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Is fasting plasma glucose in early pregnancy a better predictor of adverse obstetric outcomes than glycated haemoglobin?

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ABSTRACT

Objectives: To determine, in a multi-ethnic cohort, the suitability of first-trimester fasting plasma glucose and HbA1c levels in non-diabetic range to identify women without diabetes at increased pregnancy risk.
Study design: A retrospective analysis of a prospective cohort between April 2013 and September 2015. Universal testing for fasting plasma glucose and HbA1c levels at the first antenatal blood sampling was performed and women were screened for gestational diabetes mellitus at 24–28 weeks' gestation. Primary outcomes were macrosomia and pre-eclampsia, and secondary outcomes preterm delivery, Caesarean section and large-for-gestational age. Different fasting plasma glucose and HbA1c cut-off levels were assessed for associations with outcomes.
Results: 1,228 pregnancies were included for outcome analysis. After adjustment for potential confounders, no association was found between fasting plasma glucose levels and pregnancy outcomes. Women with an HbA1c ≥5.8% (39.9 mmol/mol) showed an increased risk of macrosomia (OR 2.69, 95% CI 1.16–6.24); an HbA1c ≥5.9% (41 mmol/mol) threshold was independently associated with a three-fold risk of pre-eclampsia (95% CI 1.03–9.9) and an HbA1c ≥6.0% (42.1 mmol/mol) with a four-fold risk of large-for-gestational age (95% CI 1.49–11.07).
Conclusions: In a multi-ethnic population, first-trimester fasting plasma glucose levels were not a better predictor of pregnancy complications than HbA1c. Further, an early HbA1c ≥5.8% (39.9 mmol/mol) threshold is already associated with an increased risk of macrosomia.

Introduction

The ongoing epidemic of obesity and rising immigration figures have led to more type 2 diabetes in women of childbearing age, with an increase in the number of pregnant women with undiagnosed type 2 diabetes [1–3]. The role of hyperglycaemia during pregnancy as an independent risk factor for adverse pregnancy outcomes has been clearly established [4–6]. Several large studies of untreated women showed a correlation between blood glucose levels during pregnancy, even below non-diabetic range, and the incidence of macrosomia [7,8], hypertension and Caesarean section rate [8,9]. Thus, detection of women at high pregnancy risk in early pregnancy is a desirable goal. Current clinical guidelines recommend testing women with risk factors for type 2 diabetes at their first prenatal visit using standard diagnostic criteria [10]. A first-trimester HbA1c level ≥6.5% (48 mmol/mol), albeit based on data in non-pregnant subjects, has been the recommended diagnostic cut-off for type 2 diabetes in pregnancy. A recent study by Hughes et al [11] conducted in New Zealand in 16,122 pregnant women found early pregnancy HbA1c ≥5.9% (41 mmol/mol) to be a predictor for adverse pregnancy outcomes. Shortly afterwards, another study stemming from our reference population sustained that early pregnancy HbA1c ≥5.9% (41 mmol/mol) identifies a group of women at high risk for poorer pregnancy outcomes regardless of a gestational diabetes mellitus (GDM) diagnosis later in pregnancy [12]. However, the usefulness of different HbA1c cut-off points in non-diabetic range has not

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been fully evaluated. On the other hand, fasting plasma glucose (FPG) is an inexpensive parameter which has been used together with HbA1c to detect unknown type 2 diabetes at the baseline prenatal visit. Previous studies also reported significant graded associations between first-trimester FPG levels below those diagnostic of diabetes and adverse pregnancy outcomes, albeit without an obvious threshold at which risk increased [13].

The aim of the present study was to compare, in a multi-ethnic cohort, associations between maternal FPG and HbA1c levels measured at the first trimester and adverse pregnancy outcomes and determine, based on those comparisons, whether FPG can be a better predictor than HbA1c.

Materials and methods

A retrospective study of a prospective observational cohort was carried out at the Hospital del Mar, Barcelona, Spain, between April 2013 and September 2015. The characteristics of this cohort and the study methods have been published elsewhere [12]. Briefly, women over 18 years of age with a singleton pregnancy were included. Exclusion criteria were known pre-existing diabetes, meeting the American Diabetes Association criteria for diabetes mellitus (fasting plasma glucose $\geq$126 mg/dl and/or an HbA1c $\geq$6.5% (48 mmol/mol)) in the first trimester but without a previous diagnosis of diabetes mellitus (unknown type 2 diabetes), miscarriage or voluntary pregnancy termination and multiple pregnancies. Women who continued follow-up or ended pregnancy at other centres were also excluded as no delivery data could be obtained from them.

Universal testing for FPG and HbA1c levels at the first antenatal blood sampling was offered per protocol. Women diagnosed of unknown type 2 diabetes were referred to the Diabetes Unit. Otherwise, they were screened for GDM at 24–28 weeks' gestation using a two-step approach.

The study was conducted according to the Declaration of Helsinki principles and approved by the Ethics Committee of Clinical Research.

Demographic, anthropometric, clinical and analytical variables and pregnancy outcome data were obtained from maternity and electronic medical records.

HbA1c was determined using high-performance liquid chromatography on a Biorad Variant II analyser (Bio-Rad Laboratories, Hercules, CA). Plasma glucose was determined with the glucose oxidase method using venous plasma obtained after at least 8 h of fasting. Blood cell count, haematocrit, haemoglobin (Hb) and mean corpuscular volume (MCV) were measured using an automated haematology system. Anaemia was defined as an Hb concentration <11 g/dl and microcytosis as MCV < 81 femtolitres.

Primary outcomes included rates of macrosomia and pre-eclampsia. Secondary outcomes were the primary Caesarean section rate, preterm delivery and large-for-gestational age (LGA). Definitions for macrosomia and pre-eclampsia are described elsewhere [12]. In cases of premature pre-eclampsia (<37th weeks of gestation), the current recommendation at our centre is to delay delivery if the maternal and foetal status remains stable, with delivery planned for 37 weeks. Preterm delivery was defined as delivery prior to 37 weeks' gestation. If the delivery was the first by Caesarean section, it was labelled as primary Caesarean section. LGA was defined as a newborn weight above the estimated 90th percentile [14].

Data were analysed using the statistical software package IBM SPSS Statistic version 22.0. Continuous variables were described as mean $\pm$ standard deviation and analysed by independent sample Student's t-test. Categorical variables were described as frequencies and percentages and examined with chi-square test or Fisher's exact test. Different FPG and HbA1c cut-off points were assessed for associations with pregnancy outcomes. Multivariate logistic regression analyses were conducted to adjust for potential confounders in determining obstetric outcomes. Variables associated on univariate analysis ($p < 0.1$) with adverse obstetric outcomes and those previously described in the literature were included. A Pearson correlation and partial correlation analysis were also performed to assess the association between FPG and HbA1c levels and birthweight after adjustment for potential confounders such as maternal age, pre-gestational body mass index (BMI), pregnancy weight gain, gestational age at delivery, GDM diagnosis and neonatal sex. Statistical significance was set at $p < 0.05$.

Results

First-trimester blood samples were drawn from 1,631 women between April 2013 and September 2015; 1,228 of whom were included for outcome analysis according to exclusion criteria (Fig. 1). Mean age of participants was 32.65 $\pm$ 5.68 years, mean pre-pregnancy BMI 25.46 $\pm$ 5.08 Kg/m^2 and mean pregnancy weight gain 10.82 $\pm$ 4.68 kg. Overall, 44.4% (541/1218) of women were nulliparous. Among multiparous women, 9.2% (57/618) had a

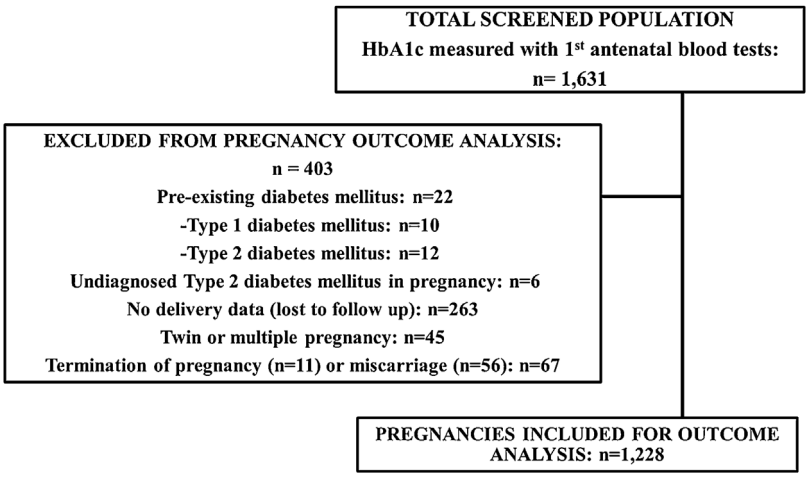

Fig. 1. Flow chart of the study protocol.
Caption: first-trimester blood samples were drawn from 1,631 women, of whom 1,228 were included for outcome analysis according to exclusion criteria.

previous GDM diagnosis and 5.5% (34/617) previous macrosomia. Regarding ethnicity, 53.6% (631/1177) of women were self-reported as Caucasian, 18.7% (220/1177) South-Central Asian, 13.5% (159/1177) Latin American, 7% (83/1177) Moroccan, 5.7% (67/1177) East Asian and 1.5% (17/1177) other ethnicities. Median FPG and HbA1c levels were 86.77 ± 9.54 mg/dl and 5.17 ± 0.36 (33 mmol/mol), respectively. One hundred and fifty-one of 1,157 women screened (13.1%) were diagnosed of GDM. Macrosomia and pre-eclampsia rates were 6.3% and 4.1%, respectively. With respect to secondary outcomes, rates of primary Caesarean section, preterm delivery and birthweight >90th percentile were 26.9%, 6.9% and 11.4%, respectively. Adjusted odds ratios for associations between different first-trimester FPG and HbA1c cut-off values and pregnancy outcomes are shown in Tables 1 and 2. A non-graded association was found between FPG >80 mg/dl and pre-eclampsia occurrence. Regarding HbA1c levels, after adjustment for potential confounding factors, women with HbA1c ≥5.8% (40 mmol/mol) showed an increased risk of macrosomia and an HbA1c ≥5.9% (41 mmol/mol) threshold was independently associated with a three-fold increased risk of pre-eclampsia. An HbA1c ≥6.0% (42 mmol/mol) was also associated with a four-fold increased risk of LGA. No relationship was found with Caesarean section or preterm delivery. Correlation analysis found no association between birthweight and FPG (partial correlation coefficient r' = 0.007, P = 0.84) or HbA1c levels (partial correlation coefficient r' = 0.012, P = 0.77) after adjustment for potential confounding factors.

Comment

In women without diabetes, first-trimester FPG levels were not found to be associated with macrosomia, preterm delivery, primary Caesarean section or LGA. A non-graded association between FPG >80 mg/dl and pre-eclampsia was found. Nonetheless, this threshold was not deemed clinically useful since it would select a very large number of women (81% in our population). Conversely, an early HbA1c ≥5.8% (40 mmol/mol) threshold was associated with an increased risk of macrosomia, an HbA1c ≥5.9% (41 mmol/mol) cut-off point was independently associated with a three-fold increased risk of pre-eclampsia and HbA1c ≥6.0% (42 mmol/mol) was also associated with a four-fold increased risk of LGA. These thresholds could have a clinical role since they would select a significantly smaller number of patients (6.9%, 3.8% and 2.4% of the entire cohort for HbA1c ≥5.8% (40 mmol/mol), ≥5.9% (41 mmol/mol) and >6% (42 mmol/mol) respectively). However, further studies would be required to assess the impact of early detection and treatment of these women on both maternal and foetal outcomes, as well as the cost-effectiveness of this approach.

Although early pregnancy HbA1c in women with pre-existing diabetes directly correlates with pregnancy outcomes, this association is less clear in those without unknown diabetes. Emerging data, including one study stemming from our reference population, support an early pregnancy HbA1c ≥5.9% (41 mmol/mol) threshold as an independent predictor of poorer pregnancy outcomes [11,12]. However, no studies to date have evaluated other first-trimester HbA1c thresholds in non-diabetic range that could predict adverse obstetric outcomes. In the current research, an early HbA1c ≥5.6% (38 mmol/mol) threshold was already related, though not statistically significant, to a gradually-increasing risk of macrosomia, and women with HbA1c ≥5.8% (40 mmol/mol) showed a significantly higher risk of macrosomia. On the other hand, the risk of pre-eclampsia only rose with HbA1c ≥5.9% (41 mmol/mol), as previously reported. Further, an HbA1c ≥6.0% (42 mmol/mol) was associated with a four-fold increased risk of LGA. No association was found between pre-eclampsia and HbA1c ≥6.0% (42 mmol/mol) or between any obstetric complication and higher cut-off points. This may be due to a loss of statistical power given the small number of women above this threshold. On the other hand, in cases of premature pre-eclampsia, the recommendation at our centre is to delay delivery if the maternal and foetal status remains stable. This may explain why, in our study, although several HbA1c cut-offs were associated with pre-eclampsia, it did not translate into a higher preterm birth rate. The results support previous evidence of the potential usefulness of adding HbA1c to the first antenatal blood screen to early identify women at high risk of adverse obstetric outcomes. Regarding FPG, a clear relationship

Table 1
Adjusted odds ratios for associations between different first-trimester FPG and HbA1c cut-off values and primary outcomes.

	Macrosomia (n) (below vs above threshold)	Odds ratio (95% CI)[a]	Pre-eclampsia (n) (below vs above threshold)	Odds ratio (95% CI)[a]
FPG 76 mg/dl	5/102 vs 72/1117	1.15 (0.39-3.38)	3/93 vs 44/1065	1.54 (0.35-6.74)
FPG 80 mg/dl	13/234 vs 64/985	0.89 (0.44-1.80)	4/219 vs 43/939	4.38 (1.02-18.72)
FPG 84 mg/dl	22/444 vs 55/775	1.14 (0.62-2.09)	13/418 vs 34/740	2.00 (0.91-4.39)
FPG 88 mg/dl	36/698 vs 41/521	1.39 (0.79-2.45)	22/665 vs 25/493	2.08 (1.04-4.16)
FPG 92 mg/dl	51/894 vs 26/325	1.36 (0.74-2.50)	32/850 vs 15/308	1.78 (0.88-3.57)
FPG 96 mg/dl	60/1041 vs 17/178	1.50 (0.72-3.10)	40/986 vs7/172	1.30 (0.54-3.17)
FPG 100 mg/dl	70/1124 vs 7/95	0.90 (0.30-2.72)	44/1067 vs 2/91	0.69 (0.15-3.03)
FPG 104 mg/dl	75/1170 vs 2/49	0.00 (0-∞)	45/1111 vs 2/47	1.64 (0.36-7.44)
FPG 108 mg/dl	75/1188 vs 2/31	0.00 (0-∞)	45/1128 vs 2/30	3.51 (0.74-16.64)
FPG 110 mg/dl	75/1192 vs 2/27	0.00 (0-∞)	45/1132 vs 2/26	4.21 (0.87-20.27)
HbA1c 4.8% (29 mmol/mol)	9/119 vs 68/1100	0.55 (0.23-1.31)	3/108 vs 44/1050	1.64 (0.38-7.07)
HbA1c 4.9% (30.1 mmol/mol)	15/206 vs 62/1013	0.74 (0.37-1.47)	7/195 vs 40/963	1.06 (0.43-2.63)
HbA1c 5.0% (31.1 mmol/mol)	21/314 vs 56/905	0.77 (0.41-1.42)	15/299 vs 32/859	0.63 (0.31-1.28)
HbA1c 5.1% (32.2 mmol/mol)	25/456 vs 52/763	1.27 (0.71-2.27)	21/431 vs 26/727	0.67 (0.34-1.32)
HbA1c 5.2% (33.3 mmol/mol)	36/604 vs 41/615	1.09 (0.62-1.92)	25/573 vs 22/585	0.92 (0.47-1.83)
HbA1c 5.3% (34.4 mmol/mol)	50/739 vs 27/480	0.88 (0.49-1.59)	31/704 vs 16/454	0.82 (0.41-1.65)
HbA1c 5.4% (35.5 mmol/mol)	57/865 vs 20/354	0.78 (0.40-1.49)	36/823 vs 11/335	0.94 (0.44-1.99)
HbA1c 5.5% (36.6 mmol/mol)	58/966 vs 19/253	1.15 (0.58-2.28)	38/924 vs 9/234	1.19 (0.53-2.66)
HbA1c 5.6% (37.7 mmol/mol)	59/1053 vs 18/166	1.99 (0.96-4.09)	38/1005 vs 9/153	2.14 (0.94-4.86)
HbA1c 5.7% (38.8 mmol/mol)	65/1099 vs 12/120	1.91 (0.86-4.23)	41/1049 vs 6/109	1.94 (0.74-5.07)
HbA1c 5.8% (39.9 mmol/mol)	67/1135 vs 10/84	2.70 (1.12-6.48)	43/1081 vs 4/77	1.71 (0.55-4.25)
HbA1c 5.9% (41 mmol/mol)	69/1171 vs 8/48	3.11 (1.12-8.60)	43/1115 vs 4/43	3.53 (1.08-11.53)
HbA1c 6.0% (42.1 mmol/mol)	69/1189 vs 8/30	7.46 (2.40-23.14)	44/1132 vs 2/26	3.02 (0.61-14.91)

We did not include any higher cut-off points given the small number of subjects above the threshold.
[a] Adjusted for nulliparity, pre-pregnancy body mass index, previous macrosomia, ethnicity, pregnancy weight gain, GDM diagnosis and anaemia.

Table 2
Adjusted odds ratios for associations between different first-trimester FPG and HbA1c cut-off values and secondary outcomes.

	Preterm delivery (n) (below vs above threshold)	Odds ratio (95% CI)[a,b]	Caesarean section (n) (below vs above threshold)	Odds ratio (95% CI)[a,c]	Birth weight > 90th percentile (n) (below vs above threshold)	Odds ratio (95% CI)[a]
FPG 76 mg/dl	6/101 vs 77/1101	0.83 (0.32-2.14)	27/102 vs 300/1114	1.10 (0.65-1.88)	6/101 vs 131/1097	1.32 (0.54-3.20)
FPG 80 mg/dl	12/230 vs 71/972	0.68 (0.34-1.38)	55/233 vs 272/983	0.89 (0.61-1.31)	18/231 vs 119/967	1.01 (0.57-1.77)
FPG 84 mg/dl	26/435 vs 57/767	0.74 (0.44-1.26)	113/442 vs 214/774	1.04 (0.76-1.41)	39/434 vs 98/764	1.07 (0.67-1.71)
FPG 88 mg/dl	42/688 vs 41/514	0.73 (0.43-1.14)	184/697 vs 143/519	1.10 (0.82-1.48)	69/687 vs 68/511	0.98 (0.63-1.54)
FPG 92 mg/dl	60/880 vs 23/322	1.08 (0.62-1.88)	228/893 vs 99/323	0.86 (0.62-1.19)	89/880 vs 48/318	1.21 (074-1.95)
FPG 96 mg/dl	72/1025 vs 11/177	1.27 (0.61-2.61)	271/1039 vs 56/177	0.75 (0.51-1.11)	106/1024 vs 31/174	1.39 (0.78-2.46)
FPG 100 mg/dl	76/1108 vs 7/94	1.11 (0.45-2.75)	298/1122 vs 29/94	0.84 (0.50-1.41)	123/1105 vs 14/93	1.03 (0.46-2.30)
FPG 104 mg/dl	79/1153 vs 4/49	0.88 (0.29-2.65)	309/1168 vs 18/48	0.62 (0.32-1.21)	131/1150 vs 6/48	0.45 (0.10-2.03)
FPG 108 mg/dl	79/1171 vs 4/31	0.53 (0.16-1.69)	316/1186 vs 11/30	0.68 (0.28-1.63)	131/1168 vs 6/30	1.22 (0.26-5.58)
FPG 110 mg/dl	79/1175 vs 4/27	0.44 (0.13-1.47)	316/1190 vs 11/26	0.51 (0.20-1.29)	131/1172 vs 6/26	1.55 (0.33-7.26)
HbA1c 4.8% (29 mmol/mol)	6/114 vs 77/1088	0.62 (0.21-1.77)	34/117 vs 293/1099	1.26 (0.77-2.04)	12/113 vs 125/1085	0.71 (0.34-1.46)
HbA1c 4.9% (30.1 mmol/mol)	12/201 vs 71/1001	0.72 (0.34-1.50)	57/205 vs 270/1011	1.10 (0.75-1.61)	23/201 vs 114/997	0.95 (0.53-1.69)
HbA1c 5.0% (31.1 mmol/mol)	24/305 vs 59/897	1.30 (0.75-2.24)	90/313 vs 237/903	1.24 (0.90-1.71)	31/307 vs 106/891	1.12 (0.67-1.86)
HbA1c 5.1% (32.2 mmol/mol)	32/445 vs 51/757	1.10 (0.66-1.82)	123/454 vs 204/762	1.05 (0.78-1.42)	43/446 vs 94/752	1.45 (0.91-2.30)
HbA1c 5.2% (33.3 mmol/mol)	38/592 vs 45/610	0.90 (0.54-1.48)	166/601 vs 161/615	1.13 (0.85-1.52)	57/593 vs 80/605	1.46 (0.94-2.27)
HbA1c 5.3% (34.4 mmol/mol)	50/726 vs 33/476	0.99 (0.60-1.65)	192/735 vs 135/481	0.94 (0.70-1.26)	84/726 vs 53/472	0.97 (0.62-1.52)
HbA1c 5.4% (35.5 mmol/mol)	58/851 vs 25/351	1.06 (0.61-1.85)	233/861 vs 94/355	1.12 (0.81-1.55)	91/850 vs 46/348	1.21 (0.75-1.94)
HbA1c 5.5% (36.6 mmol/mol)	65/953 vs 18/249	0.87 (0.48-1.59)	262/964 vs 65/252	1.20 (0.83-1.73)	102/950 vs 35/248	1.20 (0.71-2.04)
HbA1c 5.6% (37.7 mmol/mol)	71/1038 vs12/164	0.81 (0.40-1.62)	281/1051 vs 46/165	1.06 (0.69-1.62)	111/1036 vs 26/162	1.59 (0.89-2.84)
HbA1c 5.7% (38.8 mmol/mol)	76/1083 vs 7/119	1.02 (0.43-2.40)	294/1097 vs 33/119	1.07 (0.66-1.74)	121/1081 vs 16/117	1.33 (0.68-2.58)
HbA1c 5.8% (39.9 mmol/mol)	77/1119 vs 6/83	0.80 (0.31-2.01)	304/1133 vs 23/83	1.16 (0.66-2.04)	124/1117 vs 13/81	1.74 (0.83-3.63)
HbA1c 5.9% (41 mmol/mol)	78/1155 vs 5/47	0.46 (0.16-1.29)	313/1169 vs 14/47	1.07 (0.52-2.21)	128/1152 vs 9/46	1.68 (0.67-4.17)
HbA1c 6.0% (42.1 mmol/mol)	79/1172 vs 4/30	0.32 (0.098-1.07)	317/1187 vs 10/29	0.76 (0.32-1.81)	128/1169 vs 9/29	4.06 (1.49-11.07)

We did not include any higher cut-off points given the small number of subjects above the threshold.
[a] Adjusted for nulliparity, pre-pregnancy body mass index, previous macrosomia, ethnicity, pregnancy weight gain, GDM diagnosis and anaemia.
[b] Adjusted for macrosomia.
[c] Adjusted for large-for-gestational age and small-for-gestational age.

between second-trimester FPG and adverse pregnancy outcomes has been established. In this respect, in the HAPO study, significant correlations of HbA1c with individual oral glucose tolerance test (OGTT) measurements were found, with the FPG correlation being the largest. Indeed, glucose measurements in the second-trimester were more predictive of pregnancy outcomes than HbA1c values [15]. Sermer et al. proved second-trimester FPG to be an independent predictor of macrosomia after adjusting for potential confounders, but without an obvious threshold at which risk increased [16]. Similarly, Chastang et al showed the diagnosis of GDM based on a second-trimester FPG >90 mg/dl and/or post-prandial blood glucose >120 mg/dl (which represents the blood glucose thresholds used for therapeutic intervention) to be more sensitive in predicting macrosomia than conventional GDM diagnosis involving a 50 g glucose challenge test followed by a 100 g OGTT, with no great loss in specificity [17].

FPG is an easy-to-obtain, safe and inexpensive parameter which has been used with HbA1c to screen for unknown type 2 diabetes at the initial prenatal visit. FPG measurements also have the advantage of being more reproducible, unaffected by ethnic origin and reported to vary little throughout gestation [18–20]. Whereas second-trimester FPG levels have been shown to correlate with adverse obstetric outcomes, the association with early FPG levels is not clear. In the present study, first-trimester FPG did not show a significant association with any adverse pregnancy outcome except for a non-graded association between FPG >80 mg/dl and pre-eclampsia, which is not considered clinically useful. Our results differ from those of previous studies. In this respect, Riskin-Mashiah et al conducted a retrospective evaluation involving 6,129 women [13]. Graded associations between first-trimester FPG levels below those diagnostic of diabetes and primary outcomes were reported. A strong association was found between FPG and LGA and/or macrosomia, which rose as the fasting glycaemia categories increased (OR 2.41 (1.35–4.29) in the highest FPG category compared with the lowest category ($P < 0.0001$)) and remained stable even after women who developed GDM were excluded. Nevertheless, no clear threshold for FPG level was found that put pregnant women at a significantly increased risk for poorer pregnancy outcomes. It should be noted, however, that associations between FPG and macrosomia were only adjusted for parity and maternal age but not for BMI or gestational weight gain [13]. First-trimester FPG levels have been reported to correlate with pre-gravid BMI [21] and several large population studies showed an association between pregnancy weight gain and the development of macrosomia, particularly in overweight and obese women [22–24]. Thus, in our study, known risk factors for macrosomia and pre-eclampsia, including pre-pregnancy BMI, gestational weight gain, ethnicity and GDM diagnosis, were included in the multivariate analysis.

On the other hand, Liu et al analysed FPG levels as a continuous variable in 2284 women. First-trimester FPG concentration was independently associated with neonatal birthweight (partial correlation coefficient $r' = 0.089$, $P < 0.001$) after adjustment for maternal age, pre-gravid BMI, weight gain before and after OGTT, gestational age, GDM diagnosis and neonatal sex. Additionally, newborns of GDM mothers did not have higher birthweights compared to those of mothers with normal glucose tolerance, which indicates that maternal fasting glycaemia, rather than postprandial glycaemia or GDM diagnosis, strongly affects foetal growth. However, no obvious thresholds at which risks increased were defined and the association between macrosomia or LGA rates and FPG levels was not studied [21,25]. Our results also differ on this point since no correlation was found between birthweight and FPG or HbA1c levels. These discrepancies could be attributed to differences in ethnic origin of the two study populations. The research of Liu et al was conducted in a predominantly East Asian population, whereas the population in the present study had a large representation of women of Caucasian origin and other ethnicities such as South-Central Asian and Latin American. Previous studies reported an inter-racial variability in pregnancy

outcomes and in the inter-relationship between hyperglycaemia and macrosomia [26,27].

According to our results, FPG measurement did not appear to be a better predictor of adverse pregnancy outcomes than HbA1c. In this respect, it is worth highlighting that, unlike FPG, fasting is a non-mandatory requirement for measuring HbA1c. The fact that we cannot guarantee that all the glucose tests were carried out in fasting conditions could, at least in part, explain the poor association between FPG levels and adverse pregnancy outcomes reported in the present study. Moreover, variability in plasma glucose concentrations according to fast duration and an increase in FPG concentrations over time have been proposed [28]. In the general population, ethnic variation in the correlation between random and average plasma glucose and HbA1c levels has been acknowledged [29] and the relationship between HbA1c and FPG has been reported to change according to FPG range [30]. On the other hand, the day-to-day reproducibility of FPG during pregnancy has not been reported.

Our study was not without limitations, one of which was the substantial number of women (n = 263, 17.6%) who were lost to follow-up. This could act as a potential selection bias as we were unable to gather data on pregnancy outcomes. Nevertheless, this percentage was significantly lower than that reported by Hugues et al. [11]. Women diagnosed with GDM were not excluded and intervention in this group of patients could have introduced a bias by modifying pregnancy outcomes. We accounted for this factor by including the diagnosis of GDM as a confounding factor. As mentioned previously, fasting conditions are mandatory when measuring FPG levels, a drawback that could diminish the accuracy of our results if this requirement was not met. Moreover, we did not distinguish between women with mild and severe pre-eclampsia and those with early-onset pre-eclampsia (<34th week) who usually present with severe pre-eclampsia and are therefore more likely to have a preterm birth. Finally, this study was conducted in a relatively high-risk, predominantly non-Caucasian population including different ethnic groups but was underpowered to assess the specific influence of ethnicity on HbA1c and FPG levels during pregnancy.

In conclusion, in a multi-ethnic population without diabetes, first-trimester FPG levels were not a better predictor of adverse pregnancy outcomes than HbA1c since no clinically-useful correlation between FPG levels and adverse obstetric outcomes was found. Moreover, a lower first-trimester HbA1c threshold (5.8% (39 mmol/mol)) than that previously reported already identified women with an increased risk of macrosomia.

Declaration of interest

None.

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Paper presentation information

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Contribution statement

All authors met authorship requirements, actively participated in data acquisition, drafting or revising the paper, contributed to the discussion, and approved the final version. LM collected data, performed data analysis and drafted the manuscript and tables. JAFL conceived and designed the study, collected data, performed data analysis, reviewed the manuscript and contributed to discussion. JPB collected data, reviewed the manuscript and contributed to discussion. LG collected data and reviewed the manuscript. JJC collected data, performed data analysis and reviewed the manuscript. GL contributed to data analysis and reviewed the manuscript. AP conceived and designed the study, collected data, reviewed the manuscript and contributed to discussion. DB conceived and designed the study, collected data, performed data analysis, reviewed the manuscript and contributed to discussion.

JAFL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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