# Role of First-Trimester HbA1c as a Predictor of Adverse Obstetric Outcomes in a Multiethnic Cohort

Laura Mañé,[1,3] Juana Antonia Flores-Le Roux,[1,4] David Benaiges,[1,4] Marta Rodríguez,[4] Irene Marcelo,[4] Juan José Chillarón,[1,4] Juan Pedro-Botet,[1,4] Gemma Llauradó,[1] Lucía Gortazar,[1] Ramón Carreras,[2,4] and Antonio Payà[2,4]

[1]Department of Endocrinology and Nutrition and [2]Department of Gynecology and Obstetrics, Hospital del Mar, 08003 Barcelona, Spain [3]Institut Hospital del Mar d'Investigacions Mèdiques, 08003, Barcelona, Spain [4]Department of Medicine, Universitat Autònoma de Barcelona - Universitat Pompeu Fabra, Campus del Mar, 08003 Barcelona, Spain

**Context:** Risk of obstetric complications increases linearly with rising maternal glycemia. Testing hemoglobin A1c (HbA1c) is an effective option to detect hyperglycemia, but its association with adverse pregnancy outcomes remains unclear. Emerging data sustain that an early HbA1c ≥5.9% could act as a pregnancy risk marker.

**Objective:** To determine, in a multiethnic cohort, whether an early ≥5.9% HbA1c could be useful to identify women without diabetes mellitus at increased pregnancy risk.

**Design and Setting:** A prospective study was conducted at Hospital del Mar, Barcelona, between April 2013 and September 2015.

**Patients and Intervention:** A total of 1631 pregnant women had an HbA1c measurement added to their first antenatal blood tests and were screened for gestational diabetes mellitus at 24 to 28 weeks' gestation.

**Outcome Measures:** Primary outcome was macrosomia. Secondary outcomes were preeclampsia, preterm birth, and cesarean section rate.

**Results:** A total of 1228 pregnancies were included for outcome analysis. Women with HbA1c ≥5.9% (n = 48) showed a higher rate of macrosomia (16.7% vs 5.9%, $P = 0.008$) and a tendency toward a higher rate of preeclampsia (9.32% vs 3.9%, $P = 0.092$). There were no statistically significant differences in other pregnancy outcomes. After adjusting for potential confounders, an HbA1c ≥5.9% was independently associated with a 3-fold increased risk of macrosomia (95% confidence interval, 1.127 to 8.603, $P = 0.028$) and preeclampsia (95% confidence interval, 1.086 to 11.532, $P = 0.036$).

**Conclusions:** In a multiethnic population, an early HbA1c ≥5.9% measurement identifies women at high risk for poorer pregnancy outcomes independently of gestational diabetes mellitus diagnosis later in pregnancy. Further studies are required to establish cutoff points adapted to each ethnic group and to assess whether early detection and treatment are of benefit. (***J Clin Endocrinol Metab*** **102: 390–397, 2017)**

The prevalence of abnormal glucose metabolism in women of childbearing age has increased dramatically in recent years (1–4). The Hyperglycemia and Adverse Pregnancy Outcomes, a large international epidemiological study involving 25,000 pregnant women, showed that the risk of maternal and neonatal complications increased linearly with rising maternal glycemia (5). The ongoing epidemic of obesity and diabetes has led to more type 2 diabetes in women of childbearing age, with an increase in the number of pregnant women with

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Abbreviations: BMI, body mass index; GDM, gestational diabetes mellitus; Hb, hemoglobin; HbA1c, hemoglobin A1c; MCV, mean corpuscular volume; OGTT, oral glucose tolerance test.

undiagnosed type 2 diabetes. Current clinical guidelines recommend testing women with risk factors for type 2 diabetes at their initial prenatal visit, using standard diagnostic criteria (6). A hemoglobin A1c (HbA1c) level ≥6.5% (≥48 mmol/mol) is the recommended diagnostic cutoff for diabetes in pregnancy; however, this is based on data in nonpregnant subjects, and the threshold in pregnancy is likely to be lower since HbA1c levels fall in the first trimester (7–10). Moreover, when considering HbA1c as a screening test in early pregnancy to detect substantial glucose elevations in women without known diabetes, there is little evidence as to what diagnostic threshold should be recommended for intervention (11). The association between HbA1c levels and adverse pregnancy outcomes remains unclear. Most data reporting periconception and first-trimester HbA1c measurements and pregnancy outcomes stem from studies of women with preexisting diabetes (10). A recent study by Hughes *et al.* (12) conducted in New Zealand among 16,122 pregnant women found an early pregnancy HbA1c ≥5.9% (≥41 mmol/mol) to be a clinically relevant marker for major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death, although the results could not be adjusted for potential confounding factors. Further studies are required to verify these results, particularly across different ethnic groups, as others have shown an interethnic variability in HbA1c levels (13–16). The current study aimed to determine, in a multiethnic cohort, the role of a first-trimester 5.9% (41 mmol/mol) HbA1c threshold to identify women without diabetes mellitus at increased risk of adverse pregnancy outcomes who may benefit from early intervention.

## Methods

This prospective study was conducted at the Hospital del Mar, Barcelona, Spain between April 2013 and September 2015. Women older than 18 years with a singleton pregnancy were included. Exclusion criteria were known preexisting diabetes (type 1 or 2), meeting the American Diabetes Association criteria for diabetes mellitus [fasting plasma glucose ≥126 mg/dL and/or an HbA1c ≥6.5% (≥48 mmol/mol)] in the first trimester but without a previous diagnosis of diabetes mellitus (unknown type 2 diabetes) and multiple pregnancies. Women with miscarriage or voluntary pregnancy termination and those lost to follow-up in whom delivery data could not be obtained were also excluded.

The population attended to at our center has a high prevalence of women from ethnic minority groups at high risk of type 2 diabetes. For this reason, since 2013, our protocol for diabetes in pregnancy includes HbA1c and fasting plasma glucose measurements at the first antenatal blood testing of all pregnant women. Women diagnosed with unknown type 2 diabetes from the first antenatal blood results were referred to the diabetes unit for diabetes counseling and treatment. Women with an HbA1c value <6.5% (<48 mmol/mol) did not receive any dietary or medical treatment and did not undergo any additional testing until 24 to 28 weeks of gestation, when they underwent routine gestational diabetes mellitus (GDM) screening using the 2-step approach. This involved a 50-g glucose challenge test followed by a 100-g oral glucose tolerance test (OGTT) if the glucose challenge test was positive. The diagnosis of GDM was based on the recommendations of the National Diabetes Data Group, and women were referred to the diabetes unit for management. Throughout the study period, all women received standard antenatal care from a midwife and/or obstetrician.

Demographic, anthropometric, clinical, and analytical variables apart from pregnancy outcome data were collected from maternity and electronic medical records and transferred to a central database. The study was conducted according to the Declaration of Helsinki principles and approved by the Ethics Committee of Clinical Research.

HbA1c was determined using high-performance liquid chromatography on a Bio-Rad Variant II analyzer (Bio-Rad Laboratories, Hercules, CA), an assay accredited by the National Glycoprotein Standardization Program with controls traceable to the Diabetes Control and Complications Trial. The interassay coefficient of variation was 1.9% at an HbA1c level of 5.2% (33 mmol/mol) and 2.2% at an HbA1c level of 10.9% (96 mmol/mol). Blood cell count, hematocrit, hemoglobin (Hb), and mean corpuscular volume (MCV) were measured using an automated hematology system. Anemia was defined as an Hb concentration <11 g/dL and microcytosis as MCV <81 fL.

The primary outcome was macrosomia, which was defined, according to the American College of Obstetricians and Gynecologists, as newborns with a birthweight ≥4000 g. As secondary outcomes, we determined development of preeclampsia, preterm birth (before 37 weeks' gestation), and cesarean section rate.

Preeclampsia was defined by the International Society for the Study of Hypertension in Pregnancy criteria as new-onset or worsening hypertension after 20 weeks' gestation with the coexistence of one or more of the following new-onset conditions: proteinuria (protein/creatinine ratio >30 mg/mmol), other maternal organ dysfunction, or fetal growth restriction (17). Indications for elective cesarean section were suspected fetal macrosomia (defined as estimated fetal weight by ultrasound >4000 g), 2 or more previous cesarean sections, or placenta previa.

Sample size calculation was based on the hypothesis that an HbA1c ≥5.9% (≥ 41 mmol/mol) could identify pregnant women with macrosomia risk similar to that of women with GDM. On the basis of reports in the literature, we assumed a 5% rate of macrosomia in women with normal carbohydrate metabolism in pregnancy and 20% in women with GDM (18–21). In accordance with Hugues *et al.* (12), we estimated that 3% of pregnant women would meet a first-trimester HbA1c ≥5.9% (≥41 mmol/mol). Accepting an $\alpha$ risk of 0.05 and a $\beta$ risk of 0.2 in a two-sided test, 40 participants were necessary in the HbA1c ≥5.9% (≥41 mmol/mol) group and 1320 in the HbA1c <5.9% (<41 mmol/mol) group to find a proportion difference as statistically significant, expected to be 20% in the first group and 5% in the second. A 10% dropout rate was anticipated.

Statistical analysis was made using the statistical software package SPSS Statistics version 22.0 (SPSS, Inc, Chicago, IL). Data are expressed as mean ± SD for continuous variables and as frequencies and percentages for qualitative variables. Fisher exact test or $\chi^2$ test was applied to determine the association between qualitative variables and Student $t$ test to compare mean and standard deviations of quantitative variables. A

multivariate logistic regression analysis was performed to adjust for potential confounders in determining obstetric outcomes. All variables associated on univariate analysis ($P < 0.1$) with adverse obstetric outcomes and those previously described in the literature were included in the regression model. A $P$ value $<0.05$ was considered statistically significant.

## Results

First-trimester HbA1c testing was carried out in 1631 women between April 2013 and September 2015. A total of 403 women were excluded from pregnancy outcome analysis based on exclusion criteria (Fig. 1). Finally, 1228 pregnancies were included for outcome analysis.

Maternal and gestational characteristics stratified according to HbA1c measurement at the first antenatal visit are shown in Table 1. Overall, women with HbA1c ≥5.9% (≥41 mmol/mol, n = 48) compared with women who had HbA1c <5.9% (<41 mmol/mol, n = 1180) more often belonged to ethnic minorities, had higher prepregnancy body mass index (BMI), more frequently presented anemia and microcytosis, and were more frequently diagnosed with GDM.

Regarding adverse pregnancy outcomes (Table 1), women with HbA1c ≥5.9% (≥41 mmol/mol) compared with those with HbA1c <5.9% (<41 mmol/mol) had an almost 3-fold increased rate of macrosomia and a tendency toward a higher preeclampsia rate. No statistically significant differences were observed in preterm birth or in cesarean section rates.

Of the 1228 pregnancies included for outcome analysis, 1156 (94%) underwent screening for GDM using the 2-step approach. OGTT criteria for GDM were met in 151 women, and 63 met criteria for glucose intolerance. Among the 48 women with an HbA1c ≥5.9% (≥41 mmol/mol), 47 (97.9%) underwent GDM screening and 22 were diagnosed with and treated for GDM. A comparison between maternal, gestational, and obstetric outcomes in women with HbA1c ≥5.9% with and without GDM is shown in Table 2.

In multivariate analysis, a cutoff of HbA1c ≥5.9% (≥41 mmol/mol) was independently associated with a higher risk of macrosomia (odds ratio, 3.11; 95% confidence interval, 1.127 to 8.603, $P = 0.028$) and preeclampsia (odds ratio, 3.539; 95% confidence interval, 1.086 to 11.532, $P = 0.036$) (Table 3). The other variables statistically associated with macrosomia were previous macrosomia, prepregnancy BMI, and pregnancy weight gain. Other factors significantly related with preeclampsia were prepregnancy BMI, Latin American ethnicity, and pregnancy weight gain.

## Discussion

We determined that in women without preexisting diabetes, an early pregnancy HbA1c measurement of 5.9% to 6.4% (41 to 46 mmol/mol) identifies a group with a

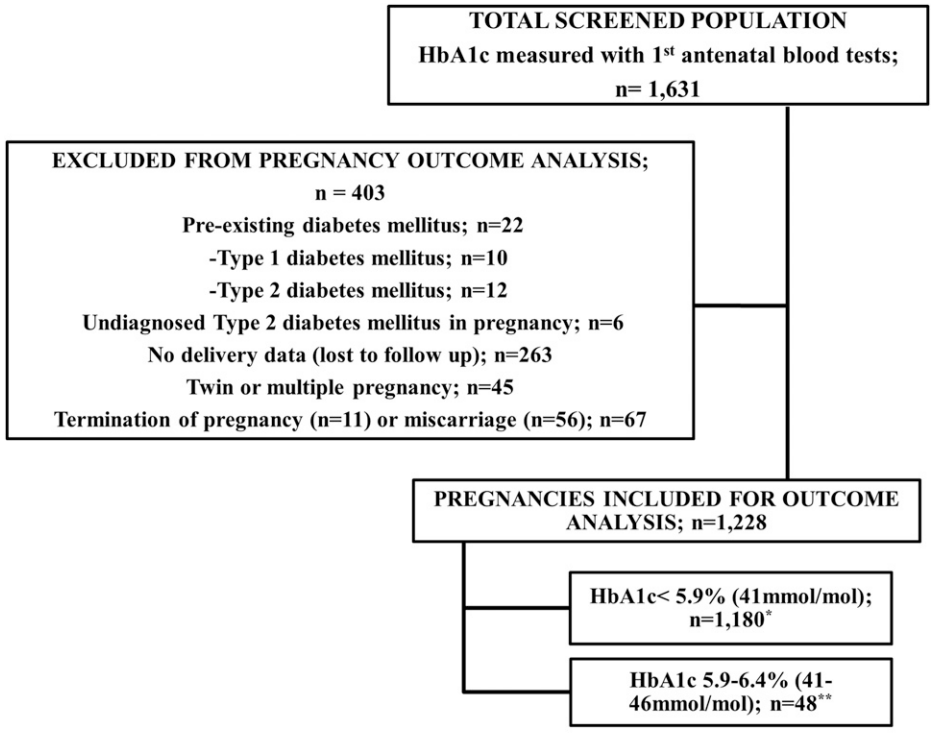


**Figure 1.** Flowchart of the study protocol.

**Table 1. Maternal and Gestational Characteristics and Pregnancy Outcomes Stratified According to HbA1c Measurement at First Antenatal Blood Tests**

| Characteristic | HbA1c <5.9% (<41 mmol/mol); n = 1180 | HbA1c 5.9% to 6.4% (41 to 46 mmol/mol); n = 48 | *P* value |
|---|---|---|---|
| Maternal and gestational characteristics | | | |
| Age, mean ± SD, y | 32.61 ± 5.69 | 33.70 ± 5.232 | 0.194 |
| Smoking | 98/639 (15.3%) | 6/32 (18.75%) | 0.616 |
| Family history of DM | 245/946 (25.9%) | 23/38 (60.5%) | <0.001 |
| Prepregnancy BMI, mean ± SD, kg/m$^2$ | 25.34 ± 5.04 | 28.10 ± 5.35 | 0.001 |
| Previous GDM | 45/1114 (4.0) | 12/45 (26.7) | <0.001 |
| Previous macrosoma | 32/1113 (2.9) | 2/45 (4.4) | 0.384 |
| Multiparous | 644/1170 (55) | 33/48 (68.7) | 0.075 |
| Ethnicity | | | |
| White | 614/1132 (54.2) | 17/45 (37.8) | 0.006 |
| South-Central Asian | 202/1132 (17.8) | 18/45 (40.0) | |
| Moroccan | 81/1132 (7.2) | 2/45 (4.4) | |
| Latin American | 155/1132 (13.7) | 4/45 (8.9) | |
| East Asian | 63/1132 (5.6) | 4/45 (8.9) | |
| Other | 17/1132 (1.5) | 0 | |
| GDM diagnosis | 129/1109 (11.6) | 22/47 (46.8) | <0.001 |
| Pregnancy weight gain, mean ± SD, kg | 10.886 ± 4.66 | 9.52 ± 5.11 | 0.055 |
| First-trimester fasting plasma glucose, mean ± SD, mg/dL | 86.4 ± 9.4 | 92.7 ± 12.4 | <0.001 |
| Anemia | 78/1180 (6.6) | 9/48 (18.8) | 0.001 |
| Microcytosis | 136/1180 (11.5) | 16/48 (33.3) | <0.001 |
| Pregnancy outcomes | | | |
| Preeclampsia | 43/1115 (3.9) | 4/43 (9.3) | 0.092 |
| Preterm birth | 78/1155 (6.8) | 5/47 (10.6) | 0.369 |
| Cesarean section | 313/1169 (26.8) | 14/47 (29.8) | 0.312 |
| Birthweight, mean ± SD, g | 3265.28 ± 502.22 | 3146.35 ± 736.84 | 0.273 |
| LGA | 128/1152 (11.1) | 9/46 (19.6) | 0.094 |
| SGA | 18/1150 (1.6) | 2/46 (4.3) | 0.166 |
| Macrosomia | 69/1171 (5.9) | 8/48 (16.7) | 0.008 |

Values are presented as number/total number (%) unless otherwise indicated. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, hemoglobin HbA1c; LGA, large for gestational age; SGA, small for gestational age.

3-fold increased risk of adverse pregnancy outcomes such as macrosomia and preeclampsia.

Although in women with preexisting diabetes, early pregnancy HbA1c directly correlates with pregnancy outcomes (22–26), this association is less clear in those without diabetes. In the Hyperglycemia and Adverse Pregnancy Outcomes study, HbA1c values measured in the second trimester were predictive of pregnancy outcomes, although less so than glucose measurements. After adjustment for glucose values, HbA1c was associated with cesarean delivery, preeclampsia, and preterm delivery but not with birthweight (27). On the same lines, Capula *et al.* (28) showed that in women diagnosed with GDM in the second trimester, albeit in nondiabetic range, HbA1c levels were strong predictors of negative outcome regardless of the type of treatment. In particular, a cutoff point of 5.3% (34 mmol/mol) was associated with a 2-fold risk of negative outcomes such as pregnancy hypertension, large for gestational age, and neonatal morbidity.

Few reports exist of pregnancy outcomes in women without unknown diabetes who had an early pregnancy HbA1c measurement. In a New Zealand study conducted by Hughes *et al.* (12) including 16,122 women mainly of non-Hispanic white origin, a first-trimester HbA1c threshold of 5.9% (41 mmol/mol) was associated with an increased risk of adverse pregnancy outcomes, including major congenital anomaly, preeclampsia, shoulder dystocia, and perinatal death. Our results support the proposed HbA1c threshold of 5.9% (41 mmol/mol) in early pregnancy, although the association found with adverse outcomes differed in several ways. The primary outcome of our study was the rate of macrosomia, the risk for which was independently associated with elevated HbA1c levels. In the New Zealand study, the authors found no correlation between first-trimester HbA1c and birthweight or macrosomia rates. These discrepancies could be, at least in part, attributed to the differences in ethnic origin of the 2 study populations. The research by Hughes *et al.* was conducted in a relatively low-risk, predominantly white population, whereas the population in the current study was characterized by a majority of women belonging to ethnic minorities such as South-Central Asian, Latin American, East Asian, and Moroccan. Previous studies reported an interracial variability in HbA1c levels and in pregnancy outcomes (13–16). Furthermore, women diagnosed with GDM

**Table 2. Maternal and Gestational Characteristics and Pregnancy Outcomes Among Women With HbA1c ≥5.9% (≥41 mmol/mol) Stratified According to GDM Diagnosis**

| Characteristic | No GDM (n = 25) | GDM (n = 22) | *P* value |
|---|---|---|---|
| Maternal and gestational characteristics | | | |
| Age, mean ± SD, y | 33.54 ± 5.72 | 33.81 ± 4.87 | 0.865 |
| Smoking | 3/16 (18.8) | 2/13 (15.4) | 1.00 |
| Family history of DM | 10/20 (50.0) | 13/18 (72.2) | 0.198 |
| Prepregnancy BMI, mean ± SD, kg/m$^2$ | 26.20 ± 4.59 | 30.41 ± 5.46 | 0.008 |
| Previous GDM | 1/24 (4.2) | 11/20 (55.0) | <0.001 |
| Previous macrosoma | 0 | 2/20 (10.0) | 0.201 |
| Multiparous | 15/25 (60.0) | 14/20 (70.0) | 0.544 |
| Ethnicity | | | 0.020 |
| White | 12/24 (50.0) | 4/20 (20.0) | |
| South-Central Asian | 7/24 (29.9) | 11/20 (55.0) | |
| Moroccan | 2/24 (8.3) | 0 | |
| Latin American | 3/24 (12.5) | 1/20 (5.0) | |
| East Asian | 0 | 4/20 (20.0) | |
| Pregnancy weight gain, mean ± SD, kg | 11.33 ± 5.52 | 7.37 ± 3.63 | 0.007 |
| Anemia | 7/25 (28.0) | 2/22 (9.1) | 0.062 |
| Microcytosis | 10/25 (40.0) | 6/22 (27.2) | 0.358 |
| Pregnancy outcomes | | | |
| Preeclampsia | 3/24 (12.5) | 1/18 (5.5) | 0.623 |
| Preterm birth | 2/25 (8.0) | 3/22 (13.6) | 0.654 |
| Cesarean section | 8/25 (32.0) | 5/21 (23.8) | 0.822 |
| Birthweight, mean ± SD, g | 3200 ± 707.89 | 3225.53 ± 665.93 | 0.905 |
| LGA | 5/25 (20.0) | 4/21 (19.0) | 1.00 |
| SGA | 1/25 (4.0) | 1/21 (4.8) | 1.00 |
| Macrosomia | 5/25 (20.0) | 3/22 (13.6) | 0.706 |

Values are presented as number/total number (%) unless otherwise indicated. BMI, body mass index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HbA1c, hemoglobin HbA1c; LGA, large for gestational age; SGA, small for gestational age.

were excluded in the New Zealand study but included in the current study, which could also account for these discrepancies.

Nevertheless, the reported increased risk of preeclampsia in women with an early HbA1c ≥5.9% (≥41 mmol/mol) concurs with the findings of the current study.

Known risk factors for macrosomia and preeclampsia, such as prepregnancy BMI, gestational weight gain, ethnicity, and GDM, and those associated in the univariate analysis ($P < 0.1$) were included in the multivariate analysis (21, 29–33). On the other hand, it is well known that hemoglobinopathies are more prevalent in some nonwhite populations and that their presence might influence HbA1c levels. In this regard, we included in the univariate and multivariate analysis data on Hb and MCV levels to account for the presence of microcytic

**Table 3. Multivariate Analysis of Predictor Factors for Macrosomia and Preeclampsia**

| Outcome/independent variables | OR | 95% CI | *P* value |
|---|---|---|---|
| Macrosomia | | | |
| Nulliparity | 0.559 | 0.303–1.031 | 0.063 |
| Prepregnancy BMI (for each 5-kg/m$^2$ increase) | 1.365 | 1.031–1.808 | 0.030 |
| Previous macrosomia | 10.499 | 4.483–24.588 | <0.001 |
| Pregnancy weight gain (for each 5-kg increase) | 2.223 | 1.646–3.002 | <0.001 |
| GDM diagnosis | 0.966 | 0.423–2.210 | 0.936 |
| HbA1c ≥5.9% (≥41 mmol/mol) | 3.114 | 1.127–8.603 | 0.028 |
| Anemia | 0.700 | 0.238–2.060 | 0.517 |
| Preeclampsia | | | |
| Nulliparity | 1.588 | 0.809–3.125 | 0.179 |
| Prepregnancy BMI (for each 5-kg/m$^2$ increase) | 1.626 | 1.166–2.266 | 0.004 |
| Latin American ethnicity | 2.362 | 1.126–5.016 | 0.025 |
| Pregnancy weight gain (for each 5-kg increase) | 1.763 | 1.239–2.511 | 0.002 |
| GDM diagnosis | 0.894 | 0.322–2.484 | 0.830 |
| HbA1c ≥5.9% (≥41 mmol/mol) | 3.539 | 1.086–11.532 | 0.036 |
| Anemia | 0.632 | 0.139–2.909 | 0.555 |

BMI, body mass index; GDM, gestational diabetes mellitus; HbA1c, hemoglobin HbA1c.

anemia, characteristic of some hemoglobin variants and of iron deficiency as well, a major factor that influences HbA1c levels during pregnancy (8, 10, 34–36). Many of the studies reporting HbA1c levels during pregnancy do not adjust for the presence of anemia, which could act as a confounding factor. Indeed, the group of women with HbA1c 5.9% to 6.4% (41 to 46 mmol/mol) had lower Hb concentrations and MCV levels (Table 1), although, as shown in the univariate analysis in Table 2, only Hb levels were different in the 2 groups, not MCV. Following these results, the presence of anemia was included in the multivariate analysis (Table 3), and it did not show an independent association with adverse obstetric outcomes. However, MCV may not be a trustable marker of hemoglobinophaties in the presence of vitamin B12 and/or folate deficiencies, and unfortunately, hemoglobin electrophoresis, the gold standard for the diagnosis of hemoglobinopathies, was not available.

Furthermore, women with HbA1c ≥ 5.9% (≥ 41 mmol/mol), although half of them do not reach hyperglycemia in the GDM diagnostic range, are likely to present higher glycemic levels, which may explain the worse pregnancy outcomes observed. Similarly, a limited overlap between HbA1c and OGTT for the diagnosis of diabetes has been described in the general population and in the postpartum of women with a history of GDM (37–39). This may lead to a substantial number of women being misclassified as healthy by OGTT criteria but who may be identified using HbA1c. Yet, with the current knowledge, it should not be suggested that first-trimester HbA1c can be the only parameter to appraise glycemic status during pregnancy but rather is an additional tool along with fasting plasma glucose, 1- and/or 2-hour glycemia, and other risk factors for GDM and related maternal and fetal outcomes. Indeed, regarding the statistical performance of early HbA1c in predicting GDM later in pregnancy, the sensitivity of a ≥5.9% (≥41 mmol/mol) cutoff point was quite low, around 14.5% (22 true positives/22 true positives + 129 false negatives); the specificity was 97.5% (1005 true negatives/1005 true negatives + 25 false positives); the positive predictive value was 46.8% (22 true positives/22 true positives + 25 false positives); and the negative predictive value was 88.3% (980 true negatives/980 true negatives + 129 false negatives).

Nonetheless, this HbA1c threshold could be clinically useful to identify women who may benefit from increased monitoring and intervention prior to routine GDM screening (10). This assumption is in line with that of Rowan *et al.* (11), who suggested that treating these women before 20 to 24 weeks of gestation may improve outcomes with reported lower rates of preeclampsia.

This is of great significance since macrosomia is a major cause of obstetric and perinatal morbidity and a risk factor for the development of obesity, insulin resistance, and metabolic syndrome in the long term (30, 32). On the other hand, HbA1c testing may provide a good opportunity to improve screening of high-risk women, being a simple, reproducible test that causes little discomfort to the patient and can be easily added to the first antenatal blood tests. This approach renders early detection much more feasible compared with the many drawbacks and low uptake rates of OGTT.

Our study had several limitations. One is the considerable amount of women (n = 263, 17.6%) who chose to continue follow-up or end pregnancy at other centers; this could act as a potential selection bias as we were unable to gather data on pregnancy outcomes. Nonetheless, this percentage was considerably lower than that described in previous studies (12). Furthermore, only 4 women (1.5%) in the lost to follow-up group had a first-trimester HbA1c ≥5.9% (≥41 mmol/mol); thus, the impact of this limitation may not affect substantially the main outcomes of our study. Moreover, we did not include other pregnancy outcomes, such as major congenital anomalies and perinatal death, due to the low frequency of these events, which, together with the low frequency of high HbA1c values, would have required a much larger study population to have enough power to detect differences in these outcomes. We chose macrosomia as the primary outcome instead of large for gestational age, mainly for its implications in adverse obstetric outcomes. Among others, it is a known risk factor for shoulder dystocia, one of the main diabetes-related complications in pregnancy, and it is also a condition that may increase the number of labor inductions (40). However, among macrosomic infants, we did not distinguish those with birthweight ≥4000 g from those over 4500 g. A further limitation was that almost 6% of women in our cohort had no GDM screening data, either due to OGTT intolerance or refusal to undergo a glucose challenge test, although this situation highlights the comparative ease of screening with an HbA1c measurement. Women diagnosed with GDM were not excluded, and intervention in this group of patients could have introduced a bias by modifying pregnancy outcomes. Nevertheless, the diagnosis of GDM was included as a confounding factor and is thus not expected to have a relevant influence on the results. This study was conducted in a relatively high-risk, predominantly nonwhite population including different ethnic groups but was underpowered to assess the specific influence of ethnicity on HbA1c levels during pregnancy and the differences in HbA1c levels between women with and without a GDM diagnosis according to their ethnic origin.

In conclusion, in a multiethnic population, an early HbA1c ≥5.9% (≥41 mmol/mol) measurement identifies a group of women at high risk for poorer pregnancy outcomes, regardless of a subsequent GDM diagnosis later in pregnancy, who could benefit from early intervention. We consider HbA1c to be a helpful addition to the initial antenatal blood testing to evaluate the risk of adverse obstetric results; however, further large-scale studies are required to establish cutoff points adapted to each ethnic group and assess whether early detection and treatment are of benefit.

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Address all correspondence and requests for reprints to: Juana Antonia Flores-Le Roux, MD, PhD, Department of Endocrinology and Nutrition, Hospital del Mar, Paseo Marítimo 25-29, E-08003 Barcelona, Spain. E-mail: 94066@parcdesalutmar.cat.

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