INVESTIGACIÓN ORIGINAL

PREVALENCE OF GESTATIONAL DIABETES MELLITUS BASED ON GLUCOSE TOLERANCE TEST ON WEEKS 24 TO 28. PROSPECTIVE COHORT IN ARMENIA, COLOMBIA, 2015-2016

Prevalencia de diabetes mellitus gestacional por curva de tolerancia a la glucosa en las semanas 24 a 28. Cohorte prospectiva en Armenia, Colombia, 2015-2016

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ABSTRACT

Objective: To determine the prevalence of gestational diabetes mellitus that appears during the second or the third trimester of pregnancy using a glucose tolerance test, and to explore the relationship with pregnancy outcomes in pregnant women in Armenia.

Materials and methods: Prospective cohort study in pregnant women coming to a Level I clinic in Armenia for prenatal care before 14 weeks of gestation who signed the informed consent. Pregnant women with hypertension or existing diabetes before pregnancy or with conditions that could alter HbA1c were excluded. Consecutive sampling: Blood sugar and HbA1c were measured on admission and the glucose tolerance test with 75 g was measured at 24-28 weeks; perinatal and maternal outcomes were measured at the time of delivery. A descriptive analysis is performed and the prevalence of gestational diabetes mellitus is presented.

Results: Of a total of 372 candidates to enter the study, there were two cases (0.5%) of pre-gestational diabetes mellitus. Of the 370 pregnant women who met the selection criteria, 43 (11.6%) had a miscarriage, and 36 (9.7%) were lost to follow-up before 24 weeks; of the remaining 291 women, 35 (12%) did not undergo the glucose tolerance test. The glucose tolerance test was performed in 256 pregnant women and it was abnormal in 12 cases, for a prevalence of gestational diabetes mellitus of 4.7% (12/256).

Conclusions: The prevalence of gestational diabetes mellitus was 4.7% in the study population, although frequency may have been underestimated due to losses before 24 weeks. No adverse perinatal outcomes were found in this group of pregnant women.

Key words: Glycosilated haemoglobin A, gestational diabetes mellitus.

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RESUMEN

Objetivo: determinar, por curva de tolerancia a la glucosa (CTG), la prevalencia de diabetes mellitus gestacional (DMG) que se inicia en el segundo o tercer trimestre del embarazo, y explorar la relación con resultados del embarazo en gestantes de Armenia.

Materiales y métodos: estudio prospectivo en cohorte de gestantes que consultaron a un centro de atención de primer nivel en Armenia, para control prenatal antes de la semana 14 y firmaron el consentimiento informado. Se excluyeron gestantes con hipertensión o diabetes previa al embarazo, o condiciones que pudieran alterar la HbA1c. Se midieron glicemia y HbA1c al ingreso, y curva de tolerancia a la glucosa (CTG) con 75 g semanas 24-28, y resultados perinatales y maternos al parto. Se hace análisis descriptivo y se presenta la prevalencia de DMG.

Resultados: de un total de 372 gestantes candidatas a ingresar al estudio se detectaron dos casos (0,5 %) de diabetes mellitus previa al embarazo. De las 370 que cumplieron los criterios de selección, un total de 43 (11,6 %) presentaron aborto, otras 36 (9,7 %) se retiraron antes de la semana 24; de las 291 restantes, 35 (12 %) no se realizaron la CTG, por lo que se tomó la CTG en 256 gestantes, de las cuales se encontró CTG anormal en 12 casos, para una prevalencia de DMG de 4,7 % (12/256).

Conclusiones: la prevalencia de DMG fue del 4,7 % en la población estudiada, podría haber subestimación de la frecuencia por pérdidas antes de la semana 24. No se encontraron resultados perinatales adversos en este grupo de gestantes.

Palabras clave: hemoglobina A glicosilada, diabetes gestacional, diabetes mellitus.

INTRODUCTION

Gestational diabetes mellitus (GDM) has been usually defined as "carbohydrate intolerance that is discovered or manifests for the first time during gestation" (1). In Colombia, the reported prevalence of GDM ranges between 1.43% (2) and 6.3% (3); at present, international publications estimate a prevalence between 10.3% (4) and 15% (5), 5% corresponding to type II diabetes, 7.5% type I who become pregnant, and the remaining 87.5% are true gestational diabetes cases (6). Recently, emphasis has been placed on the difference between a diagnosis of diabetes mellitus (DM) before pregnancy, diagnosed early in pregnancy, or overt diabetes, in relation to DM of gestational onset, stating that the former presents with higher glucose values, resulting in a greater probability of complications and pharmacological management (7). In fact, the American Diabetes Association (ADA) currently defines GDM or diabetes of gestational onset as "Diabetes diagnosed during the second or third trimester that is not clearly overt diabetes" (8).

Diabetes of gestational onset is more common in obese women, with a personal or family history of diabetes, or with a history of foetal demise or macrosomic neonates (9, 10). Moreover, pregnant women with GDM are more frequently affected by maternal complications such as preeclampsia, present in 10% to 25% of GDM cases (11-14). Also, the frequency of cesarean section is higher in diabetic women, mainly due to foetal macrosomia (15, 16) which is, in turn, the most important perinatal complication in GDM. Foetal macrosomia is defined as "birthweight greater than 4,000 g" (16), although some authors establish a minimum threshold of 4,500 g (17).

In Colombia, the diagnosis of GDM according to the Clinical Practice Guidelines for the prevention, early detection and treatment of abnormalities during pregnancy, delivery or puerperium, published by the Ministry of Health and Social Protection in 2013 (18), and the Clinical Practice Guidelines for the diagnosis, treatment and follow-up of gestational diabetes published in 2016 (19), recommend giving all pregnant women an oral glucose tolerance test (OGTT) with 75 g of glucose between 24 and 28 weeks of pregnancy, using the following diagnostic thresholds: fasting $\geq$ 92 mg/dl, 1 hour after challenge $\geq$ 180 mg/dl, and 2 hours after challenge

≥ 153 mg/dl. This is in accordance with the recommendations of the International Association of Diabetes and Pregnancy Study Groups (IADPSG) (20), which modified the traditional "two-step" diagnostic system based on a screening test at 24-28 weeks with a challenge of 50 g of glucose and a normal threshold of < 140 mg/dl 1 hour after the challenge (O'Sullivan test), giving pregnant women with abnormal results another challenge with 100 g of glucose and, if the two values are abnormal, the diagnosis is confirmed (21).

Bearing in mind that if the diagnosis is made early in gestation it is considered as overt diabetes and not GDM (22-24), and considering also that several studies confirm the benefits of early intervention in DM during pregnancy using dietary measures and exercise in order to reduce adverse outcomes (15, 25), it has been of interest to search for early diagnostic and prognostic factors of DM during pregnancy, such as fasting blood sugar in early gestation (26), and measurement HbA1c levels (27).

HbA1c measurement has been used as follow-up test for DM control (28); however, it was approved in 2010 for DM diagnosis when the level is ≥ 6.5%, as long as a diagnostic test certified by the National Glycohaemoglobin Standardisation Program (NGSP), standardised with the Diabetes Control and Complications Trial (DCCT) reference is used (29). HbA1c is not altered with dietary changes, does not require fasting and has little variation between tests (30); it may appear falsely elevated in the presence of salicylates, diuretics hypertriglyceridaemia, polycythaemia and splenectomy, and falsely low after transfusion, haemodialysis, haemolytic anaemia, and use of vitamins C and E (31, 32).

In Colombia, although the potential role of early markers has been studied (33) together with risk factors (3, 10) and the prevalence of GDM (2, 3), research has been conducted in populations subjected to traditional diagnostic tests and not to the use of the new thresholds suggested in the national guidelines or the use of HbA1c; and it has

not focused on the identification of individuals with full-blown diabetes or who really present with GDM. The use of the new diagnostic criteria for GDM in pregnant women needs to focus on several aspects: the local frequency of full-blown diabetes or onset of diabetes during the second or the third trimester of pregnancy, the measurement of adverse maternal and perinatal outcomes of pregnancy in each category (34), and the financial implications for the health system (35).

The objective of this study is to approach the prevalence of GDM and its complications, as well as the prevalence of overt DM in the first trimester of pregnancy.

MATERIALS AND METHODS

Design and population. Prospective cohort study in pregnant women 14 years or older who came to consultation before 14 weeks of gestation and agreed to participate in the study and who had initiated prenatal care between February 2015 and July 2016 in a level I healthcare centre of the Redsalud public health network that provides care to the subsidised population in the city of Armenia, capital of the department of Quindío in central Colombia. Excluded were all women with hypertension, know diabetes or diabetes confirmed at entry by HbA1C > 6.5%, use of medications (salicylates, vitamin E and C), or medical conditions (anaemia, haemoglobinopathies, splenectomy, renal failure) that could affect HbA1c results. *Consecutive sampling.* A sample size of 249 patients was estimated based on a total population of 1,600 pregnant women seen per year: miscarriages 10%: subtotal 1,440; 40% recruited before 14 weeks: N = 576. Estimated prevalence of gestational diabetes, 6%; 95% confidence level for three age groups and a 10% loss.

Procedure. A licensed practical nurse with prior experience in patient recruitment, completion of forms, and trained in the estimation of gestational age at the time of entry and verification of inclusion and exclusion criteria, recruited the candidates on their arrival at the laboratory of the healthcare

provider institution. Women who met the selection criteria and agreed to participate in the study were explained the objectives of the project and were asked to fill the informed consent. Laboratory samples were then taken, and sociodemographic and clinical information was documented. The date of the last menstruation and the results of first-trimester ultrasound scans were considered for gestational age estimation. Blood sugar and HbA1c on entry to the study were determined using blood samples for fasting blood sugar and HbA1c in separate tubes. The samples were processed immediately, the glucose test in the institution's internal laboratory and the HbA1c in a reference laboratory: D-10-™ Haemoglobin A1c Program (Bio-Rad Laboratories), which ensures compliance with international standards (certified by NGSP as a DCCT traceable test). The results were returned daily to the healthcare centre, emphasising abnormal results; a second sample was taken when the HbA1c was ≥ 6.5%, and the persistence of this value was considered abnormal, leading to the exclusion of the patients from the study. An oral glucose tolerance test (OGTT) with 75 g was performed on weeks 24-28, using three samples: fasting, 1 and 2 hours after the glucose challenge, with the following diagnostic thresholds: fasting 92 mg/dl, 180 mg/dl after 1 hour and 153 mg/dl after 2 hours. One abnormal value confirmed the diagnosis of GDM. Laboratory test results and physical findings were documented in the clinical record and in a special form designed by the researchers. Patients were followed through to the end of pregnancy and, when required, patients were contacted by phone to obtain or confirm information. The researchers did not participate in the final care process.

Measured variables. Age, baseline BMI, maternal weight gain, neonatal birthweight, preeclampsia, primary cesarean section (non-iterative), macrosomia (newborn weight ≥ 4.000 g). Full-blown diabetes was considered to exist with a confirmed baseline result of HbA1c ≥ 6.5%, or fasting blood sugar ≥ 126 mg/dl. The following were considered adverse pregnancy outcomes: preeclampsia, primary cesarean section and macrosomia.

Analysis. Data were analysed using the SPSS 19.0 software. A descriptive univariate analysis was performed, estimating relative frequencies; the prevalence of gestational diabetes in patients with abnormal glucose tolerance test after 24 weeks was estimated using the total number of participants who were tested as the denominator. Normality was determined for quantitative variables using the Kolmogorov-Smirnov test, and central trend and scatter were calculated for continuous variables, based on the distribution found.

Bioethical considerations. The study was approved by the Bioethics Committee of the Health Sciences School of Quindío University, a pre-requisite for the approval of all forms of research in the University. Participants were asked for their informed consent and data confidentiality was guaranteed. Patients with abnormal results in diagnostic tests at the start of the study or on weeks 24-28 (blood sugar, HbA1c, GTT) were included in the institution's protocol for the management of high-risk pregnancies and were managed by specialised medical and nutrition staff.

RESULTS

Out of a total of 372 candidates to enter the study, there were two cases (0.5%) of pre-gestational diabetes mellitus, with HbA1c greater than 6.5% measured in the first sample and confirmed in the second sample (9.5% and 9.8%, respectively); moreover, the two patients had a fasting blood sugar > 126 mg/dl. Of the 370 patients who met the selection criteria, 43 (11.6%) miscarried and another 36 (9.7%) dropped out before 24 weeks; of the remaining 291, 35 pregnant women (12%) did not undergo the OGTT. Therefore, a total of 256 patients were tested with OGTT and HbA1c.

Overall, 370 pregnant women entered the study. The mean age was 22.9 years (SD ± 6.1), and the majority of the women were housewives affiliated to the subsidised healthcare regime, with ages ranging between 18 and 35 years. The mean BMI

at entry was 24.2 (SD ± 6.1), 35.3% had a BMI ≥ 25 (Table 1).

Blood sugar, HbA1c and OGTT results. The average baseline blood sugar level was 82.3 mg/dl (SD ± 7.8). Baseline blood sugar was ≥ 92 mg/dl in 11.6% of the women and, of them, only one had an abnormal OGTT performed at 24-48 weeks. Noticeably higher HbA1c figures were observed in the group of patients with a baseline blood sugar ≥ 92 mg/dl (5.7 vs. 5.2). The average HbA1c was 5.1% (SD ± 0.4). Of the 256 women in whom was performed at 24 to 28 weeks, 12 had some abnormal result, for a prevalence of GDM of 4.7% (12/256).

Maternal and neonatal outcomes. Follow-up was completed until the time of delivery in 283 patients. The incidence of preeclampsia in the group of women studied was 2.1%; there were no cases of preeclampsia or foetal macrosomia among the women with GDM; 21.9% required cesarean section, while in the group with GDM, cesarean section was performed in 33.3% of cases; neonatal macrosomia was found in 3.5%, and the incidence of hyaline membrane was 0.7%, with no cases in the GDM group. The most frequent causes of cesarean section were dystocia and cephalopelvic disproportion.

Table 1. Distribution according to history and first trimester findings in pregnant women assessed for gestational diabetes mellitus in Armenia, Colombia, 2015- 2016	
Characteristics	**N/Frequency**
Sociodemographic	
Age < 18	65 (17.6)
Age: 18-35	291 (78.9)
Age > 35	13 (3.5)
Healthcare Regime:	
Subsidised	307 (84.1)
Attached	56 (15.3)
Other	7 (1.9)
History	
Primigravida	178 (48.1)
Second gestation	115 (31.1)
Multigravida	77 (20.8)
BMI Current pregnancy	
< 20	59 (15.9)
20-24.9	180 (48.6)

Source: Study data.

DISCUSSION

In this study, the prevalence of GDM was 4.7% (12 out of 256). Based on the result of the OGTT with 75 g at 24 to 28 weeks, two cases of overt diabetes were found in the first trimester (excluded from the study) in patients who were unaware of their diabetic condition and whose history had not given rise to suspicion. Therefore, the prevalence of overt diabetes was 0.5% in accordance with the recommendation of the World Health Organisation (WHO) of investigating the possibility of DM in the first trimester (7). The incidence of preeclampsia, macrosomic foetus and hyaline membrane was 2.1%, 3.5% and 0.7%, respectively.

The average fasting blood sugar levels in the first trimester (82.3 mg/dl) were found to be slightly higher than reported in the literature (34, 36). Although recent studies focus on the usefulness of HbA1c for the diagnosis of GDM (27, 37, 38), in this study there were only two cases with an HbA1c ≥ 6.5%.

Historically, the diagnosis of GDM has been controversial (39). The prevalence of GDM diagnosis has increased with the generalised application of the IADPSG criteria (40). In a review of the literature, Brown *et al.* report a prevalence of GDM ranging between 3.5% and 45.3%, which is lower than the range between 9.3% and 25.5% reported by Sacks *et al.* (41) in a retrospective analysis of the HAPO study (Hyperglycaemia and Adverse Pregnancy Outcome), Duran *et al.* (42) report a prevalence of GDM of 35.5%, but in their study the mean age of the patients was notoriously higher than in ours (33 *vs.* 22.9), and the hispanic population included (34.4%) was smaller than the caucasian population (62%). On the other hand, the study by Mayo *et al.* (4), which reports an increase in the prevalence of GDM from 3.2 to 10.3% with the use of new diagnostic thresholds, is a retrospective study of a population tested with the traditional "two-step" approach and not with the 75 g glucose test. Differences with the results of our studies might be attributed to potential underestimation due to losses to follow-up or because they are related to intrinsic factors of our population which were not investigated. The limitation of our study in terms of comparison with prior studies conducted in Colombia is that GDM prevalence studies published in the past two decades used as a basis the two-step system suggested by the ADA (21).

Regarding maternal complications, our data are similar to those reported by Hirst in Vietnam in a population of 386 women with a BMI of 21.1% diagnosed with GDM using the IADPSG criteria, where the frequency of preeclampsia, large foetus for gestational age and admission to the ICU was 2.1%, 16% and 4%, respectively (43). These figures are lower than those reported by Crowther *et al.* in 510 women with GDM diagnosed on the basis of a single measurement on weeks 24-48, with no treatment, where the incidence of preeclampsia, foetal macrosomia and neonatal respiratory distress syndrome was 19%, 21%, and 4%, respectively; this was a study conducted in an Australian population with a mean BMI of 26 (44).

Regarding weaknesses of our study, the small sample size resulted in a small population of women with GDM, affecting our ability to assess the frequency of complications related to this condition. On the other hand, losses to follow-up (33%) might result in an underestimation of the prevalence of GDM and its complications. These were related to the presence of miscarriage (11.6%), found to be present in a similar range as that reported in international publications (45, 46). Another cause of loss to follow-up was the fact that 36 patients (9.67%) dropped out from the study when they were transferred from the state-subsidised regime to the contributive regime resulting in a change of healthcare provider, and a 12.3% of patients who did not come for the OGTT between weeks 24 and 48. Another weakness was the inability to know whether the patients were assessed and followed by the nutritionist, given that this service at the

institution is dependent on the insurance organisation; this would have shed light on the low incidence of maternal and perinatal complications.

Strengths include the fact that all pregnant women were tested for HbA1c and blood sugar levels upon entry in the study; HbA1c samples were processed in accordance with international standards and the results were reported to the researchers on the same day and immediately to the healthcare centre; a second confirmatory test was performed in all the pregnant women who had an initial HbA1c ≥ 6.5%.

CONCLUSIONS

In this sample, the prevalence of GDM was found to be 4.7% (12/256) in accordance with the 75 g OGTT result in the period between 24 and 28 weeks. Population studies are needed in order to arrive at more accurate and valid estimates and gain a better understanding of the size of the problem in Colombia.

FUNDING

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