%)	39 (31.0%)
Prior cesarean delivery	19 (15.5%)	20 (15.9%)
Chronic hypertension	11 (8.9%)	12 (9.5%)
PCOS	1 (0.8%)	2 (1.6%)

Data are presented as mean ± standard deviation or as number (percentage).
GDM: gestational diabetes mellitus; PCOS: polycystic ovarian syndrome; BMI, body mass index; GDM, gestational diabetes mellitus; PCOS, polycystic ovarian syndrome.
p values not significant for all variables.

Table 2. Maternal outcomes.

	One-step ($n = 123$)	Two-step ($n = 126$)	*p* value
GDM	10 (8.1%)	7 (5.6%)	.42
Women with GDM receiving medical treatment[a]	5 (4.1%)	4 (3.2%)	.34
Secondary outcomes	**One-step ($n = 110$)**	**Two-step ($n = 116$)**	
Preeclampsia	10 (9.1%)	9 (7.8%)	.78
Preterm birth	12 (10.9%)	10 (8.6%)	.56
Induction of labor	51 (46.4%)	52 (44.8%)	.69
Vaginal Delivery	70 (63.6%)	75 (64.7%)	.87
Cesarean delivery	35 (31.8%)	36 (31.0%)	.89
Cesarean delivery for arrested labor	3 (2.7%)	10 (8.6%)	.57
Operative vaginal delivery	5 (4.6%)	5 (4.3%)	.93
OASIS	3 (2.7%)	5 (4.3%)	.51

Data are presented as mean ± standard deviation or as number (percentage).
GDM: gestational diabetes mellitus; GA: gestational age; OASIS: obstetrical anal sphincter injuries.
[a]Medical treatment included metformin, glyburide and insulin.

All women who started the screening test in the one step approach group completed the diagnostic testing, while 5 (4.2%) in the two-step approach group did not complete it ($p = .04$). The latter was due to not presenting for the 3 h OGTT test after an abnormal result of the nonfasting 1-h 50-g glucose loading dose.

GDM occurred in 10 women (8.1%) in the one-step group, and 7 women (5.6%) in the two-step group ($p = .42$) (Table 2).

Data for secondary outcomes were available for 110 women in the one-step group, and for 116 women in the two-step group (Figure 1). Preeclampsia, PTB, induction of labor, mode of delivery, and incidence of OASIS were not significantly different between the groups (Table 2). Perinatal outcomes were similar as well (Table 3).

Table 3. Perinatal outcomes.

	One-Step ($n = 110$)	Two-Step ($n = 116$)	*p* value
Birth weight (g)	3214 ± 679	3256 ± 482	.82
LGA	3 (2.7%)	5 (4.3%)	.51
IUGR	7 (6.4%)	8 (6.9%)	.87
Polyhydramnios	6 (5.5%)	4 (3.5%)	.46
Macrosomia	9 (8.2%)	7 (6.0%)	.53
Shoulder dystocia	0	1 (0.86%)	.99
5-min Apgar score < 7	1 (0.9%)	2 (1.7%)	.59
Neonatal hypoglycemia	8 (7.3%)	12 (10.4%)	.42
Neonatal hyperbilirubinemia requiring phototherapy	8 (7.3%)	2 (1.7%)	.05
Fetal demise >20 weeks	1 (0.9%)	1 (0.9%)	.97

Data are presented as mean ± standard deviation or as number (percentage).
LGA: large for gestational age; IUGR: intrauterine growth restriction.

One stillbirth occurred in each group, both in women diagnosed with GDM by early screening. In the one-step group, it was associated with a Dandy Walker malformation. In the two-step group, it was associated with a spontaneous preterm loss at 22 weeks. No cases of neonatal death were reported in either group.

Discussion

This nonblinded randomized trial showed that screening for GDM with the one-step approach, compared with the two-step approach, resulted in a similar incidence of GDM. The one-step approach was also associated with a similar incidence of maternal and perinatal outcomes compared to the two-step approach.

The 8.1% incidence of GDM using the one-step IADPSG screening approach was far less than the anticipated 18% [20]. Studies have reported varying GDM incidences using the one-step approach, ranging from 3.6% to 35.5% [9,15–19]. This discrepancy is likely due to different populations with different predisposing factors for GDM.

The findings from a recent meta-analysis of the three RCTs published so far in the literature comparing the one-step to the two-step approach which included 2333 women, showed that the one-step approach for GDM screening was associated with similar incidences of GDM (8.4% versus 4.3%), but with significantly lower incidences of PTB (3.7% versus 7.6%), cesarean delivery (16.3% versus 22.0%), macrosomia (2.9% versus 6.9%), neonatal hypoglycemia (1.7 versus 4.5%), and admission to the intensive care unit (4.4% versus 9.0%) compared to two-step screening [21]. The results of our RCT reveal very similar nonsignificant

incidences of GDM with the one-step versus the two-step approaches. We found no significant differences in maternal or perinatal outcomes.

Our study has several strengths. This is the largest RCT in the USA assessing GDM incidence with the two most widely used screening approaches. Our study population is a diverse urban population in the USA representing a multiethnic cohort along with comorbid predisposing factors to GDM.

Our study has several limitations as well. Our primary outcome was GDM incidence and not a maternal or perinatal outcome, which are the ultimate goals for choosing a certain screening test. It was underpowered as there was around a 10% loss rate for the primary outcome due to some women never having GDM screening, and the numbers for the secondary outcomes were about another 10% less due to loss to follow up. Understandably, our population characteristics may not be reflective of populations in other geographical locations in the USA or other countries that may have other GDM predisposing factors.

Since the HAPO study results were published [7] and endorsed by IADPSG [8] and subsequently WHO [16] and FIGO [17], there were several concerns in the USA for adopting the one-step 2-h approach. The NIH consensus in 2013 rejected the one-step approach as the preferred GDM screening test due to concern over additional burden on the American health care system in view of the 18% anticipated GDM incidence [22].

The performance of a one-step approach, although fasting, gives the advantage of performing the test only once. In our study, about 4% of women who had the two-step approach and an abnormal result on the 1-h GCT, never performed the diagnostic 3-hour GTT test. More importantly, the one-step approach may improve the identification of women who had an abnormal 1-h GCT but a normal 3-h GTT. These women in particular are at risk of adverse maternal and perinatal outcomes, such as, for example, gestational hypertension, preeclampsia, preterm birth, macrosomia and cesarean delivery [23]. This may be explained by the fact that the two-step approach was designed to identify women at increased risk for developing type 2 diabetes [7], while the one-step approach was designed to identify adverse pregnancy outcomes based on the HAPO study findings [8].

Given the findings of our RCT, the concern about a major increase in the incidence of GDM by applying the IADPSG screening and criteria cutoffs for diagnosis may not be justified. As such, the cost implications may not be as high as projected [22]. Also, the identification of women with GDM and therefore at risk of developing type 2 diabetes later in life is another example of using pregnancy as window for future health [24].

In summary, screening for GDM with one-step, compared with the two-step approach, resulted in a similar incidence of GDM. A large, multicenter RCT in the USA representing different geographic locations with pregnancy outcomes as a primary outcome, and a cost-effectiveness analysis, is needed. This may answer the question if the one-step IADPSG GDM screening approach is beneficial for mothers and their babies, and cost-effective.

Disclosure statement

No potential conflict of interest was reported by the authors.

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