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Sensitivity of fasting glucose for gestational diabetes mellitus screening in Mexican adolescents based on the International Association of Diabetes and Pregnancy Study Groups criteria: a diagnostic accuracy study based on retrospective data analysis

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ABSTRACT

Objective: To evaluate the usefulness of fasting glucose for gestational diabetes mellitus (GDM) screening in Mexican adolescents using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. Secondary goals were to report the prevalence of GDM and perinatal outcomes in adolescent women with and without GDM.

Design: Retrospective cohort study

Setting: Level-three medical institution in Mexico City.

Participants: We included 1061 adolescent women aged 12 to 19 years with singleton pregnancy, 75-g oral glucose tolerance test (OGTT) administered between 11 and 35 weeks of gestation and had delivered in our institution.

Primary and secondary outcome measures: We calculated sensitivity, specificity, positive and negative predictive values (PPV and NPV, respectively), and positive and negative likelihood ratios (LR+ and –, respectively) with 95% confidence intervals for five fasting glucose cut-offs for GDM screening. We used IADPSG criteria to diagnose GDM. Different fasting glucose cut-offs were determined based on the receiver operating characteristic curve. Secondary measures were the prevalence of GDM and the frequency of perinatal outcomes in women with and without GDM.

Results: GDM was presented in 71 (6.7%) women. Fasting glucose ≥ 80 (4.5 mmol/L), 85 (4.7 mmol/L), and 90 mg/dL (5.0 mmol/L) were evaluated as cut-offs for the detection of GDM. These three cut-offs were characterized as follows: sensitivity: 97%, 94%, and 91%; specificity: 50%, 79%, and 97%; PPV: 12%, 23%, and 64%; NPV: 99% at all three points; LR (+): 1.9, 4.3, and 26.7; and LR (-): 0.06, 0.07, and 0.09, respectively. No significant differences in perinatal outcomes were found between adolescents with and without GDM.

Conclusions: A fasting glucose cut-off of ≥90 mg/dL (5.0 mmol/L) could be useful for GDM screening in Mexican adolescent women. This value provides an adequate detection rate and is a lower cost than the universal administration of one-step OGTT screening

Strengths and limitations of this research

- We show that a fasting glucose cut-off of ≥90 mg/dL (5.0 mmol/L) could be useful for GDM screening in Mexican adolescent women.
- This is the first study in Mexico and Latin America that explores the prevalence of GDM in adolescent women using IADPSG criteria.
- The study was retrospective, in a single centre and the results could be applicable to only Mexican, and, potentially, Latin women.
- The diagnostic validity of the test was not confirmed in a second independent population.
- The sample size is limited to compare perinatal outcomes.

INTRODUCTION

Roughly 16 million women between the ages of 15 and 19 give birth each year, accounting for approximately 11% of all births worldwide. Ninety-five percent of these births occur in low- and middle-income countries: 18% in Latin America and the Caribbean and more than 50% in sub-Saharan Africa. [1] Latin women (including Mexican women) are considered a high-risk population for diabetes and gestational diabetes mellitus (GDM). [2]

GDM refers to diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes. [2] A recently published adolescent pregnancy guideline recommended testing all adolescent women for GDM, similar to adult women, although the prevalence of GDM is generally lower in adolescent populations. [3]

Previous studies have reported GDM prevalence rates of 1.7% among North American adolescent women [4] and 0.97% in Mexican adolescent women; [5] both of these studies used Carpenter and Coustan criteria to diagnose GDM. [6] However, reports about the prevalence of GDM in adolescents diagnosed using the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria are limited. In adult Mexican women, we previously reported a prevalence of 30.3% of GDM using the IADPSG criteria; this figure is three-fold more than the prevalence obtained using the previous American Diabetes Association (ADA) criteria, which was valid until 2010. [7]

Pregnant adolescent women have less prevalence of being overweight or obese than the general pregnant population in Mexico. Additionally, most pregnant Mexican adolescent women are primigravid. In part, these characteristics contribute to a low prevalence of GDM in adolescent women. [8,9] However, most pregnant Mexican adolescent women have lower socio-economic status than adult women, [8] and lower socioeconomic status has been associated

with a higher frequency of consumption of unhealthy foods such as soft drinks, [10] which are associated with increased risk of GDM among Mexican women.

Currently, the screening and diagnosis of GDM in adolescent women is controversial because there is a low prevalence of GDM in this population and the strategies for diagnosing GDM are non-universal. The hyperglycaemia and adverse pregnancy outcomes (HAPO) study revealed significant associations between fasting and both 1- and 2-h glucose values during 75-g/2-h oral glucose tolerance test (75-g/2-h OGTT) and adverse perinatal outcomes. [11] Following the HAPO study results, the IADPSG recommended new criteria for the diagnosis and classification of hyperglycaemia during pregnancy. [12] According to the IADPSG, these new glucose thresholds correspond to 1.75 times the estimated odds for neonatal birth weight >90th percentile, cord C-peptide >90th percentile, and body fat percentage >90th percentile. [12] Some international associations support the use of the IADPSG criteria, including the ADA, [2] Endocrine Society, [13] World Health Organization (WHO), [14] and International Federation of Gynaecology and Obstetrics (FIGO). [15] However, other organizations such as the American Congress of Obstetricians and Gynecologists (ACOG) and the National Institute of Child Health and Human Development (NICHHD) recommend that health care providers continue to use a two-step approach to screen and diagnose GDM. [16,17] They argue that no evidence supports clinically significant improvements in maternal or new-born outcomes as a result of using IADPSG criteria to diagnose GDM and that following these criteria leads to a significant increase in health care costs. [16,17] All of the abovementioned organizations recommend universal screening for GDM using a one or two step strategy and do not have specific recommendations regarding GDM screening for adolescent women.

In contrast, the National Institute for Health and Care Excellence's (NICE) recent guidelines on diabetes in pregnancy recommend conducting 75-g/2-h OGTT at 24–28 weeks to test for GDM in women with risk factors, and proposed a diagnosis of GDM if women have one of the

following: a fasting glucose level ≥100 mg/dL (5.6 mmol/L) or a 2-h glucose level ≥140 mg/dL (7.8 mmol/L) during a 75-g/2h OGTT. [18] In accordance with this guideline, adolescent women should be tested for GDM if they have body mass index (BMI) ≥30 kg/m^2, a previous macrosomic baby weighing ≥4.5 kg or gestational diabetes, a first-degree relative with diabetes, and an ethnic family origin with a high prevalence of diabetes.

Agarwal MM, et al. recommended that the fasting plasma glucose can be used to decide if the OGTT is needed or not. This would ease the burden on the laboratory and save resources as the IADPSG recommendation to make every pregnant woman undergo the 75-g/2-h OGTT is too demanding. [19]

A systematic review and meta-analysis on GDM screening tests concluded that glucose challenge tests and fasting plasma glucose levels at 24 weeks of gestation are useful for identifying women who do not have GDM. [20] However, there are no studies that have analysed the utility of fasting glucose for the screening of GDM in adolescent women.

Our goal was to evaluate the usefulness of fasting glucose for GDM screening in Mexican adolescent women using IADPSG diagnostic criteria. Secondary goals were to report the prevalence of GDM and perinatal outcomes in adolescent women with and without GDM.

METHODS

Study design and participants

We conducted a retrospective cohort study and included adolescents who received prenatal care at Instituto Nacional de Perinatología (INPer), in Mexico City, from June 1st, 2011 to June 30th, 2014. Our institution is a reference centre that attends to high risk pregnancies, including those in adolescent women. Nearly 4000 births are attended at out institution every year. This

study was approved by the Internal Review Board of the INPer (Register number 212250-42081). Written informed consent from participants is not required by the Internal Review Board at our institution for retrospective studies. The inclusion criteria were women who were 12 to 19 years old, had a singleton pregnancy, had received a 75-g/2-h OGTT administered between 11 and 35 weeks of gestation, and had delivered in our institution. We excluded women with any pathology, including any type of pre-gestational diabetes, lupus, heart disease, substance abuse, hypothyroidism, epilepsy, leukaemia, bulimia, anorexia, depressive disorder, autoimmune cirrhosis, asthma, and multiple sclerosis. Adolescent women with pre-gestational diabetes (type 1 or 2) or GDM were referred from level-one or level-two attention centres to our institution and OGTT was avoided in this population.

Procedure

First, we identified adolescent women who delivered during the study period from the electronic register of births. After that we reviewed each non-electronic clinical record to check if the adolescent women had received an OGTT and in which week of gestation the test was performed. We selected pregnant adolescent women with OGTT between 11 and 35 weeks of gestation and if the inclusion criteria were fulfilled then the maternal and neonatal clinical records were requested to obtain data for analysis. Glucose was measured using the Vitros DT60 II chemistry system (OrthoClinical Diagnostics, Tilburg, The Netherlands), which has a sensitivity of 20 mg/dL (1.11 mmol/L) and a coefficient of variation of 1.4–1.8% according to the manufacturer´s instructions. The laboratory fulfils the Official Mexican Norm, NOM-007-SSA3-2011, for the organization and functioning of clinical laboratories in Mexico and is certified by the Global Certification Bureau for quality management systems in concordance with the ISO 9001:2015 norm. Gestational age was calculated from the last menstrual period; if women were unaware of when their last menstrual period was, or if the date was not reliable, we used the first trimester ultrasound measurement. In our institution GDM is diagnosed based on the

observation of two or more abnormal values during a 75-g/2-h OGTT: fasting ≥95 mg/dL (5.3 mmol/L), 1-h ≥180 mg/dL (10 mmol/L), and 2-h ≥155 mg/dL (8.6 mmol/L), according to recommendations from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus. [21] A single abnormal value was not considered sufficient for GDM diagnosis, and women who exhibited one such value did not receive GDM-specific treatment. Women with two or more abnormal glucose values during OGTT received medical nutrition therapy (MNT) and subsequent evaluation of glycaemic control at intervals of 2–4 weeks. For women who did not achieve glycaemic control with MNT, metformin was added at doses of 1500–2550 mg and/or insulin therapy (0.3–1.0 U/kg of body weight) in order to achieve goals for capillary glucose (self-monitoring): fasting <95 mg/dL (5.3 mmol/L) and 1-h postprandial <140 mg/dL (7.8 mmol/L).

Study variables

Fasting glucose was determined as part of the 75-g/2-h OGTT, and a receiver operating characteristic (ROC) curve and Youden's index was used to establish the cut-offs. The glucose values during the OGTTs were re-analysed according to IADPSG criteria, and GDM diagnosis was defined as one or more abnormal glucose values: fasting ≥92 mg/dL (5.1 mmol/L), 1-h ≥180 mg/dL (10 mmol/L), and 2-h ≥153 mg/dL (8.5 mmol/L). [12]

We also explored perinatal outcomes between women with and without GDM, for this analysis we included only GDM women without treatment. Large for gestational age was defined as a birth weight above the 90th percentile for sex and gestational age for Mexican people [22], and small for gestational age was defined as a birth weight below the 10th percentile for sex and gestational age for Mexican people. [22] Preeclampsia was defined as having a blood pressure of ≥140/90 mmHg, and proteinuria was defined as having a blood pressure of >300 mg/24 h. In the absence of proteinuria, we considered a diagnosis of preeclampsia based on a blood pressure of ≥140/90 mmHg and one or more of the following severity criteria outlined by the ACOG: thrombocytopenia, abnormal liver function, recent development of renal failure,

pulmonary oedema or brain or visual disturbances. [23] Gestational hypertension was defined as having a blood pressure of ≥140/90 mmHg after 20 weeks of gestation in the absence of proteinuria and severity criteria. [23] Intrauterine growth restriction was defined as the presence of an estimated foetal weight below the third percentile. [24] Polyhydramnios was defined by an amniotic fluid index of >18 cm. [25] Preterm birth was defined as birth after 20 and before 37 weeks of gestation. [26] Maternal overweight was defined as a BMI for age that was greater than a +1 Z-score, and obesity was defined as a BMI for age greater than a +2 Z-score based on the WHO references. [27]

Sample size

The sample size was calculated using recommendations for sample size estimation in diagnostic test studies. [28] In order to find a 90% fasting glucose sensitivity for GDM screening, considering a prevalence of GDM of 6% and a maximum marginal error of 15% with a 95% confidence level, a sample size of 345 participants was required. We decided to include all adolescent pregnant women who fulfil the inclusion criteria during the period of study.

Statistical Analysis

We used the Statistical Package for Social Science Software to conduct data analysis (SPSS 15, Chicago, IL, USA). Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as frequencies and proportions. Student's t- or Mann-Whitney U-tests were used to compare continuous variables according to the variable distribution, and the chi-square test or Fisher's exact test was used to evaluate differences in proportions. Statistical significance was considered if $p \leq 0.05$. Contingency tables were determined to calculate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR +), and negative (LR-) with 95% confidence intervals (CI) using different cut-off points that were determined based on the ROC curve and

Youden´s index. The difference in the risk of adverse perinatal outcomes between adolescents with and without GDM was determined by calculating the odds ratio (OR) with a 95% CI.

RESULTS

During the study period, there were 11,618 births at our institution of which 2,122 occurred in adolescent women. In total 1,315 pregnant adolescent women had received a 75-g/2-h OGTT. Of these women 1,061 met the inclusion criteria and 254 were excluded because of incomplete clinical records (n=105), twin pregnancies (n=13), incomplete OGTT (n=11), pregestational diabetes (n=2) and some additional pathology (n=123).

Most adolescent women who do not receive OGTT only received attention for hospitalization or delivery from various causes including: preterm labor, premature rupture of membranes, preeclampsia and labor in active phase. During the study period 32 pregnant adolescent women were referred to our institution with a previous diagnosis of some type of diabetes and had not received an OGTT, 19 adolescents with pre-gestational diabetes (8 with type 1 diabetes and 9 with type 2 diabetes), and 13 with GDM.

Seventy-one women were diagnosed with GDM, corresponding to a prevalence of 6.7% (CI 95% 5.3-8.4). The baseline data of adolescents with and without GDM collected upon study enrolment are listed in Table 1. Adolescents with GDM had higher weight and body mass index than adolescents without GDM. Prevalence of obesity was higher among GDM women compared to adolescents without GDM, (p=0.001). Among the 71 adolescents with GDM diagnosed according to IADPSG criteria, the frequencies of abnormal glucose values during the 75-g/2-h OGTT were as follows: fasting, 64 (90.1%); 1-h, 5 (7.0%), and 2-h, 7 (9.9%). Only, one adolescent had three abnormal glucose values and three adolescents had two abnormal glucose values.

Table 1. Characteristics of 1061 adolescent women at study admission.

Characteristics	Total adolescents n=1061	Adolescents without GDM n=990	Adolescents with GDM n=71	p*
Age (years)	16.1 ± 1.6	16.1 ± 1.5	16.2 ± 1.6	0.51
Weight (Kg)	59.1 ± 10.0	58.7 ± 9.8	63.9 ± 11.5	0.0001
Height (m)	1.56 ± 0.05	1.56 ± 0.05	1.56 ± 0.05	0.69
Body mass index (Kg/m^2)	24.3 ± 3.6	24.1 ± 3.5	26.2 ± 4.1	0.0001
Gestational age at 75-g/2-h OGTT (Weeks)	25.0 ± 4.4	24.1 ± 3.5	26.1 ± 4.1	0.008
Glucose (mg/dL)				
Fasting	80.2 ± 7.3	79.2 ± 6.2	94.4 ± 6.2	0.0001
1 h	105.2 ± 25.7	103.6 ± 24.6	127.9 ± 29.5	0.0001
2 h	97.9 ± 19.4	96.6 ± 18.4	114 ± 24.4	0.0001
Number of pregnancies				
1	923 (86.9)	865 (87.3)	58 (81.7)	0.08
2	121 (11.4)	110 (11.1)	11 (15.5)	0.17
3 or more	18 (1.7)	16 (1.6)	2 (2.8)	0.61
Normal weight	582 (55.6)	559 (57.3)	23 (32.4)	0.001
Overweight	357 (34.1)	324 (33.2)	33 (46.5)	0.01
Obesity	92 (8.8)	77 (7.9)	15 (21.1)	0.001
First-degree relative with type 2 diabetes	157 (14.8)	140 (14.1)	17(23.9)	0.0.2

Value expressed as mean ± standard deviation and/or frequency and (percentage). *Student t or Chi square test.

Figure 1 shows the ROC curve. The area under the curve was 0.96 (95% CI 0.93-0.99) with p= 0.0001. Table 2 shows the results of the characterization of the five fasting glucose cut-offs—75, 80, 85, 90, and 92 mg/dL (4.2, 4.5, 4.7, 5.0 and 5.1 mmol/L, respectively)—for GDM screening. We decided to choose five cut-off points for fasting glucose, based on Youden´s index, and to round the cut-off points up to the nearest integer (mg/dL). The best cut-off for fasting glucose according to Youden´s index was 90mg/dL. Using a cut-off of 85 mg/dL (4.72 mmol/L), a total of 275 (26%) OGTTs would be necessary, whereas only 95 (8.9%) would be required with a cut-off of 90 mg/dL (5.0 mmol/L).

Figure 1. Receiver operating characteristic curve shows area under the curve of 0.96

Table 2. Gestational diabetes mellitus screening capacity among Mexican adolescents with different fasting glucose cut-offs.

Fasting Glucose Cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	OGTT for perform
75 mg/dL (4.2 mmol/L)	98.5 (92-99)	22.4 (20-25)	7.9 (6-10)	99.6 (97-99.9)	1.3 (1.2-1.3)	0.06 (0.01-0.46)	834 (79%)
80 mg/dL (4.5 mmol/L)	97 (89–99)	50.1 (47–53)	11.6 (9–15)	99.6 (98.5–99.9)	1.9 (1.8–2.1)	0.06 (0.02–0.23)	559 (52.9%)
85 mg/dL (4.7 mmol/L)	94 (86–97)	78.6 (76–81)	22.9 (18–28)	99.5 (98–99.8)	4.3 (3.8–5.0)	0.07 (0.03–0.19)	275 (26%)
90 mg/dL (5.0 mmol/L)	91 (82–95)	96.6 (95–97)	64.2 (54–73)	99.4 (98.6–99.7)	26.7 (18.8–37.1)	0.09 (0.04–0.19)	95 (8.9%)
92 mg/dL 5.1 mmol/L	88.4 (78-94)	99.9 (99-100)	99.2 (91-99)	99.2 (98-99)	884 (123-6231)	0.12 (0.06-0.22)	60 (5.7%)

PPV= Predictive positive value, NPV= Negative predictive value, LR = Likelihood ratio, OGTT: Oral glucose tolerance test.

We observed no differences in perinatal outcomes among Mexican adolescent women with GDM without treatment and adolescent women without GDM, such as intrauterine growth restriction, polyhydramnios, gestational hypertension, preeclampsia, preterm birth, premature rupture of membranes, caesarean section, obstetric haemorrhage, large for gestational age, small for gestational age, and congenital malformations (Table 3). However, we did observe a higher incidence of neonates that were small for gestational age in adolescents without GDM. We excluded of this analysis four GDM women that received specific treatment for GDM, three with MNT and one with MNT plus metformin.

Table 3. Risk of adverse perinatal outcomes among Mexican adolescent women with GDM diagnosed by IADPSG criteria without treatment.

Adverse perinatal outcomes	Total n=1057	Without GDM n=990 n (%)	With GDM n=67 n (%)	Odds ratio (95% CI)	p
Intrauterine growth restriction	36 (3.4)	35 (3.5)	1 (1.5)	0.41 (0.06–3.1)	0.37
Polyhydramnios	13 (1.2)	12 (1.2)	1 (1.5)	1.2 (0.41 – 3.4)	0.84
Gestational hypertension	54 (5.1)	50 (5.1)	4 (6.0)	1.2 (0.28–5.5)	0.74
Preeclampsia	52 (4.9)	49 (4.9)	3 (4.5)	0.9 (0.27 – 2.9)	0.86
Preterm birth	140 (13.3)	130 (13.1)	10 (14.9)	1.15 (0.57 – 2.3)	0.67
Premature rupture of membranes	15 (1.4)	13 (1.3)	2 (3.0)	2.3 (0.51–20.5)	0.26
Caesarean section	542 (51.3)	505 (51)	37 (55.2)	1.18 (0.72–1.95)	0.50
Obstetric haemorrhage	28 (2.6)	26 (2.6)	2 (3.0)	1.14 (0.26–4.9)	0.86
Neonate large for gestational age	33 (3.1)	32 (3.3)	1 (1.5)	0.45 (0.06 – 3.3)	0.42
Neonate small for gestational age	122 (11.6)	117 (11.2)	5 (7.5)	0.59 (0.23 – 1.5)	0.27
Congenital malformations	28 (2.6)	28 (2.6)	2 (3.0)	1.14 (0.26–4.9)	0.86

DISCUSSION

Our study shows that a fasting glucose cut-off of ≥90 mg/dL (5.0 mmol/L) exhibited good sensitivity and specificity for GDM screening in Mexican adolescents. Thus, using this cut-off improved the ability to identify healthy patients and, thus, reduced the need to perform an OGTT to confirm or exclude the diagnosis of GDM, resulting in similar detection rates. This study is the first to report the prevalence of GDM using IADPSG criteria in adolescent population and to describe perinatal outcomes in GDM adolescent women without treatment.

Fasting glucose was altered in 90.1% of the GDM cases (n=64), but only 7% and 9.9% had altered glucose values at 1-h and 2-h during the 75-g/2-h OGTT, respectively. Therefore, in this population, fasting glucose can be used as a screening tool for GDM. Although the possibility of using fasting glucose as a screening strategy has been reported in previous studies in adult women, [20,29] no studies have attempted to use IADPSG criteria to diagnose GDM in adolescent women. The first unbiased study to suggest this diagnostic strategy was published in 1998 by Reichelt et al., who reported a sensitivity of 94% and a specificity of 66% using a fasting glucose cut-off of ≥85 mg/dL (4.72 mmol/dL) in adult Brazilian women. [30] A meta-analysis conducted by Donovan et al. reported seven studies in which fasting glucose was used for GDM screening. However, all of these studies utilized Carpenter and Counstan's criteria to diagnose GDM. In their work, fasting glucose cut-offs of ≥85 mg/dL (4.72 mmol/L) and ≥95 mg/dL (5.27 mmol/L) resulted in sensitivity and specificity values of 87% and 52% and 54% and 93%, respectively. [20]

In 2010, Agarwal et al. published a study of 10,283 pregnant women (maternal age: 28.3 ± 6.1 years) from the United Arab Emirates. Using the IADPSG criteria, these authors reported that fasting glucose cut-offs of 75 mg/dL (4.16 mmol/L), 85 mg/dL (4.72 mmol/L), and 92 mg/dL (5.11 mmol/L) resulted in the sensitivity and specificity values of 98.3% and 11.3%, 88.9 and 60%, and 76.8% and 100%, respectively, for GDM screening. [19] Although these populations are not

comparable, the sensitivity and specificity found in our study using glucose cut-offs of 85 and 90 mg/dL (4.72 and 5.0 mmol/L) in Mexican adolescents were higher. In our study, the abnormal fasting glucose rate was higher than that of the HAPO study for diagnosis of GDM, in which the higher rate was 74% for women from Barbados and 73% for women from Bellflower, CA. [31] This discrepancy could be explained by maternal age and ethnic group; in our study, the mean of maternal age was 16.2 ± 1.6 while in the HAPO study the mean of maternal age was 29.2 ± 5.8. Gopalakrishnan et al. reported that 91.4% of adult North Indian women with GDM according to IADPSG criteria had abnormal fasting plasma glucose, which is similar to our findings. [32] Likewise, Trujillo et al. reported in adult Brazilian women an AUC of 0.96 for fasting glucose values to detect GDM as defined by the IADPSG diagnostic criteria. In the same study, using a fasting plasma glucose cut-off value of 85 mg/dL indicated that only 18.7% of all women needed to undergo an OGTT with a detection rate of 92.5% of all GDM cases while the 90 mg/dl cutoff had a detection rate of 88.3% cases of GDM and an OGTT could be necessary in only 4.2% of all women. [33] These findings are similar to those of our study. If our results are confirmed, the OGTT could be avoided in Mexican adolescent women because 90.1% of GDM women can be diagnosed using fasting glucose in accordance with IADPSG criteria.

The prevalence of GDM in adolescent women at our institution increased significantly from 0.4% using current criteria to 6.7% using IADPSG criteria, however 38% of pregnant adolescent attended at our institution during the study period did not have GDM screening in clinical records because they only arrived for delivery.

The perinatal outcomes in our study were similar in adolescents with and without GDM even though 94.3% of the adolescents with GDM did not receive GDM-specific treatment. This finding was consistent with the cost-benefit analysis reported by Werner et al., who concluded that the perinatal benefits associated with use of the IADPSG criteria do not justify the additional cost associated with increasing the number of women diagnosed with GDM three-fold. [34] However,

using the IADPSG criteria could be beneficial because this is a young and vulnerable group—thus, if their conversion rate to type 2 diabetes is the same as what has been shown in different systematic review and meta-analysis, [35,36] they would likely develop type 2 diabetes at a very young age and an opportune intervention could reduce the long-term incidence of type 2 diabetes. A recent systematic review indicates that intervention addressing health behaviour in women with previous GDM starting up till one year postpartum is superior to no intervention with regard to T2DM prevention. [37] Also, these women are likely to have subsequent pregnancies and recurrent GDM. [38]

The limitations of our study are as follows: the study was retrospective: the diagnostic validity of the test has not been yet confirmed in a second independent population; and the results are only applicable to Mexican, and, potentially, Latin, adolescent women. Future prospective and multicentre studies are required to corroborate our findings. Another limitation was that the sample size for comparing perinatal outcomes between women with and without GDM was insufficient, and future studies with appropriated power are needed to corroborate our results.

Most adolescent women in our institution request prenatal care in the middle of the second trimester that is similar to previous study by Lira-Plascencia et al., who reported that the mean gestational age on the first prenatal visit among the 2,315 pregnant in our institution was 24.2 ± 6.7 weeks of gestation. [39] It is important to point out that we found two adolescents with overt diabetes (type 2 diabetes) in early pregnancy that were excluded of analysis, this is consistent with the reported trends in the prevalence of type 1 and type 2 diabetes that increased from 0.96 to 1.29 and 0.45 to 0.79 per 1000, respectively, among the Hispanic youth population between 2001 and 2009. [40]

According to the IADPSG, [12] the ADA, [2] the Endocrine Society, [12] the WHO, [14] the FIGO, [15] the ACOG, [16] the NICHHD, [18] and the Society of Obstetricians and Gynaecologists of Canada, [3] all adolescents should be screening for GDM between 24 and 28 weeks of

gestation. This intervention has an impact on the cost of prenatal care in the health systems of low and middle-income countries including Mexico regardless of the low prevalence of GDM in adolescents compared with the adult population and the lack of evidence about the beneficial of treatment on perinatal outcomes using IADPSG criteria. On the other hand, the diagnosis of GDM in adolescents along with an appropriate intervention program could decrease the prevalence of type 2 diabetes in the young population in the long term.

Future research should corroborate the use of fasting glucose as a screening tool to identify candidates for OGTT, the benefit of treating GDM in adolescent women, the prevalence of type 2 diabetes during the first trimester of pregnancy, and the risk of type 2 diabetes in GDM adolescent women in the long term.

CONCLUSIONS

A fasting glucose of ≥90 mg/dL (5.0 mmol/L) could be a useful cut-off for GDM screening in Mexican adolescents, as it provides adequate sensitivity and specificity and a good detection rate. Additionally, implementing this strategy decreases costs compared to the universal application of one-step OGTT-based screening. More studies are necessary to evaluate the effect of GDM on perinatal outcomes among adolescent women.

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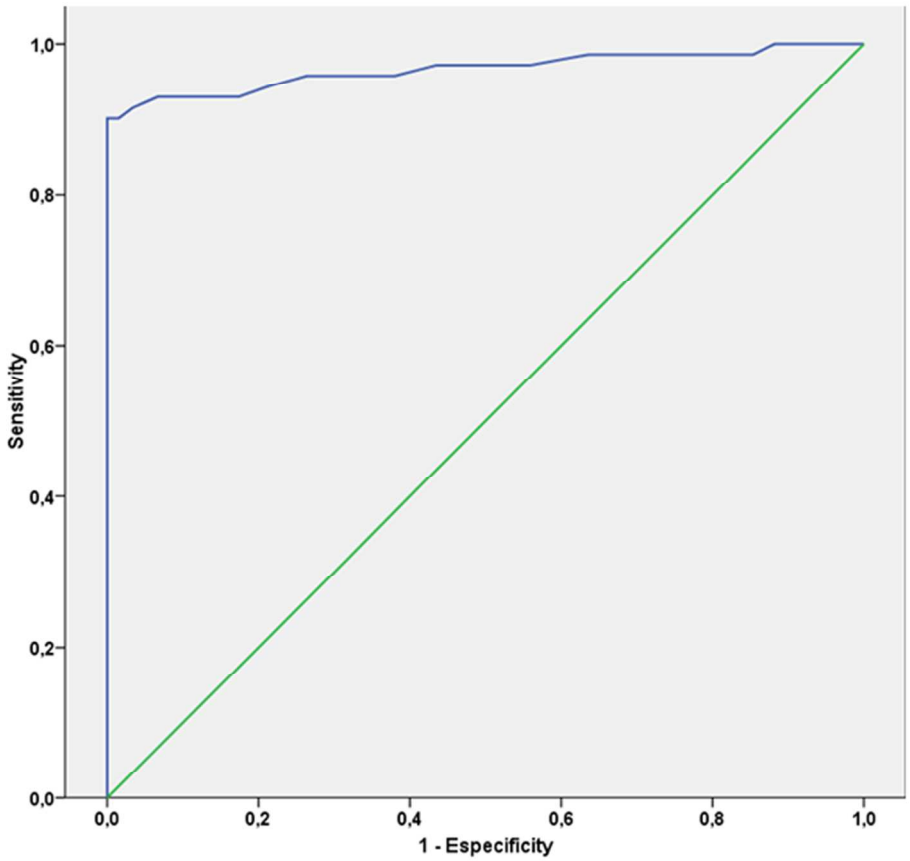

Receiver operating characteristic curve shows area under the curve of 0.96

139x123mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	Title and page 2
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2,3
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4-6
	4	Study objectives and hypotheses	6
METHODS			
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	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	7
	8	Where and when potentially eligible participants were identified (setting, location and dates)	6,7
	9	Whether participants formed a consecutive, random or convenience series	7
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	10b	Reference standard, in sufficient detail to allow replication	7,8
	11	Rationale for choosing the reference standard (if alternatives exist)	7,8
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	8
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9
	15	How indeterminate index test or reference standard results were handled	9
	16	How missing data on the index test and reference standard were handled	NA
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	18	Intended sample size and how it was determined	9
RESULTS			
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	20	Baseline demographic and clinical characteristics of participants	11
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	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	13
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DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	15-18
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STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.

BMJ Open

Sensitivity of fasting glucose for gestational diabetes mellitus screening in Mexican adolescents based on International Association of Diabetes and Pregnancy Study Groups criteria: a diagnostic accuracy study based on retrospective data analysis

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Sensitivity of fasting glucose for gestational diabetes mellitus screening in Mexican adolescents based on International Association of Diabetes and Pregnancy Study Groups criteria: a diagnostic accuracy study based on retrospective data analysis

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ABSTRACT

Objective: To evaluate fasting plasma glucose (FPG) as a screening test for gestational diabetes mellitus (GDM) among Mexican adolescents using International Association of Diabetes and Pregnancy Study Groups criteria.

Design: Retrospective cohort study.

Setting: Level-three medical institution in Mexico City.

Participants: The study population comprised of 1,061 adolescent women aged 12–19 years with singleton pregnancies, who underwent a 75-g oral glucose tolerance test (OGTT) between 11 and 35 weeks of gestation.

Primary and secondary outcome measures: The sensitivity (Sn), specificity (Sp), positive and negative predictive values (PPV and NPV, respectively), and positive and negative likelihood ratios LR (+) and LR (-), respectively) with 95% confidence intervals (CI) for selected FPG cut-off values were compared. Secondary measures were perinatal outcomes in women with and without GDM.

Results: GDM was present in 71 women (6.7%, 95% CI: 5.3%–8.4%). The performance of FPG at thresholds of ≥ 80 (4.5 mmol/L), 85 (4.7 mmol/L), and 90 mg/dL (5.0 mmol/L) was as follows, (95% CI) respectively: Sn: 97% (89%–99%), 94% (86%–97%) and 91% (82%–95%); Sp: 50% (47%–53%), 79% (76%–81%) and 97% (95%–97%); PPV: 12% (9%–15%), 23% (18%–28%) and 64% (54%–73%); NPV: 99% (98.5%–99.9%) for all three cut-offs; LR (+): 1.9 (1.8–2.1), 4.3 (3.8–5.0), and 26.7 (18.8–37.1); and LR (-): 0.06 (0.02–0.23), 0.07 (0.03–0.19), and 0.09 (0.04–0.19), respectively. No significant differences in perinatal outcomes were found between adolescents with and without GDM.

Conclusions: A FPG cut-off of ≥90 mg/dL (5.0 mmol/L) is ideal for GDM screening in Mexican adolescent women. A FPG threshold of 90 mg/dl would miss 6 (8.5%) women with GDM, pick up 34 (3.4%) women without GDM, and avoid 962 (90.7%) OGTTs.

Strengths and limitations of this research

- A fasting glucose cut-off of ≥90 mg/dL (5.0 mmol/L) is ideal for GDM screening among Mexican adolescent women.
- This is the first study in Mexico and Latin America addressing the prevalence of GDM in adolescent women using International Association of Diabetes and Pregnancy Study Groups criteria.
- The study was retrospective; the findings are only applicable to Mexican, and potentially, Latin women.
- The diagnostic validity of the test was not confirmed in a second independent population.
- The sample size available to compare perinatal outcomes was limited.

INTRODUCTION

Around 16 million women aged 15–19 years give birth each year, accounting for approximately 11% of all births worldwide. In total, 95% of these births occur in low- and middle-income countries; 18% in Latin America and the Caribbean and more than 50% in sub-Saharan Africa.[1] Latin women (including Mexican women) are considered a high-risk population for diabetes and gestational diabetes mellitus (GDM).[2]

GDM refers to diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt diabetes.[2] Although the prevalence of GDM is generally lower in adolescent populations, a recently published guideline concerning adolescent pregnancy recommended GDM testing for all pregnant adolescent women, similar to recommendations for adult women.[3]

Previous studies reported GDM prevalence rates of 1.7% among North American adolescent women[4] and 0.97% among Mexican adolescent women;[5] both studies diagnosed GDM using Carpenter and Coustan criteria.[6] However, reports about the prevalence of GDM in adolescents diagnosed using the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria are limited. The present authors previously reported a prevalence of GDM among adult Mexican women of 30.3% using IADPSG criteria; a figure three-fold higher than that obtained using the previous American Diabetes Association (ADA) criteria (valid until 2010).[7]

In Mexico, pregnant adolescent women have a lower prevalence of overweight and obesity than the general pregnant population. Additionally, most pregnant Mexican adolescent women are primigravid. In part, these characteristics contribute to the low prevalence of GDM in this population.[8,9] However, most pregnant Mexican adolescent women have lower socio-economic status than adult women.[8] Lower socioeconomic status has been associated with a

higher frequency of consumption of unhealthy foods (e.g. soft drinks[10]), which are associated with increased risk of GDM among Mexican women.

Currently, GDM screening and diagnosis in adolescent women is controversial because of the low prevalence of GDM in this population and non-universal strategies for diagnosing GDM. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study revealed significant associations between adverse perinatal outcomes and fasting, 1- and 2-h glucose values during a 2-h 75-g oral glucose tolerance test (OGTT).[11] Following these results, the IADPSG recommended new criteria for the diagnosis and classification of hyperglycaemia during pregnancy.[12] The new glucose thresholds corresponded to 1.75 times the estimated odds for neonatal birth weight >90th percentile, cord C-peptide >90th percentile, and body fat percentage >90th percentile.[12] Use of IADPSG criteria is supported by various international associations, including the ADA,[2] Endocrine Society,[13] World Health Organization (WHO)[14] and International Federation of Gynaecology and Obstetrics (FIGO).[15] However, other organisations, including the American Congress of Obstetricians and Gynecologists (ACOG) and the National Institute of Child Health and Human Development (NICHHD), recommend that healthcare providers continue to use a two-step approach to screen and diagnose GDM.[16,17] They argue that there is no evidence to support clinically significant improvements in maternal or new-born outcomes after using IADPSG criteria to diagnose GDM, and that following these criteria leads to a significant increase in healthcare costs.[16,17] All of the abovementioned organisations recommend universal screening for GDM using a one- or two-step strategy, and none have specific recommendations regarding GDM screening for adolescent women.

In contrast, recent guidelines from the National Institute for Health and Care Excellence on diabetes in pregnancy recommend 2-h 75-g OGTT at 24–28 gestational weeks to test for GDM in women with risk factors. These guidelines also propose a diagnosis of GDM if a 2h 75-g OGTT shows women have either a fasting glucose level ≥100 mg/dL (5.6 mmol/L) or a 2-h

glucose level ≥140 mg/dL (7.8 mmol/L).[18] In accordance with this guideline, adolescent women should be tested for GDM if they have body mass index (BMI) ≥30 kg/m^2, a previous baby with macrosomia weighing ≥4.5 kg or with gestational diabetes, a first-degree relative with diabetes, or an ethnic family origin with a high prevalence of diabetes.

Agarwal, et al.[19] suggested fasting plasma glucose can be used to decide if an OGTT is needed or not. This would ease the burden on laboratories and save resources, as the IADPSG recommendation that every pregnant woman undergoes a 2h 75-g OGTT is too demanding.[19] A systematic review and meta-analysis of GDM screening tests concluded that glucose challenge tests and fasting plasma glucose levels at 24 gestational weeks are useful for identifying women who do not have GDM.[20] However, no studies have analysed the utility of fasting glucose for screening GDM in adolescent women.

This study aimed to evaluate the usefulness of fasting glucose for GDM screening among Mexican adolescent women using IADPSG diagnostic criteria. Secondary goals were to report the prevalence of GDM and perinatal outcomes in adolescent women with and without GDM.

METHODS

Study design and participants

A retrospective cohort study was conducted. The study population was adolescents who received prenatal care at Instituto Nacional de Perinatología (INPer), in Mexico City, from June 1, 2011 to June 30, 2014. INPer is a reference centre that attends to high risk pregnancies, including adolescent women. Nearly 4000 births are attended at INPer every year. This study was approved by the INPer Internal Review Board (Register number 212250-42081). Written informed consent from participants is not required by the Internal Review Board for retrospective studies. The inclusion criteria were women who: were aged 12–19 years, had a singleton

pregnancy, had received a 2-h 75-g OGTT administered at 11–35 weeks of gestation and had delivered at INPer. The exclusion criterion was women with any pathology, including any type of pre-gestational diabetes, lupus, heart disease, substance abuse, hypothyroidism, epilepsy, leukaemia, bulimia, anorexia, depressive disorder, autoimmune cirrhosis, asthma or multiple sclerosis. Adolescent women with pre-gestational diabetes (type 1 or 2) or GDM were referred to INPer from level-one or level-two attention centres, and OGTT was avoided in this population.

Procedure

First, adolescent women who delivered during the study period were identified from the electronic register of births. Next, non-electronic clinical records were reviewed to check if these women had received an OGTT, and in which week of gestation the test was performed. Pregnant adolescent women with an OGTT between 11 and 35 weeks of gestation were selected; if the inclusion criteria were fulfilled, their maternal and neonatal clinical records were requested to obtain data for analysis. Glucose was measured using the Vitros DT60 II chemistry system (OrthoClinical Diagnostics, Tilburg, the Netherlands), which has a sensitivity of 20 mg/dL (1.11 mmol/L) and a coefficient of variation of 1.4%–1.8%, according to the manufacturer's instructions. The laboratory fulfils the official Mexican norm (NOM-007-SSA3-2011) for the organisation and functioning of clinical laboratories in Mexico, and is certified by the Global Certification Bureau for quality management systems in concordance with the International Standards Organization 9001:2015 norm.

Gestational age was calculated from the last menstrual period. If women were unaware of when their last menstrual period was or if the date was not reliable, the first trimester ultrasound measurement was used. At INPer, GDM is diagnosed based on the observation of two or more abnormal values during a 2-h 75-g OGTT: fasting ≥95 mg/dL (5.3 mmol/L), 1-h ≥180 mg/dL (10 mmol/L) and 2-h ≥155 mg/dL (8.6 mmol/L), according to recommendations from the Fifth International Workshop-Conference on Gestational Diabetes Mellitus.[21] A single abnormal

value was not considered sufficient for GDM diagnosis, and women who showed one value did not receive GDM-specific treatment. Women with two or more abnormal glucose values during OGTT received medical nutrition therapy (MNT) and subsequent evaluation of glycaemic control at 2–4 week intervals. For women who did not achieve glycaemic control with MNT, metformin was added at doses of 1500–2550 mg and/or insulin therapy (0.3–1.0 U/kg of body weight) to achieve goals for capillary glucose (self-monitoring): fasting <95 mg/dL (5.3 mmol/L) and 1-h postprandial <140 mg/dL (7.8 mmol/L).

Study variables

Fasting glucose was determined as part of the 2-h 75-g OGTT. Cut-off values were established using a receiver operating characteristic (ROC) curve and Youden's index. Glucose values obtained during the OGTTs were re-analysed according to IADPSG criteria, and GDM diagnosis was defined as one or more abnormal glucose value: fasting ≥92 mg/dL (5.1 mmol/L), 1-h ≥180 mg/dL (10 mmol/L) and 2-h ≥153 mg/dL (8.5 mmol/L).[12]

Additionally, perinatal outcomes were compared between women with and without GDM. This analysis only included GDM women without treatment. Large for gestational age was defined as a birth weight above the 90th percentile for sex and gestational age for Mexican people,[22] and small for gestational age as a birth weight below the 10th percentile for sex and gestational age for Mexican people.[22] Preeclampsia was defined as a blood pressure of ≥140/90 mmHg, and proteinuria as blood pressure >300 mg/24 h. In the absence of proteinuria, the diagnosis of preeclampsia was based on a blood pressure of ≥140/90 mmHg and one or more severity criteria: thrombocytopenia, abnormal liver function, recent development of renal failure, pulmonary oedema or brain or visual disturbances. Gestational hypertension was defined as blood pressure ≥140/90 mmHg after 20 gestational weeks in the absence of proteinuria and severity criteria. Intrauterine growth restriction was defined as the presence of an estimated foetal weight below the third percentile. Polyhydramnios was defined by an amniotic fluid index

of >18 cm. Preterm birth was defined as birth after 20 and before 37 weeks of gestation. Maternal overweight was defined as a BMI for age greater than a +1 *Z*-score, and obesity as a BMI for age greater than a +2 *Z*-score, based on WHO references.

Sample size

The sample size was calculated using recommendations for sample size estimation in diagnostic test studies. To find a 90% fasting glucose sensitivity for GDM screening, considering a prevalence of GDM of 6% and a maximum marginal error of 15% with a 95% confidence level (CI), a sample size of 345 participants was required. However, all adolescent pregnant women who met the inclusion criteria during the study period were included in the analysis.

Statistical analysis

SPSS version 15 (Chicago, IL, USA) was used for the statistical analyses. Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and proportions. Student's t- or Mann-Whitney U-tests were used to compare continuous variables according to the variable distribution. Chi-square or Fisher's exact tests were used to evaluate differences in proportions. Statistical significance was considered as $p \leq 0.05$. Contingency tables were determined to calculate sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR−) with 95% CIs, using different cut-off values based on the ROC curve and Youden's index. The difference in the risk for adverse perinatal outcomes between adolescents with and without GDM was determined by calculating the odds ratio with a 95% CI.

Patient and Public Involvement: Patients and public were not involved in this study.

RESULTS

During the study period, there were 11,618 births at the study institution, 2,122 of which occurred in adolescent women. In total, 1,315 pregnant adolescent women had received a 2-h 75-g OGTT. Of these women, 1,061 met the inclusion criteria; 254 were excluded because of incomplete clinical records (n=105), twin pregnancies (n=13), incomplete OGTT (n=11), pregestational diabetes (n=2), or some additional pathology (n=123).

Most adolescent women who did not receive an OGTT received attention for hospitalisation or delivery for various reasons including: preterm labour, premature rupture of membranes, preeclampsia, and labour in active phase. During the study period, 32 pregnant adolescent women were referred to INPer with a previous diagnosis of some type of diabetes and had not received an OGTT; 19 with pre-gestational diabetes (eight with type 1 diabetes and nine with type 2 diabetes), and 13 with GDM.

Seventy-one women were diagnosed with GDM, corresponding to a prevalence rate of 6.7% (95% CI 5.3%–8.4%). Baseline data for adolescents with and without GDM collected on study enrolment are shown in Table 1. Adolescents with GDM had higher weight and BMI than adolescents without GDM. The prevalence of obesity was higher among GDM women compared with those without GDM (p=0.001). Among the 71 adolescents with GDM diagnosed according to IADPSG criteria, the frequencies of abnormal glucose values during the 2-h 75-g OGTT were: fasting 64 (90.1%), 1-h 5 (7.0%) and 2-h 7 (9.9%). Only one adolescent had three abnormal glucose values, and three adolescents had two abnormal glucose values.

Table 1. Characteristics of adolescent women at study admission (N=1,061)

Characteristics	Total adoles	Adolescents without GDM n=990	Adolescents with GDM n=71	*p**

	cents N=1061			
Age (years)	16.1 ± 1.6	16.1 ± 1.5	16.2 ± 1.6	0.51
Weight (kg)	59.1 ± 10.0	58.7 ± 9.8	63.9 ± 11.5	0.0001
Height (m)	1.56 ± 0.05	1.56 ± 0.05	1.56 ± 0.05	0.69
Body mass index (kg/m^2)	24.3 ± 3.6	24.1 ± 3.5	26.2 ± 4.1	0.0001
Gestational age at 2-h 75-g OGTT (weeks)	25.0 ± 4.4	24.1 ± 3.5	26.1 ± 4.1	0.008
Glucose (mg/dL)				
Fasting	80.2 ± 7.3	79.2 ± 6.2	94.4 ± 6.2	0.0001
1-h	105.2 ± 25.7	103.6 ± 24.6	127.9 ± 29.5	0.0001
2-h	97.9 ± 19.4	96.6 ± 18.4	114 ± 24.4	0.0001
Number of pregnancies				
1	923 (86.9)	865 (87.3)	58 (81.7)	0.08
2	121 (11.4)	110 (11.1)	11 (15.5)	0.17
3 or more	18 (1.7)	16 (1.6)	2 (2.8)	0.61
Normal weight	582 (55.6)	559 (57.3)	23 (32.4)	0.001
Overweight	357 (34.1)	324 (33.2)	33 (46.5)	0.01
Obesity	92 (8.8)	77 (7.9)	15 (21.1)	0.001
First-degree relative with type 2 diabetes	157 (14.8)	140 (14.1)	17(23.9)	0.0.2

Values expressed as mean ± standard deviation or frequency (percentage). *Student's t- or chi square test. OGTT, oral glucose tolerance test.

Figure 1 shows the ROC curve. The area under the curve was 0.96 (95% CI 0.93–0.99) (p=0.0001). Table 2 shows the results of the characterisation of the five fasting glucose cut-off values for GDM screening: 75, 80, 85, 90 and 92 mg/dL (4.2, 4.5, 4.7, 5.0 and 5.1 mmol/L, respectively). These cut-off values for fasting glucose were chosen based on Youden's index, and rounded up to the nearest integer (mg/dL). The best cut-off for fasting glucose according to Youden's index was 90 mg/dL. Using a cut-off of 85 mg/dL (4.72 mmol/L), a total of 279 (26.3%) OGTTs would be necessary, whereas only 99 (9.3%) would be required with a cut-off of 90 mg/dL (5.0 mmol/L).

Figure 1. Receiver operating characteristic curve shows an area under the curve of 0.96

Table 2. Gestational diabetes mellitus screening capacity among Mexican adolescents at different fasting glucose cut-off values

Fasting glucose cut-off	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	LR+ (95% CI)	LR– (95% CI)	OGTT
75 mg/dL (4.2 mmol/L)	98.5 (92–99)	22.4 (20–25)	7.9 (6–10)	99.6 (97–99.9)	1.3 (1.2–1.3)	0.06 (0.01–0.46)	838 (79%)
80 mg/dL (4.5 mmol/L)	97 (89–99)	50.1 (47–53)	11.6 (9–15)	99.6 (98.5–99.9)	1.9 (1.8–2.1)	0.06 (0.02–0.23)	563 (53.1%)
85 mg/dL (4.7 mmol/L)	94 (86–97)	78.6 (76–81)	22.9 (18–28)	99.5 (98–99.8)	4.3 (3.8–5.0)	0.07 (0.03–0.19)	279 (26.3%)
90 mg/dL (5.0 mmol/L)	91 (82–95)	96.6 (95–97)	64.2 (54–73)	99.4 (98.6–99.7)	26.7 (18.8–37)	0.09 (0.04–0.19)	99 (9.3%)
92 mg/dL 5.1 mmol/L	88.4 (78–94)	99.9 (99–100)	99.2 (91–99)	99.2 (98–99)	884 (123–6231)	0.12 (0.06–0.22)	64 (6%)

CI = confidence interval, PPV = predictive positive value, NPV = negative predictive value, LR = likelihood ratio, OGTT = oral glucose tolerance test.

There were no differences in perinatal outcomes among Mexican adolescent women with GDM without treatment and those without GDM (Table 3). However, there was a higher incidence of neonates that were small for gestational age among adolescents without GDM. Four women with GDM that received specific GDM treatment were excluded from this analysis; three with MNT and one with MNT plus metformin.

Table 3. Risk of adverse perinatal outcomes among Mexican adolescent women with gestational diabetes mellitus[a] without treatment

Adverse perinatal outcomes	To tal N=1057	Without GDM n=990 n (%)	With GDM n=67 n (%)	Odds ratio (95% CI)	p
Intrauterine growth restriction	36 (3.4)	35 (3.5)	1 (1.5)	0.41 (0.06–3.1)	0.37
Polyhydramnios	13 (1.2)	12 (1.2)	1 (1.5)	1.2 (0.41–3.4)	0.84
Gestational hypertension	54 (5.1)	50 (5.1)	4 (6.0)	1.2 (0.28–5.5)	0.74
Preeclampsia	52 (4.9)	49 (4.9)	3 (4.5)	0.9 (0.27–2.9)	0.86
Preterm birth	140 (13.3)	130 (13.1)	10 (14.9)	1.15 (0.57–2.3)	0.67
Premature rupture of membranes	15 (1.4)	13 (1.3)	2 (3.0)	2.3 (0.51–20.5)	0.26
Caesarean section	542 (51.3)	505 (51)	37 (55.2)	1.18 (0.72–1.95)	0.50

Obstetric haemorrhage	28 (2.6)	26 (2.6)	2 (3.0)	1.14 (0.26–4.9)	0.86
Neonate large for gestational age	33 (3.1)	32 (3.3)	1 (1.5)	0.45 (0.06–3.3)	0.42
Neonate small for gestational age	122 (11.6)	117 (11.2)	5 (7.5)	0.59 (0.23–1.5)	0.27
Congenital malformations	28 (2.6)	28 (2.6)	2 (3.0)	1.14 (0.26–4.9)	0.86

[a] diagnosed using International Association of Diabetes and Pregnancy Study Groups criteria

CI = confidence interval, GDM = gestational diabetes mellitus.

DISCUSSION

The present study showed that a fasting glucose cut-off value of ≥90 mg/dL (5.0 mmol/L) exhibited good sensitivity and specificity for GDM screening in Mexican adolescents. Using this cut-off value improved the ability to identify healthy patients and reduced the need to perform an OGTT to confirm/exclude the diagnosis of GDM, resulting in similar detection rates. This study is the first to report the prevalence of GDM in an adolescent population using IADPSG criteria, and describe perinatal outcomes in GDM adolescent women without treatment.

Fasting glucose was altered in 90.1% of GDM cases (n=64), but altered glucose values in the 2-h 75-g OGTT were only found in 7% of women at 1-h and 9.9% at 2-h. This suggests that fasting glucose can be used as a screening tool for GDM in this population. Although the potential of fasting glucose as a screening strategy has been reported in previous studies in adult women,[20,23] no studies have used IADPSG criteria to diagnose GDM in adolescent women. The first unbiased study to suggest this diagnostic strategy was published in 1998 by Reichelt et al.,[24] who reported sensitivity of 94% and specificity of 66% using a fasting glucose cut-off

value of ≥85 mg/dL (4.72 mmol/dL) in adult Brazilian women. A meta-analysis conducted by Donovan et al.[20] reported seven studies that used fasting glucose for GDM screening; however, all of those studies diagnosed GDM with Carpenter and Coustan criteria, and fasting glucose cut-offs values of ≥85 mg/dL (4.72 mmol/L) and ≥95 mg/dL (5.27 mmol/L) resulted in sensitivity and specificity values of 87% and 52%, and 54% and 93%, respectively.

In 2010, Agarwal et al.[19] published a study involving 10,283 pregnant women (maternal age: 28.3 ± 6.1 years) from the United Arab Emirates. Using IADPSG criteria, those authors reported that fasting glucose cut-offs of 75 mg/dL (4.16 mmol/L), 85 mg/dL (4.72 mmol/L) and 92 mg/dL (5.11 mmol/L) resulted in sensitivity and specificity values of 98.3% and 11.3%, 88.9 and 60%, and 76.8% and 100%, respectively.[19] Although these populations are not comparable, the sensitivity and specificity found in this study using glucose cut-off values of 85 and 90 mg/dL (4.72 and 5.0 mmol/L) in Mexican adolescents were higher. In the present study, the abnormal fasting glucose rate was higher than that used in the HAPO study for GDM diagnosis, in which the higher rates were 74% for women from Barbados and 73% for women from Bellflower, CA.[25] This discrepancy may be explained by maternal age and ethnic group. The mean maternal age in the present study was 16.2 ± 1.6 years, while that in the HAPO study was 29.2 ± 5.8 years. Gopalakrishnan et al.[26] reported that 91.4% of adult North Indian women with GDM according to IADPSG criteria had abnormal fasting plasma glucose, which was similar to findings in the present study. Similarly, Trujillo et al.[27] reported an area under the curve of 0.96 in adult Brazilian women for fasting glucose values to detect GDM as defined by IADPSG diagnostic criteria. In the same study, a fasting plasma glucose cut-off value of 85 mg/dL indicated that only 18.7% of all women needed to undergo an OGTT, with a detection rate of 92.5% of all GDM cases, whereas a cut-off of 90 mg/dl had a detection rate of 88.3% GDM cases (indicating an OGTT would be necessary in only 4.2% of all women).[27] These findings were similar to those of the present study. If these results are confirmed, OGTT could be

avoided in Mexican adolescent women because 90.1% of women with GDM can be diagnosed using fasting glucose, in accordance with IADPSG criteria.

The prevalence of GDM in adolescent women at INPer increased significantly from 0.4% using current criteria to 6.7% using IADPSG criteria; however, 38% of pregnant adolescents attended during the study period did not have clinical records of GDM screening because they only arrived for delivery. The perinatal outcomes in the present study were similar in adolescents with and without GDM, even though 94.3% of adolescents with GDM did not receive GDM-specific treatment. This finding was consistent with the cost-benefit analysis reported by Werner et al.,[28] who concluded that the perinatal benefits associated with use of the IADPSG criteria did not justify the additional costs associated with a three-fold increase in the number of women diagnosed with GDM. However, using the IADPSG criteria may be beneficial for this young and vulnerable group. If their conversion rate to type 2 diabetes is the same as shown in previous systematic reviews and meta-analyses,[29,30] they would likely develop type 2 diabetes at a young age; an opportune intervention could reduce the long-term incidence of type 2 diabetes. A recent systematic review indicated that interventions addressing health behaviour in women with previous GDM starting up to 1 year postpartum was superior to no intervention with regard to type 2 diabetes prevention.[31] In addition, these women are likely to have subsequent pregnancies and recurrent GDM.[32]

This study had several limitations. The study was retrospective, the diagnostic validity of the test has not yet been confirmed in a second independent population, and the results are only applicable to Mexican (and potentially Latin) adolescent women. Future prospective and multicentre studies are required to corroborate these findings. Another limitation was that the available sample size to compare perinatal outcomes between women with and without GDM was insufficient. Future studies with appropriate power are needed to confirm these results.

Most adolescent women at INPer request prenatal care in the middle of the second trimester. This is similar to a study by Lira-Plascencia et al.[33] that reported the mean gestational age at the first prenatal visit among 2,315 pregnant in the same institution was 24.2 ± 6.7 weeks of gestation. It is important to note that two adolescents with overt diabetes (type 2 diabetes) were identified in early pregnancy and were excluded from the analysis; this is consistent with reported trends in the prevalence of type 1 and type 2 diabetes among the Hispanic youth population that increased from 0.96 to 1.29 and 0.45 to 0.79 per 1000 women, respectively, between 2001 and 2009.[34]

According to the IADPSG,[12] ADA,[2] Endocrine Society,[12] WHO,[14] FIGO,[15] ACOG,[16] NICHHD[18] and the Society of Obstetricians and Gynaecologists of Canada,[3] all pregnant adolescents should be screened for GDM between 24 and 28 weeks of gestation. This intervention has an impact on the cost of prenatal care in the health systems of low- and middle-income countries including Mexico, regardless of the low prevalence of GDM in adolescents compared with the adult population and the lack of evidence about the benefits of treatment on perinatal outcomes using IADPSG criteria. However, the diagnosis of GDM in adolescents along with an appropriate intervention programme may decrease the prevalence of type 2 diabetes in this population in the long term.

Future research should further investigate the use of fasting glucose as a screening tool to identify candidates for OGTT, the benefits of treating GDM in adolescent women, the prevalence of type 2 diabetes during the first trimester of pregnancy, and the risk for type 2 diabetes in adolescent women with GDM in the long term.

CONCLUSIONS

A fasting plasma glucose cut-off value of ≥90 mg/dL (5.0 mmol/L) is ideal for GDM screening in Mexican adolescent women. A fasting plasma glucose threshold of 90 mg/dl would miss 6

(8.5%) women with GDM, pick up 34 (3.4%) women without GDM and avoid 962 (90.7%) OGTTs.

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Ethics approval and consent to participate: The study was approved by the Ethics and Research Internal Review Board of the Instituto Nacional de Perinatología in Mexico City (register number: 212250-3402-10102-02-14). Written informed consent from participants is not required by the Internal Review Board for retrospective studies.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: No support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions: ERM, NSO and JLP conceived and designed the study, analysed the data, and wrote the paper. NMC, LAS, COG and GEG analysed the data and reviewed the paper. NSO, CRM, ART and AME acquired the data, interpreted the results and reviewed the paper.

Data sharing statement: All relevant data are within the paper. No additional data are available.

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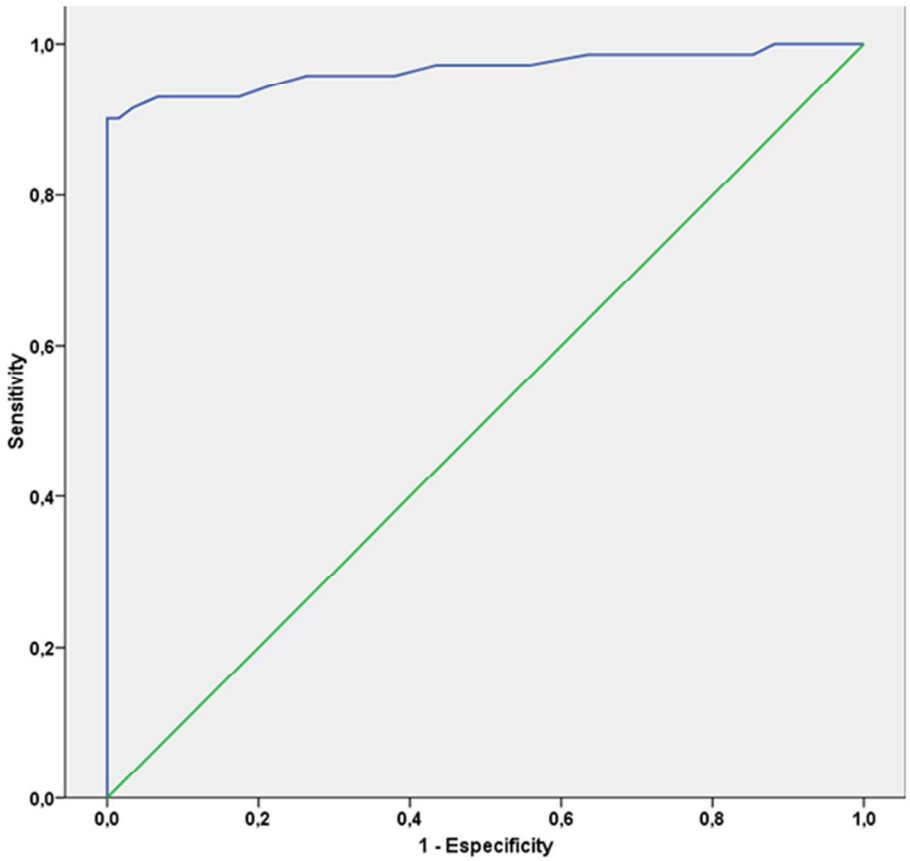

Receiver operating characteristic curve shows an area under the curve of 0.96

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	11	Rationale for choosing the reference standard (if alternatives exist)	7,8
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	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	8
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	8
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	8
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	9
	15	How indeterminate index test or reference standard results were handled	9
	16	How missing data on the index test and reference standard were handled	NA
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	8,9
	18	Intended sample size and how it was determined	9
RESULTS			
Participants	**19**	Flow of participants, using a diagram	9,10
	20	Baseline demographic and clinical characteristics of participants	10, 11
	21a	Distribution of severity of disease in those with the target condition	10
	21b	Distribution of alternative diagnoses in those without the target condition	10
	22	Time interval and any clinical interventions between index test and reference standard	NA
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	12
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	13
	25	Any adverse events from performing the index test or the reference standard	NA
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	17-18
	27	Implications for practice, including the intended use and clinical role of the index test	15-18
OTHER INFORMATION			
	28	Registration number and name of registry	18
	29	Where the full study protocol can be accessed	NA
	30	Sources of funding and other support; role of funders	18

STARD 2015

AIM

STARD stands for "Standards for Reporting Diagnostic accuracy studies". This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

EXPLANATION

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition.** This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test.** A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or "2x2" table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on http://www.equator-network.org/reporting-guidelines/stard.