



Contents available at [ScienceDirect](https://www.sciencedirect.com)

Diabetes Research
and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres



International
Diabetes
Federation



Association of first-trimester HbA1c levels with adverse pregnancy outcomes in different ethnic groups

Laura Mañé^{a,b}, Juana Antonia Flores-Le Roux^{a,b,*}, Nàdia Gómez^b, Juan José Chillarón^{a,b}, Gemma Llauradó^{a,b}, Lucía Gortazar^a, Antonio Payà^{b,c}, Juan Pedro-Botet^{a,b}, David Benaiges^{a,b}

^a Department of Endocrinology and Nutrition, Hospital del Mar, E-08003 Barcelona, Spain

^b Department of Medicine, Universitat Autònoma de Barcelona, E-08003 Barcelona, Spain

^c Department of Gynaecology and Obstetrics, Hospital del Mar, E-08003 Barcelona, Spain

ARTICLE INFO

Article history:

Received 2 October 2018

Received in revised form

16 December 2018

Accepted 7 March 2019

Available online 15 March 2019

Keywords:

Pregnancy outcome

Glycosylated haemoglobin

Macrosomia

Preeclampsia

Large-for-gestational age

Ethnicity

ABSTRACT

Aim: To determine, in a multi-ethnic cohort, the association of first-trimester HbA1c levels with the development of pregnancy complications.

Methods: A prospective study between April 2013–October 2016. Participants were stratified in five ethnic groups. Women had an HbA1c measurement added to their first antenatal bloods. Primary outcome was macrosomia and secondary outcomes included preeclampsia and large-for-gestational age (LGA). A multivariate logistic regression analysis was performed to adjust for potential confounders in determining the association between different HbA1c cut-off points and obstetric outcomes on each ethnic group.

Results: 1,882 pregnancies were included. Analysis was limited to the three main ethnic groups: Caucasian (54.3%), South-Central Asian (19%) and Latin-American (12.2%). There was no association between HbA1c levels and obstetric outcomes among Caucasians. In Latin-Americans, an HbA1c $\geq 5.8\%$ (40 mmol/mol) was associated with higher risk of macrosomia, whereas an HbA1c $\geq 5.9\%$ (41 mmol/mol) was associated with LGA. In South-Central Asian, an HbA1c $\geq 5.7\%$ (39 mmol/mol) was associated with increased risk of macrosomia and a continuous graded relationship between HbA1c levels and preeclampsia and LGA was detected starting at HbA1c levels of 5.4% (36 mmol/mol).

Conclusion: First-trimester HbA1c levels perform as a suitable predictor of pregnancy complications in South-Central Asian and Latin-American women whereas in Caucasian no significant associations were found.

© 2019 Elsevier B.V. All rights reserved.

* Corresponding author at: Department of Endocrinology and Nutrition, Hospital del Mar, Paseo Marítimo 25-29, E-08003 Barcelona, Spain.

E-mail addresses: 94066@parcdesalutmar.cat (J.A. Flores-Le Roux), JChillarón@parcdesalutmar.cat (J.J. Chillarón), GLlaurado@parcdesalutmar.cat (G. Llauradó), 88858@parcdesalutmar.cat (A. Payà), 86620@parcdesalutmar.cat (J. Pedro-Botet), DBenaiges@parcdesalutmar.cat (D. Benaiges).

<https://doi.org/10.1016/j.diabres.2019.03.017>

0168-8227/© 2019 Elsevier B.V. All rights reserved.

1. Introduction

In recent years, the ongoing epidemic of obesity and the rising immigration figures in developed countries have led to an increase in the number of pregnant women with impaired glucose metabolism [1–3]. The role of hyperglycaemia during pregnancy as an independent predictor for poorer pregnancy outcomes has been clearly established [4–6] and several large studies of untreated women have shown a correlation between blood glucose levels, even below the non-diabetic range, and the incidence of obstetric complications [7–9]. Hence, early detection of women at high pregnancy risk is a desirable goal. A recent study conducted in New Zealand [10] found an early pregnancy HbA1c $\geq 5.9\%$ (41 mmol/mol) to be a clinically relevant marker for adverse obstetrical outcomes. Shortly afterwards, another study stemming from our reference population, supported the proposed HbA1c threshold of 5.9% (41 mmol/mol), although the association found with adverse outcomes differed in several ways [11]. These discrepancies were partly attributed to the differences in ethnic origin of the two study populations. Hughes et al. research was conducted in a predominantly Caucasian population, whereas our cohort was characterised by a majority of women belonging to ethnic minorities. However, our study was underpowered to assess the specific influence of ethnicity on HbA1c levels during pregnancy. Previous studies have reported an interracial variability in HbA1c levels in non-diabetic and in diabetic populations within organized systems of health care and after adjusting for processes of care [12–15]. Despite HbA1c levels have been broadly acknowledged to be significantly lower in Caucasian populations when compared to other ethnicities, studies exploring normal first-trimester HbA1c levels according to ethnicity are scarce. In this regard, Hartland et al. assessed trimester- and ethnic group-related reference ranges for HbA1c in Caucasian and Asian pregnant women without diabetes and reported significantly higher levels among Asians [16]. On the other hand, ethnic differences have also been described in terms of obstetric results [17,18] and in the interrelationship between hyperglycaemia and pregnancy outcomes [19–21].

The present study aimed to determine, in a multi-ethnic cohort, the association of first-trimester HbA1c levels with the development of adverse pregnancy outcomes in different ethnic groups.

2. Subjects, materials and methods

This prospective study was conducted at the Hospital del Mar, Barcelona, Spain between April 2013 and October 2016. Women over 18 years with a singleton pregnancy were included. Exclusion criteria were known pre-existing diabetes (type 1 or 2), meeting the *American Diabetes Association* criteria for diabetes mellitus [fasting plasma glucose (FPG) ≥ 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) and multiple pregnancies [22]. Women with miscarriage or voluntary pregnancy termination and those lost to follow-up in whom delivery data could not be obtained were also excluded. Participants were

stratified in five ethnic groups according to self-reported ethnicity (Caucasian, Latin American, South Central Asian, Moroccan and East Asian). Women belonging to other ethnicities and those in whom there was no information about ethnicity were not included for outcome analysis.

Universal testing for FPG and HbA1c levels at the first antenatal bloods was offered per protocol. Women with fasting plasma glucose (FPG) ≥ 126 mg/dl and/or an HbA1c $\geq 6.5\%$, (48 mmol/mol) were diagnosed of unknown type 2 diabetes and were referred to the Diabetes Unit at the first trimester. Otherwise, they did not receive any dietary or medical treatment and underwent routine gestational diabetes mellitus (GDM) screening at 24–28 weeks of gestation using a two-step approach. The diagnosis of GDM was based on the recommendations of the *National Diabetes Data Group* (NDDG) and women were referred to the Diabetes Unit for management [23].

Demographic, anthropometric, clinical and analytical variables and pregnancy outcome data were obtained from maternity and electronic medical records. Maternal information regarding age, smoking habit, family history of type 2 diabetes, pre-gestational body mass index (BMI), previous GDM, previous macrosomia, ethnicity and nulliparity was included. Pregnancy weight gain was calculated as the difference between weight at the last prenatal visit and that reported by the participant as pre-pregnancy weight.

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 Biorad Variant II analyser (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, 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 fl.

Primary outcome was macrosomia and secondary outcomes included preeclampsia and large-for-gestational age (LGA). Macrosomia was defined, according to the *American College of Obstetricians and Gynecologists*, as newborns with birth weight ≥ 4000 g. 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 foetal growth restriction [24]. The percentiles for gestational age (30–44 weeks) were determined using customized birthweight curves for newborns according to maternal ancestry (Latin American, South Central Asian, Moroccan or East Asian) with adjustment for gestational age and gender [25]. For Caucasian women newborn birthweight curves based on a Spanish population were employed [26]. A newborn was considered to be LGA if birthweight was greater than the estimated customized 90th percentile for the baby's sex, gestational age and ethnicity.

We calculated the sample size necessary for each ethnic group to assess the association between an HbA1c $\geq 5.9\%$ (41 mmol/mol) and the occurrence of macrosomia. Calculation was based on previous literature reporting the association between an HbA1c $\geq 5.9\%$ (41 mmol/mol) and macrosomia. We assumed a 5% rate of macrosomia in women with normal carbohydrate metabolism in pregnancy and a 30% rate in women with an HbA1c $\geq 5.9\%$ (41 mmol/mol). In accordance with Hugues et al. and Mañe et al. [10,11], we estimated that 6% of pregnant women would meet a first trimester HbA1c $\geq 5.9\%$ (41 mmol/mol). Accepting an α risk of 0.05 and a β risk of 0.2 in a two-sided test, 17 participants were necessary in the HbA1c $\geq 5.9\%$ (41 mmol/mol) group and 291 in the HbA1c $< 5.9\%$ (41 mmol/mol) group to find a proportion difference as statistically significant, expected to be 30% in the first group and 5% in the second. A 5% dropout rate was anticipated.

Statistical analysis was performed using the statistical software package IBM SPSS Statistic version 22.0. Data are expressed as mean \pm standard deviation for continuous variables and as frequencies and percentages for qualitative variables. Chi square test or Fisher's exact test were applied to determine the association between qualitative variables and Student's t-test and ANOVA to compare mean and standard deviations of quantitative variables between two groups or more than two, respectively. A crude odds ratio was calculated to determine the association between different HbA1c cut-off points and obstetric outcomes on each ethnic group and a multivariate logistic regression analysis was performed to adjust for potential confounders. All variables associated on univariate analysis ($p < 0.1$) with adverse pregnancy outcomes and those previously described in the literature were included in the regression model. Statistical significance was set at $p < 0.05$.

3. Results

First-trimester HbA1c testing was drawn out from 2,534 women between April 2013 and October 2016 of which 652 were excluded based on exclusion criteria (Fig. 1). Finally, 1,882 pregnancies were included for pregnancy outcome analysis. Of those, nearly half of the cohort belonged to ethnic minorities such as Latin American (12.2%), South Central Asian (19%), Moroccan (7.4%) and East Asian (7.1%). As shown in Table 1, there were several significant differences on maternal and pregnancy outcomes among ethnicities and when comparing with the Caucasian group. From highest to lowest, mean first-trimester HbA1c levels were, 5.2 ± 0.4 (33 mmol/mol) for South Central Asian women, 5.1 ± 0.4 (32 mmol/mol) for East Asian, 5.1 ± 0.4 (32 mmol/mol) for Latin American, 5.1 ± 0.3 (32 mmol/mol) for Moroccan and 5.0 ± 0.3 (31 mmol/mol) for Caucasian. Accordingly, South Central Asian women had the highest prevalence of GDM (25.8%) followed by East Asian (24.6%) and Caucasian showed the lowest prevalence (6.2%).

Regarding pregnancy outcomes, Moroccan women exhibit the highest rates of macrosomia (10.9%) whereas Latin American women had the highest rates of LGA (16.2%) followed by Moroccan (13.9%). South Central Asian showed the lowest rates of macrosomia (3.4%) and LGA (7.9%). For preeclampsia

East Asian had the highest rates (9.3%) followed by Latin American (5.7%) and Moroccan women had the lowest rates (0.7%).

Odds ratios for associations between different first-trimester HbA1c cut-off values and obstetric outcomes for each ethnicity are shown in Tables 2–4. Moroccan and East Asian women were excluded from the analysis given the small sample size of the groups. After adjusting for potential confounding factors, Latin American women with an HbA1c $\geq 5.8\%$ (40 mmol/mol) showed an increased risk of macrosomia and an HbA1c $\geq 5.9\%$ (41 mmol/mol) threshold was statistically associated with a higher risk of LGA. Among South-Central Asian women an HbA1c $\geq 5.7\%$ (39 mmol/mol) was associated with an increased risk of macrosomia and a continuous graded relationship between rising HbA1c levels and the occurrence of preeclampsia and LGA was also detected starting at HbA1c values of 5.4% (36 mmol/mol). There was no association between HbA1c levels and any obstetric outcome in the Caucasian group.

4. Discussion

We determined that, in women without diabetes, the association between first-trimester HbA1c levels and pregnancy outcomes differs according to ethnicity. While it can perform as an independent predictor of adverse obstetric results in Latin American and South Central Asian women, no significant association has been detected in Caucasian women.

The present study is the first to describe ethnic differences in the association between first-trimester HbA1c levels and the development of obstetric complications. A previous study by Hughes et al. carried out in 16,122 women of mainly Caucasian origin found that an early HbA1c $\geq 5.9\%$ (41 mmol/mol) was associated with adverse pregnancy results including congenital malformations, perinatal death, preeclampsia and shoulder dystocia [10]. In this study the authors did not analyse differences in ethnic associations with the primary outcome as the majority of the cohort was of Caucasian ancestry. If we compare their results with those found in the present study in the Caucasian group, some similarities and differences can be highlighted. In both studies, no significant association was found between HbA1c levels and the occurrence of macrosomia or LGA when adjusting for ethnicity using customized birthweight percentiles. The discordant findings regarding preeclampsia could partly be related to differences in the size of the cohort. It should be noted that, in the present study, sample size was calculated to assess the association between an HbA1c $\geq 5.9\%$ (41 mmol/mol) and the risk of macrosomia regardless of the occurrence of secondary outcomes. Conversely, Hughes et al. research was conducted in a remarkably larger cohort that allowed analysis of low frequency events such as preeclampsia. On the other hand, discrepancies concerning preeclampsia could also be attributed to the different populations evaluated. Even though in the New Zealand study a high proportion of the cohort was of Caucasian ancestry, more than 20% belonged to other ethnic minorities, mainly Maoris and Pacific Islanders. Previous studies have shown that these ethnic groups have significant differences in terms of obstet-

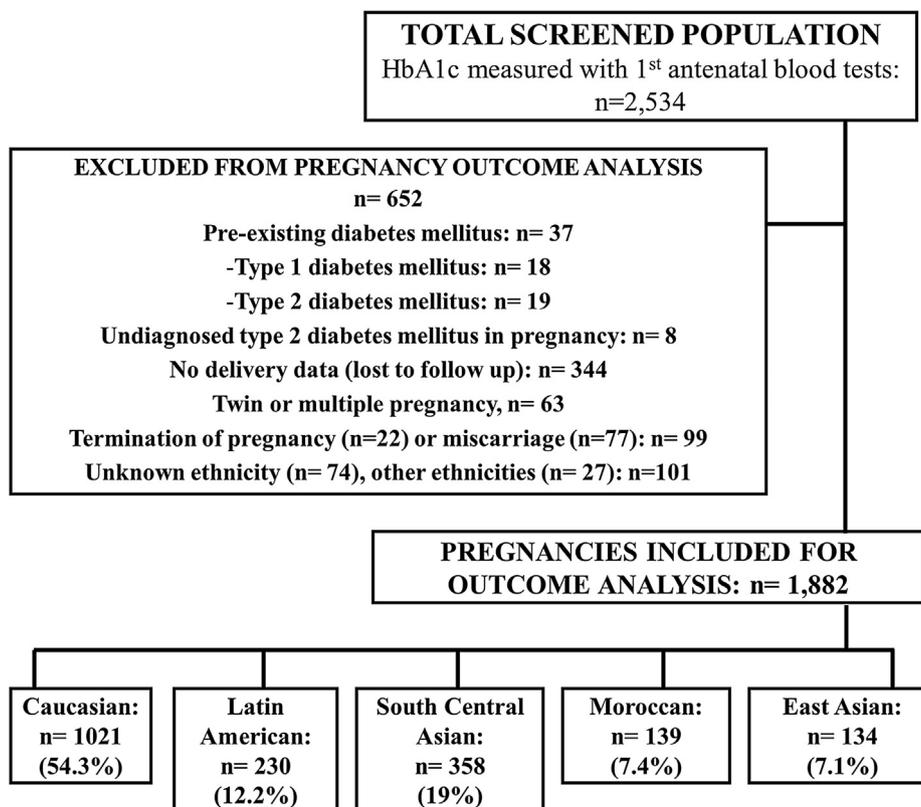


Fig. 1 – Flow chart of the study population. Caption: First-trimester HbA1c testing was drawn out from 2,534 women of whom 652 were excluded based on exclusion criteria. Finally, 1,882 pregnancies were included for pregnancy outcome analysis.

ric outcomes and a higher risk of diabetes when compared to Caucasians [27,28]. Moreover, it has also been argued that race/ethnicity may be too ambiguous a concept for clinical usage. Definition of ethnicity should consider aspects such as cultural, economic, social and biological factors as well as geographical origins. Caucasian women from Spain and those from New Zealand may not share the same metabolic profile and, probably, these cultural and socioeconomic factors may also play a relevant role in obstetric outcomes that is difficult to measure. Therefore, trying to interpret the meaning of differences related to ethnicity is always a challenge. Despite the major limitations of using ethnicity as a predictive and explanatory variable in health research, there is still a dire need to conduct research on ethnic differences in health outcomes. Finally, as mentioned above, Hughes et al. research was conducted in a remarkably large cohort that allowed analysis of low frequency events such as shoulder dystocia, perinatal death and congenital malformations whereas the present study was underpowered to detect differences in these outcomes.

Studies in the general population in groups with similar glucose tolerance by glucose measures have demonstrated lower HbA1c levels among Caucasian subjects when compared to other ethnicities such as African-American and Latin American [12–15]. The mechanism of this ethnic disparity in HbA1c levels has not been clearly identified. Differences in the prevalence of conditions affecting erythrocyte turnover, haemoglobinopathies and thalassemia syndromes, genetic determinants of haemoglobin glycation or differences in gly-

caemia that are not represented by the fasting and 2-h plasma glucose levels of the OGTT have been explored as contributors [29]. Research on this disparity in pregnant women is limited. Hartland et al. [16] assessed trimester and ethnic group-related reference ranges for HbA1c in pregnant women without diabetes and reported significantly higher levels in Asians compared to their Caucasian counterparts. These results concur with the findings of the present study where South Central Asian and East Asian women showed the highest mean first-trimester HbA1c levels and Caucasian the lowest.

Racial disparities in perinatal outcomes among women with and without diabetes have also been described and some authors have even suggested a lower risk of adverse pregnancy outcomes in groups at high risk of GDM [20]. Several reports have found ethnic differences in the incidence of macrosomia and LGA and some of them indicate a higher risk in Latin American and Moroccan women [17,18,30] and a lower risk among South Central Asian women [31,32]. Our results are in general agreement with those of previous studies. Gong et al. assessed the risk of preeclampsia by ethnicity, in New York City, among 902,460 women. Mexican and African American women exhibit the highest risk of preeclampsia whereas East Asian women had the lowest [33]. These results differ partially from ours as, in our cohort, East Asians showed the highest rates of preeclampsia. However, it should be taken into account that, in the present study, East Asian women were all grouped together whereas Gong et al distinguished between South East Asian and East Asian women.

Table 1 – Maternal and gestational characteristics and pregnancy outcomes according to ethnicity.

	Caucasian n = 1021	Latin American n = 230	South Central Asian n = 358	Moroccan n = 139	East Asian n = 134	P value*
<i>Maternal and gestational characteristics</i>						
Age, years, mean ± SD	33.71 ± 5.32	32.29 ± 5.90 [‡]	30.39 ± 5.73 [‡]	32.80 ± 6.03	32.53 ± 5.32 [†]	<0.001
Smoking, n (%)	150/697 (21.5)	10/154 (6.5) [‡]	1/258 (0.4) [‡]	7/103 (6.8) [‡]	5/105 (4.8) [‡]	<0.001
Family history of DM, n (%)	131/793 (16.5)	63/205 (30.7) [‡]	126/297 (42.4) [‡]	44/118 (37.3) [‡]	39/116 (33.6) [‡]	<0.001
Pre-pregnancy BMI, Kg/m ² , mean ± SD	24.68 ± 5.18	26.43 ± 4.72 [‡]	27.57 ± 5.00 [‡]	27.72 ± 5.05 [‡]	23.57 ± 3.80 [†]	<0.001
Previous GDM, n (%)	23/987 (2.3)	4/214 (1.9)	38/331 (11.5) [‡]	7/135 (5.2)	9/125 (7.2) [†]	<0.001
Previous macrosoma, n (%)	13/991 (1.3)	7/214 (3.3) [†]	12/331 (3.6) [†]	14/133 (10.5) [‡]	6/127 (4.7) [†]	<0.001
Nulliparous, n (%)	561/1017 (55.2)	82/228 (36.0) [‡]	105/357 (29.4) [‡]	35/138 (25.4) [‡]	48/134 (35.8) [‡]	<0.001
GDM diagnosis, n (%)	60/963 (6.2)	24/217 (11.1) [†]	85/330 (25.8) [‡]	17/133 (12.8) [†]	33/134 (24.6) [‡]	<0.001
Pregnancy weight gain, Kg, mean ± SD	11.38 ± 4.77	10.75 ± 4.32	8.59 ± 4.78 [‡]	9.72 ± 5.11 [‡]	11.09 ± 4.27	<0.001
1st trimester fasting plasma glucose, mg/dl, mean ± SD	85.11 ± 8.22	85.99 ± 8.52	90.49 ± 9.97 [‡]	87.82 ± 8.74 [‡]	86.45 ± 9.61	<0.001
1st trimester HbA1c, %, mean ± SD	5.04 ± 0.35	5.14 ± 0.37 [‡]	5.21 ± 0.41 [‡]	5.06 ± 0.33	5.15 ± 0.39 [‡]	<0.001
Anaemia, n (%)	45/1013 (4.4)	9/229 (3.9)	46/355 (13.0) [‡]	11/139 (7.9)	10/134 (7.5)	<0.001
Microcytosis, n (%)	48/806 (6.0)	12/173 (6.9)	130/304 (42.8) [‡]	24/118 (20.3) [‡]	19/117 (16.2) [‡]	<0.001
<i>Pregnancy outcomes</i>						
Gestational age at delivery, week, mean ± SD	39.31 ± 1.76	39.03 ± 1.73 [†]	39.05 ± 2.22 [†]	39.35 ± 1.80	38.92 ± 1.61 [†]	0.035
Preterm delivery, n (%)	65/1000 (6.5)	20/229 (8.7)	26/355 (7.3)	6/138 (4.3)	10/134 (7.5)	0.694
Caesarean section rate, n (%)	260/1010 (25.7)	63/230 (27.4)	94/354 (26.6)	30/138 (21.7)	34/134 (25.4)	0.644
Preeclampsia, n (%)	31/976 (3.2)	14/220 (5.7) [†]	10/351 (2.8)	1/137 (0.7)	12/129 (9.3) [†]	0.001
Birth weight, grams, mean ± SD	3247.42 ± 522.21	3365.73 ± 463.63 [†]	3155.14 ± 537.36 [†]	3392.01 ± 508.50 [†]	3236.54 ± 522.86	<0.001
LGA, n (%)	98/999 (9.9)	37/228 (16.2) [†]	28/352 (7.9)	19/137 (13.9)	14/133 (10.5)	0.016
Macrosomia, n (%)	66/1008 (6.5)	15/230 (6.5)	12/354 (3.4) [†]	15/138 (10.9)	8/131 (6.1)	0.033

DM: diabetes mellitus. BMI: body mass index. GDM: gestational diabetes mellitus. LGA: large-for-gestational age. SGA: small-for-gestational age.

* P value for comparisons between all ethnicities.

† P value for comparisons with the Caucasian group < 0.05.

‡ P value for comparisons with the Caucasian group < 0.001.

Table 2 – Odds ratios for associations between different first-trimester HbA1c cut-off values and obstetric outcomes among Caucasian women.

	Macroemia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	Preeclampsia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	LGA (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)
HbA1c 5.0% (31 mmol/mol)	35/288 vs. 31/620	0.53 (0.32–0.88)	0.60 (0.33–1.09)	13/381 vs. 18/595	0.88 (0.43–1.82)	0.49 (0.20–1.20)	89/285 vs. 103/613	0.67 (0.49–0.92)	0.68 (0.46–1.01)
HbA1c 5.1% (32 mmol/mol)	38/525 vs. 28/483	0.79 (0.48–1.31)	0.87 (0.47–1.58)	18/512 vs. 13/464	0.79 (0.38–1.63)	0.45 (0.17–1.17)	112/519 vs. 80/479	0.73 (0.53–1.00)	0.75 (0.51–1.11)
HbA1c 5.2% (33 mmol/mol)	46/649 vs. 20/359	1.29 (0.75–2.22)	0.82 (0.43–1.56)	20/629 vs. 11/347	1.00 (0.47–2.11)	0.75 (0.29–1.94)	130/643 vs. 62/355	0.84 (0.60–1.17)	0.83 (0.55–1.25)
HbA1c 5.3% (34 mmol/mol)	53/737 vs. 13/271	0.65 (0.35–1.21)	0.71 (0.33–1.48)	22/714 vs. 9/262	1.12 (0.51–2.46)	0.89 (0.33–2.41)	144/731 vs. 48/267	0.89 (0.62–1.28)	1.04 (0.67–1.61)
HbA1c 5.4% (36 mmol/mol)	60/831 vs. 6/177	0.45 (0.19–1.06)	0.53 (0.20–1.42)	26/805 vs. 5/171	0.90 (0.34–2.38)	1.01 (0.32–3.15)	163/823 vs. 29/175	0.80 (0.52–1.24)	1.05 (0.63–1.74)
HbA1c 5.5% (37 mmol/mol)	61/890 vs. 5/118	0.60 (0.24–1.53)	0.65 (0.21–1.92)	27/866 vs. 4/110	1.17 (0.40–3.42)	1.15 (0.31–4.2)	174/881 vs. 18/117	0.74 (0.44–1.25)	0.86 (0.46–1.61)
HbA1c 5.6% (38 mmol/mol)	62/938 vs. 4/70	0.86 (0.30–2.43)	0.90 (0.25–3.22)	27/911 vs. 4/65	2.15 (0.73–6.33)	2.02 (0.52–7.8)	181/929 vs. 11/69	0.78 (0.40–1.52)	0.86 (0.39–1.91)
HbA1c 5.7% (39 mmol/mol)	64/955 vs. 2/53	0.55 (0.13–2.29)	0.68 (0.15–3.13)	29/926 vs. 2/50	1.29 (0.30–5.56)	1.41 (0.28–6.98)	185/946 vs. 7/52	0.44 (0.20–0.98)	0.64 (0.25–1.63)
HbA1c 5.8% (40 mmol/mol)	64/975 vs. 2/33	0.92 (0.21–3.92)	1.09 (0.22–5.25)	30/944 vs. 1/32	0.98 (0.13–7.44)	0.90 (0.10–8.16)	186/966 vs. 6/32	0.97 (0.39–2.39)	0.83 (0.28–2.42)
HbA1c 5.9% (41 mmol/mol)	64/988 vs. 2/20	1.60 (0.36–7.07)	2.10 (0.39–11.1)	30/957 vs. 1/19	1.72 (0.22–13.29)	1.65 (0.17–15.84)	189/979 vs. 3/19	0.78 (0.23–2.72)	0.77 (0.19–3.03)
HbA1c 6.0% (42 mmol/mol)	64/997 vs. 2/11	3.24 (0.69–15.31)	4.21 (0.70–25.4)	29/965 vs. 1/11	3.23 (0.40–26.06)	3.61 (0.36–35.4)	189/987 vs. 3/11	1.58 (0.42–6.02)	1.98 (0.42–9.28)

* Adjusted p value < 0.05. † Adjusted p value < 0.001. LGA: large-for-gestational age.

P value adjusted for nulliparity, pre-pregnancy body mass index, previous macrosomia, ethnicity, pregnancy weight gain, GDM diagnosis and anaemia.

Other studies have highlighted a marked heterogeneity within the Asian population, with different phenotypes, geography, culture and religion, and have suggested that treating these subgroups as one racial group could mask the effects of ethnicity on perinatal outcomes. In this sense, Gong et al. reported a higher risk of preeclampsia among women from South East Asia compared to those from East Asia with a two-fold increased risk among women from Philippines [33]. This association is consistent with previous studies [28,34]. On the other hand, in the current study, Moroccan women had the lowest prevalence of preeclampsia which concurs with previous studies where pregnant North African women showed the lowest risk [35].

However, the critical question is not whether racial differences in first-trimester HbA1c levels or pregnancy outcomes exist; but whether the observed differences in HbA1c levels among ethnic groups are clinically meaningful. To our knowledge, this is the first prospective study to evaluate differences in the association of first-trimester HbA1c with adverse pregnancy outcomes according to ethnicity. In non-pregnant populations others have found conflicting results in terms of chronic complications. Harris et al. concluded that racial differences among individuals with type 2 diabetes in risk of developing retinopathy existed and that these differences could be caused by differential genetic susceptibility to the adverse effects of increased blood glucose levels [36]. On the same lines, Tsugawa et al. showed that the risk for diabetic retinopathy was higher for blacks compared to whites at any given HbA1c level between 5.0% (31 mmol/mol) and 7.0% (53 mmol/mol) and that the risk of retinopathy at an HbA1c level of 5.5% (37 mmol/mol) to 5.9% (41 mmol/mol) for blacks was similar to the risk at an HbA1c level of 6.0% (42 mmol/mol) to 6.4% (46 mmol/mol) among whites [37]. Kehl et al explored the association between HbA1c and cardiovascular mortality in the adult population without diabetes of the NHANES III, focussing on the impact of race–ethnicity. A significant association of non-diabetic HbA1c levels with increased risk of cardiovascular mortality in non-Hispanic whites was found whereas no significant associations were observed in Mexican–American or non-Hispanic blacks [38]. Conversely, subsequent studies have suggested that the association of HbA1c with risk for chronic complications might be similar among ethnicities [39]. In this context, no strict consensus has been reached on whether different diagnostic cut-offs of HbA1c should be used for different racial populations in the association with chronic complications. Our study adds to this debate suggesting that the association of HbA1c with adverse obstetric outcomes may also differ by ethnicity. Longitudinal studies with larger samples are warranted to determine whether different thresholds of HbA1c should be considered to identify women at high risk of adverse pregnancy outcomes. Further, a greater impact of ethnicity on the association between hyperglycaemia and adverse results during pregnancy, and particularly during first-trimester, could also be argued. Finally, the lower HbA1c levels observed among Caucasian women could also be proposed as contributors of this controversy.

The strengths of our study include a large number of subjects and the diverse racial origin of the population. Further, birthweight percentile was adjusted to maternal ethnicity

Table 3 – Odds ratios for associations between different first-trimester HbA1c cut-off values and obstetric outcomes among Latin American women.

	Macrosomia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	Preeclampsia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	LGA (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)
HbA1c 5.0% (31 mmol/mol)	4/68 vs. 11/162	1.17 (0.36–3.80)	1.43 (0.29–6.92)	8/67 vs. 6/153	0.30 (0.10–0.91)	0.26 (0.07–0.91) [†]	10/67 vs. 37/161	1.70 (0.79–3.66)	2.24 (0.87–5.78)
HbA1c 5.1% (32 msol/mol)	5/85 vs. 10/145	1.19 (0.39–3.59)	1.11 (0.26–4.65)	8/82 vs. 6/138	0.42 (0.14–1.26)	0.37 (0.11–1.26)	13/84 vs. 34/144	1.69 (0.83–3.42)	1.84 (0.80–4.24)
HbA1c 5.2% (33 mmol/mol)	6/105 vs. 9/125	1.28 (0.44–3.72)	1.13 (0.29–4.41)	8/102 vs. 6/118	0.63 (0.21–1.88)	0.64 (0.19–2.16)	16/104 vs. 31/124	1.83 (0.94–3.58)	2.07 (0.93–4.59)
HbA1c 5.3% (34 mmol/mol)	9/140 vs. 6/90	1.04 (0.36–3.03)	0.99 (0.25–3.83)	11/137 vs. 3/83	0.43 (0.12–1.59)	0.41 (0.10–1.64)	25/138 vs. 22/90	1.46 (0.77–2.79)	1.47 (0.69–3.13)
HbA1c 5.4% (36 mmol/mol)	12/160 vs. 3/70	0.55 (0.15–2.02)	0.40 (0.07–2.16)	12/156 vs. 2/64	0.39 (0.08–1.78)	0.37 (0.07–1.84)	31/158 vs. 16/70	1.21 (0.61–2.40)	1.13 (0.51–2.52)
HbA1c 5.5% (37 mmol/mol)	12/182 vs. 3/48	0.94 (0.26–3.49)	0.74 (0.12–4.30)	12/176 vs. 2/44	0.65 (0.14–3.02)	0.63 (0.12–3.27)	26/180 vs. 11/48	1.76 (0.80–3.88)	0.84 (0.32–2.19)
HbA1c 5.6% (38 mmol/mol)	12/204 vs. 3/26	1.00 (0.26–3.84)	1.61 (0.25–10.33)	12/197 vs. 2/23	1.47 (0.31–7.01)	1.55 (0.29–8.2)	39/202 vs. 8/26	1.86 (0.75–4.58)	1.36 (0.43–4.26)
HbA1c 5.7% (39 mmol/mol)	12/214 vs. 3/16	3.88 (0.97–15.50)	3.23 (0.41–25.23)	12/207 vs. 2/13	2.95 (0.59–14.86)	4.19 (0.69–25.5)	41/212 vs. 6/16	2.50 (0.86–7.28)	2.20 (0.55–8.79)
HbA1c 5.8% (40 mmol/mol)	13/218 vs. 2/12	3.15 (0.63–15.91)	7.13 (1.03–49.17) [†]	13/210 vs. 1/10	1.68 (0.20–14.32)	2.05 (0.21–19.47)	43/216 vs. 4/12	2.01 (0.58–6.99)	1.98 (0.44–8.74)
HbA1c 5.9% (41 mmol/mol)	13/225 vs. 2/5	10.87 (1.67–70.88)	32.72 (2.64–405.6) [†]	13/216 vs. 1/4	5.21 (0.51–53.59)	6.71 (0.44–101.9)	44/223 vs. 3/5	6.10 (0.99–37.64)	7.90 (1.06–58.45) [†]
HbA1c 6.0% (42 mmol/mol)	13/227 vs. 2/3	32.92 (2.80–387.26)	453.5 (12.3–16631.5) [†]	14/218 vs. 0/2	NC	–	45/225 vs. 2/3	8.00 (0.71–90.20)	15.0 (0.86–260.83)

[†]Adjusted p value < 0.05. ^{††}Adjusted p value < 0.001. LGA: large-for-gestational age. NC: non-calculable.

P value adjusted for nulliparity, pre-pregnancy body mass index, previous macrosomia, ethnicity, pregnancy weight gain, GDM diagnosis and anaemia.

Table 4 – Odds ratios for associations between different first-trimester HbA1c cut-off values and obstetric outcomes among South Central Asian women.

	Macrosomia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	Preeclampsia (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)	LGA (n) (below vs. above threshold)	Crude OR (95% CI)	Adjusted OR (95% CI)
HbA1c 5.0% (31 mmol/mol)	2/89 vs. 10/265	1.71 (0.37–7.94)	1.37 (0.24–7.68)	1/87 vs. 9/264	3.04 (0.38–24.31)	–	4/89 vs. 32/263	2.94 (1.01–8.57)	3.38 (0.90–12.60)
HbA1c 5.1% (32 msol/mol)	3/118 vs. 9/236	1.52 (0.40–5.72)	1.61 (0.35–7.29)	1/116 vs. 9/235	4.58 (0.57–36.59)	–	6/118 vs. 30/234	2.75 (1.11–6.79)	2.74 (0.92–8.13)
HbA1c 5.2% (33 mmol/mol)	5/151 vs. 7/203	1.04 (0.32–3.35)	1.26 (0.29–5.36)	3/150 vs. 7/201	1.77 (0.45–6.95)	–	9/151 vs. 27/201	2.45 (1.12–5.37)	2.24 (0.83–6.0)
HbA1c 5.3% (34 mmol/mol)	7/191 vs. 5/163	0.83 (0.26–2.67)	1.03 (0.23–4.58)	4/190 vs. 6/161	1.80 (0.50–6.49)	77.54 (2.10–2858.8) [†]	14/191 vs. 22/161	2.00 (0.99–4.05)	2.19 (0.84–5.68)
HbA1c 5.4% (36 mmol/mol)	7/221 vs. 5/132	1.20 (0.37–3.87)	1.46 (0.31–6.73)	5/219 vs. 5/131	1.70 (0.48–5.98)	11.74 (1.02–134.03) [†]	16/221 vs. 20/130	2.33 (1.16–4.68)	2.78 (1.07–7.23)
HbA1c 5.5% (37 mmol/mol)	7/253 vs. 5/101	1.83 (0.57–5.91)	2.19 (0.44–10.76)	5/252 vs. 5/99	2.63 (0.74–9.28)	17.34 (1.41–212.6) [†]	18/253 vs. 18/99	2.90 (1.44–5.84)	3.99 (1.49–10.66) [†]
HbA1c 5.6% (38 mmol/mol)	7/280 vs. 5/74	2.83 (0.87–9.18)	4.60 (0.92–22.94)	5/278 vs. 5/73	4.01 (1.13–14.26)	34.01 (2.06–559.7) [†]	22/290 vs. 14/72	2.94 (1.42–6.09)	5.70 (2.06–15.79) ^{††}
HbA1c 5.7% (39 mmol/mol)	8/306 vs. 4/48	3.39 (0.98–11.72)	7.22 (1.19–43.58) [†]	7/304 vs. 3/47	2.89 (0.72–11.60)	11.9 (0.97–147.9)	27/306 vs. 9/46	2.51 (1.10–5.76)	4.73 (1.55–14.41) [†]
HbA1c 5.8% (40 mmol/mol)	8/318 vs. 4/36	4.84 (1.38–16.98)	10.15 (1.64–62.8)	7/316 vs. 3/35	4.14 (1.02–16.79)	20.49 (1.66–252.5) [†]	29/318 vs. 7/34	2.58 (1.04–6.45)	5.00 (1.58–15.80) [†]
HbA1c 5.9% (41 mmol/mol)	9/333 vs. 3/21	6.00 (1.49–24.09)	6.50 (0.94–44.7)	7/331 vs. 3/20	8.17 (1.94–34.40)	32.77 (2.56–419.6) [†]	31/333 vs. 5/19	3.48 (1.17–10.31)	4.57 (1.20–17.44) [†]
HbA1c 6.0% (42 mmol/mol)	9/340 vs. 3/14	10.03 (2.38–42.26)	14.01 (1.51–129.9) [†]	9/338 vs. 1/13	3.05 (0.36–26.02)	18.19 (0.9–366.7)	32/339 vs. 4/13	4.26 (1.24–14.63)	6.08 (1.20–30.63) [†]

[†]Adjusted p value < 0.05. ^{††}Adjusted p value < 0.001. LGA: large-for-gestational age.

P value adjusted for nulliparity, pre-pregnancy body mass index, previous macrosomia, ethnicity, pregnancy weight gain, GDM diagnosis and anaemia.

through ethnicity-specific growth curves. A large number of maternal, gestational and newborn characteristics were evaluated which permitted precise analysis of factors potentially influencing the development of adverse perinatal outcomes. Finally, we used self-report of ethnicity which is thought to be more reliable than administrative data given that responses are based on self-perception [35].

This study was not without limitations. One is the considerable number of women ($n = 344$, 15.4%) who chose to continue follow-up or end pregnancy at other centers, which could act as a potential selection bias as we were unable to gather data on pregnancy outcomes. Nonetheless, this percentage was significantly lower than that described in previous studies [10,11]. Secondly, GDM women 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 thus, it is not expected to have a relevant influence on the results. Thirdly, no data on socioeconomic parameters involving income inequality, education and discrimination, which have been reported to influence perinatal outcome regardless of ethnicity, and on paternal ethnicity was collected. Adjusted Odds Ratio included significantly wide confidence intervals, probably due to the drop of sample size, which prevents from assessing accurately the association between ethnicity and obstetric outcomes. Thus, the results should be interpreted with caution. Finally, another important limitation stems from the fact that the estimated sample size was only achieved in Caucasian and South Central Asian women whereas Moroccan and East Asian women were excluded given the small sample size of these groups. Nevertheless, the sample size in Latin-American women was close to the estimated one and we were able to find a significant association between HbA1c levels and the development of obstetric complications.

In conclusion, the present study highlights ethnic differences in the association of first-trimester HbA1c levels and adverse obstetric outcomes: it performs as an independent predictor in Latin-American and South-Central Asian women whereas in those of Caucasian origin no significant associations were found. Further studies are necessary to ascertain whether early detection and treatment of these women can improve gestational outcomes. In communities with diverse ethnic backgrounds, the use of first-trimester HbA1c as a predictor of adverse pregnancy outcomes should be individualized according to ethnic origin.

5. Contribution statement

All authors met authorship requirements, actively participated in data acquisition, drafting or revising the paper, contributed to the discussion and gave approval of 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. NG collected data, performed data analysis and drafted the manuscript. JJC collected data, performed data analysis and reviewed the manuscript. GL contributed to data analysis

and reviewed the manuscript. LG collected data and reviewed the manuscript. AP conceived and designed the study, collected data, reviewed the manuscript and contributed to discussion. JPB 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 the accuracy of the data analysis.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Declaration of interest

None.

Acknowledgments

We thank Miss Christine O'Hara, Hospital del Mar, for review of the English version of the manuscript.

REFERENCES

- [1] Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es study. *Diabetologia* 2012;55(1):88–93.
- [2] Lawrence JM, Contreras R, Chen W, Sacks DA. Trends in the prevalence of preexisting diabetes and gestational diabetes mellitus among a racially/ethnically diverse population of pregnant women, 1999–2005. *Diabetes Care* 2008;31(5):899–904.
- [3] Lapolla A, Dalfrà MG, Lencioni C, Di Cianni G. Epidemiology of diabetes in pregnancy: a review of Italian data. *Diabetes Nutr Metab.* 2004;17(6):358–67.
- [4] Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, et al. HAPO study cooperative research group. Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med.* 2008;358(19):1991–2002.
- [5] Nordin NM, Wei JW, Naing NN, Symonds EM. Comparison of maternal-fetal outcomes in gestational diabetes and lesser degrees of glucose intolerance. *J Obstet Gynaecol Res* 2006;32(1):107–14.
- [6] Jensen DM, Damm P, Sørensen B, Mølsted-Pedersen L, Westergaard JG, Klebe J, et al. Clinical impact of mild carbohydrate intolerance in pregnancy: a study of 2904 nondiabetic Danish women with risk factors for gestational diabetes mellitus. *Am J Obstet Gynecol* 2001;185(2):413–9.
- [7] Tallarigo L, Giampetrio O, Penno G, Miccoli R, Gregori G, Navalesi R. Relation of glucose tolerance to complications of pregnancy in non-diabetic women. *N Engl J Med* 1986;315:989–92.
- [8] Sermer M, Naylor CD, Farine D, Kenshole AB, Ritchie JW, Gare DJ, et al. The Toronto tri-hospital gestational diabetes project: a preliminary review. *Diabetes Care* 1998;21(Suppl. 2):B33–42.
- [9] Moses RG, Calvert D. Pregnancy outcomes in women without gestational diabetes mellitus related to the maternal glucose

- level: is there a continuum of risk? *Diabetes Care* 1995;18(12):1527–33.
- [10] Hughes RC, Moore MP, Gullam JE, Mohamed K, Rowan J. An early pregnancy A1c \geq 5.9% (41 mmol/mol) is optimal for detecting diabetes and identifies women at increased risk of adverse pregnancy outcomes. *Diabetes Care* 2014;37(11):2953–9.
- [11] Mañé L, Flores-Le Roux JA, Benaiges D, Rodríguez M, Marcelo I, Chillarón JJ, et al. Role of first-trimester A1c as a predictor of adverse obstetric outcomes in a multi-ethnic cohort. *J Clin Endocrinol Metab* 2017;102(2):390–7.
- [12] Saaddine JB, Fagot-Campagna A, Rolka D, Narayan KM, Geiss L, Eberhardt M, et al. Distribution of HbA(1c) levels for children and young adults in the U.S.: third national health and nutrition examination survey. *Diabetes Care* 2002;25(8):1326–30.
- [13] Herman WH, Ma Y, Uwaifo G, Haffner S, Kahn SE, Horton ES, et al. Diabetes prevention program research group. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. *Diabetes Care* 2007;30(10):2453–7.
- [14] Brown AF, Gregg EW, Stevens MR, Karter AJ, Weinberger M, Safford MM, et al. Race, ethnicity, socioeconomic position, and quality of care for adults with diabetes enrolled in managed care: the Translating Research Into Action for Diabetes (TRIAD) Study. *Diabetes Care* 2005;28(12):2864–70.
- [15] Herman WH. Do race and ethnicity impact hemoglobin A1c independent of glycemia? *J Diabetes Sci Technol* 2009;3(4):656–60.
- [16] Hartland AJ, Smith JM, Clark PM, Webber J, Chowdhury T, Dunne F. Establishing trimester- and ethnic group-related reference ranges for fructosamine and A1c in non-diabetic pregnant women. *Ann Clin Biochem* 1999;36(Pt.2):235–7.
- [17] Aulinas A, Biagetti B, Vinagre I, Capel I, Ubeda J, María MÁ, et al. Gestational diabetes mellitus and maternal ethnicity: high prevalence of fetal macrosomia in non-Caucasian women. *Med Clin (Barc)* 2013;141(6):240–5.
- [18] Hernandez-Rivas E, Flores-Le Roux JA, Benaiges D, Sagarra E, Chillaron JJ, Paya A, et al. Gestational diabetes in a multiethnic population of Spain: clinical characteristics and perinatal outcomes. *Diabetes Res Clin Pract* 2013;100(2):215–21.
- [19] Bowers K, Laughon SK, Kiely M, Brite J, Chen Z, Zhang C. Gestational diabetes, pre-pregnancy obesity and pregnancy weight gain in relation to excess fetal growth: variations by race/ethnicity. *Diabetologia* 2013;56(6):1263–71.
- [20] Mocarski M, Savitz DA. Ethnic differences in the association between gestational diabetes and pregnancy outcome. *Matern Child Health J* 2012;16(2):364–73.
- [21] Bryson CL, Ioannou GN, Rulyak SJ, Critchlow C. Association between gestational diabetes and pregnancy-induced hypertension. *Am J Epidemiol* 2003;158(12):1148–53.
- [22] American Diabetes Association. Standards of medical care in diabetes 2016. *Diabetes Care* 2016;39(Suppl. 1):S4–5.
- [23] Metzger BE. Summary and recommendations of the third international workshop-conference on gestational diabetes mellitus. *Diabetes* 1991;40(Suppl. 2):197–201.
- [24] Tranquilli AL, Dekker G, Magee L, Roberts J, Sibai BM, Steyn W, et al. The classification, diagnosis and management of the hypertensive disorders of pregnancy: a revised statement from the ISSHP. *Pregnancy Hypertens* 2014;4(2):97–104.
- [25] Ray JG, Sgro M, Glazier R, Bocking A, Hilliard R, Mamdani M, et al. Birthweight curves for newborns according to maternal ancestry. Available at <<http://www.stmichaelshospital.com/birthweights.php#>> [Accessed March 1, 2018].
- [26] Carrascosa A, Fernández JM, Fernández C, Ferrández Longás A, López-Siguero JP, Sánchez González E, et al. Spanish cross-sectional growth study 2008. Part II. Height, weight and body mass index values from birth to adulthood. *An Pediatr (Barc)*. 2008;68(6):552–569.
- [27] Ekeroma AJ, Craig ED, Stewart AW, Mantell CD, Mitchell EA. Ethnicity and birth outcome: New Zealand trends 1980–2001: Part 3. Pregnancy outcomes for Pacific women. *Aust N Z J Obstet Gynaecol* 2004;44(6):541–4.
- [28] Rao AK, Daniels K, El-Sayed YY, Moshesh MK, Caughey AB. Perinatal outcomes among Asian American and Pacific Islander women. *Am J Obstet Gynecol* 2006;195:834–8.
- [29] Herman W, Cohen R. Racial and ethnic differences in the relationship between A1c and blood glucose: implications for the diagnosis of diabetes. *J Clin Endocrinol Metab* 2012;97(4):1067–72.
- [30] Homko CJ, Sivan E, Nyirjesy P, Reece EA. The interrelationship between ethnicity and gestational diabetes in fetal macrosomia. *Diabetes Care* 1995;18:1442–5.
- [31] Khalil A, Rezende J, Akolekar R, Syngelaki A, Nicolaidis KH. Maternal racial origin and adverse pregnancy outcome: a cohort study. *Ultrasound Obstet Gynecol* 2013;41(3):278–85.
- [32] Esakoff TF, Caughey AB, Block-Kurbisch I, Inturrisi M, Cheng YW. Perinatal outcomes in patients with gestational diabetes mellitus by race/ethnicity. *J Matern Fetal Neonatal Med* 2011;24(3):422–6.
- [33] Gong J, Savitz DA, Stein CR, Engel SM. Maternal ethnicity and pre-eclampsia in New York City, 1995–2003. *Paediatr Perinat Epidemiol* 2012;26(1):45–52.
- [34] Wong LF, Caughey AB, Nakagawa S, Kaimal AJ, Tran SH, Cheng YW. Perinatal outcomes among different Asian-American subgroups. *Am J Obstet Gynecol* 2008;199(4):382.e1–6.
- [35] Silva JK, Kaholokula JK, Ratner R, Mau M. Ethnic differences in perinatal outcome of gestational diabetes mellitus. *Diabetes Care* 2006;29:2058–63.
- [36] Harris EL, Sherman SH, Georgopoulos A. Black-white differences in risk of developing retinopathy among individuals with type 2 diabetes. *Diabetes Care* 1999;22:779–83.
- [37] Tsugawa Y, Mukamal KJ, Davis RB, Taylor WC, Wee CC. Should the hemoglobin A1c diagnostic cutoff differ between blacks and whites? A cross-sectional study. *Ann Int Med* 2012;157:153–9.
- [38] Kehl KG, Findeisen HM, Fardo DW, Bruemmer D, Mannino DM, Sanderson WT. Race-ethnicity as an effect modifier of the association between HbA1c and mortality in U.S. adults without diagnosed diabetes. *Eur J Endocrinol* 2011;165(2):275–81.
- [39] Selvin E. Are there clinical implications of racial differences in A1c? A difference, to be a difference, must make a difference. *Diabetes Care* 2016;39:1462–7.