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High Level of Maternal Glycated Hemoglobin and Low Birth Weight

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Abstract

Background: The present study investigated the possible association between elevated maternal glycated haemoglobin levels (HbA1c%) and infants with low birth weight (LBW).

Methods: This case-control study included 1,142 women admitted to three public hospitals in the northeast region of Brazil. The participants were classified based on their glycaemic levels, using glycated haemoglobin measurement: Group 1 (HbA1c% <5.6%), Group 2 (HbA1c% ≥ 5.6% and <6.5%), Group 3 (HbA1c% ≥ 6.5% and <7.0%) and Group 4 (HbA1c% ≥ 7.0%). The main association was assessed via a logistic regression, considering Group 1 (HbA1c <5.6%) as the reference.

Results: No association between glycated haemoglobin levels and LBW for any of the groups, even after adjustment for the following confounders: maternal age, arterial hypertension, smoking during pregnancy, primiparity, body mass index before pregnancy, number of prenatal care visits, and maternal occupation during pregnancy (Group 2 - $OR_{adjusted}$: 0.83 IC95%: 0.59-1.16; Group 3-$OR_{adjusted}$: 0.27 IC95%: 0.34-1.26; Group 4-$OR_{adjusted}$: 2.39 IC95%: 0.70-8.19)

Conclusion: These results showed that elevated maternal glycated hemoglobin levels are not a risk factor for low birth weight.

Keywords: Low birth weight neonate; Epidemiology; Diabetes mellitus; Glycated haemoglobin

Introduction

Low birth weight (LBW) is a significant predictor of child morbidity and mortality [1]. Currently, 18 million infants are born every year with LBW worldwide, and one third of them die within the first year of life [1,2]. Considering the risk of sequelae among survivors, LBW might be one of the most important public health problems affecting the paediatric population throughout the world, especially in less developed countries and areas.

Associations between LBW and several factors including unfavourable socioeconomic conditions, inadequate prenatal care, pregnancy in extreme age, maternal malnutrition and obesity, maternal low height, smoking, and intrauterine infection are well established [3,4]. However, evidence is emerging that other factors might cause LBW, including blood sugar level abnormalities in pregnant women [5-7].

The association between elevated maternal glycaemia and macrosomia is well documented in the specialised literature [8-12]. However, elevated maternal glycaemia might paradoxically lead to either LBW (by restricting intrauterine growth) or macrosomia, depending on the increase in blood sugar level [5-7]. The biological plausibility supporting this hypothesis is summarised through the argument that high blood sugar levels hinder placental exchange, potentially causing foetal hypoxia and reduced development [13-15].

In addition, recent studies indicate the need for glycaemia control during pregnancy because levels lower than those defining diabetes are associated with perinatal complications. One multicentre study that addressed glycaemic control during the last trimester of pregnancy in Japanese women suggested a reference range for glycated haemoglobin of 4.5-5.7% (i.e., lower than that accepted for the overall population) [16].

Of the studies that support the hypothesised association between elevated glycaemia during pregnancy and LBW, only a few have reported significant results [5,6,13,15]. Studies using consistent

methodologies in this research area are rare; therefore, the present study investigated the possible association between elevated glycaemia during pregnancy and LBW.

Materials and Methods

This case-control study was conducted with mothers of live neonates from March 2011 to January 2012 at Dom Malan Hospital, Professor Fernando Figueira Institute of Integrated Medicine (Instituto de Medicina Integral Professor Fernando Figueira; IMIP), Petrolina, Pernambuco (PE); Inácia Pintos dos Santos Hospital, Feira de Santana, Bahia (BA); and Municipal Maternity Hospital of Juazeiro, Juazeiro, BA, Brazil.

The research ethics committees of Professor Fernando Figueira Institute of Integrated Medicine and State University of Feira de Santana approved this study (no. 2215/11 and 048/2009, respectively), in accordance with the Helsinki Declaration as revised in 2013. All of the participants signed an informed consent document.

To compose the group of cases, mothers of neonates with LBW (below 2,500 g) up to 7 days after delivery who remained at the participating hospitals at the time of recruitment were invited to participate. Following the identification of each participant with a neonate with birth weight below 2,500 g (case), a woman with a child with a birth weight of equal to or over 2,500 g (control) was selected. The control group was composed of mothers of neonates randomly selected from the birth records of the participating hospitals. The infant birth weight data were taken from the same records or the infants' medical records.

Mothers of neonates who exhibited bleeding disorders during the third trimester of pregnancy, pre-gestational diabetes, congenital malformations, multiple pregnancy, cardiovascular disease, or any other systemic disorder requiring antibiotic prophylaxis for dental procedures were excluded from this study.

The sample size was calculated using STALTCALC in Epi Info 3.5. This step was conducted through a pilot study conducted in Feira de Santana, BA, that resulted in the following parameters: odds ratio=1.8 and an exposure (HbA1c ≥ 6.0%) proportion of approximately 9% for controls. A confidence level of 95%, a power of 80% and a 1:2.5 ratio between cases and controls were used. Thus, the minimum sample size was calculated as 299 cases and 747 controls.

A duly trained healthcare professional collected the blood samples used to assess maternal glycaemia based on the glycated haemoglobin (HbA1c) level. Sample collection was performed in a standardised manner using a vacuum system; 3 ml of blood were collected in tubes containing EDTA (ethylenediaminetetraacetic acid) conditioned to 2°C. The tubes were sent to a laboratory for processing and analysis.

The HbA1c levels were measured via high-performance liquid chromatography (HPLC), the method certified by the National Programme of Glycohaemoglobin Normalisation.

Based on their serum HbA1c levels, the participants were divided in four groups: Group 1, <5.6% (reference range); Group 2, ≥ 5.6% and <6.5%; Group 3, ≥ 6.5% and <7%; and Group 4, ≥ 7% [16,17].

Statistical analysis

The data analysis was performed using STATA version 10.0. First, The main exposure variable (glycated haemoglobin level) were considered in their four strata (Group 1, Group 2, Group 3 and Group 4) and the outcome variable (LBW-dichotomous) was defined as: case (<2,500 g) and control (≥ 2,500 g). The covariables were classified as follows. Sociodemographic characteristics of the mother were collected: age (10 to 35 and ≥ 35 years old), years of education (≤ 4 and >4), race/skin color (brown/black and white/asian), family income (1 minimum wages and above one minimum wages), marital status (married/stable union and single/widowed/divorced), and paid activity (yes and no), and household density (≤ 4 and >4 persons). The reproductive, prenatal and health status characteristics were: primiparity (no and yes), history of LBW neonates (no and yes), history of preterm neonates (no and yes), smoking during pregnancy (no and yes), drinking during pregnancy (no and yes), number of prenatal care visits (<6 visits and ≥ 6 visits), urinary tract infection (yes and no), arterial hypertension (yes and no), preeclampsia (yes and no), body mass index before pregnancy (>18.5 and ≤ 18.5), prematurity (<37 weeks and ≥ 37 weeks) and high-risk pregnancy (yes and no).

The main exposure, in its diferent levels, and the covariables were subjected to a descriptive analysis with regard to cases and controls. Simple frequencies were obtained to assess the data distribution via the chi-square or Fisher's exact test depending on the number of observations at the 5% significance level.

Next, a stratified analysis was performed to select the covariates that might confound or modify the main relationship. Potentially modifying covariates were identified via the Breslow-Day homogeneity test at a 20% significance level. Potentially confounding covariates were identified by adopting a proportional difference greater than 10% between the crude and adjusted measures of each covariate.

An unconditional logistic regression was performed via backward selection to obtain odds ratios (OR) with corresponding 95% confidence intervals (95% CI). The association hypothesis test for each level of glycated hemoglobin (Groups 2, 3 and 4) and low birth weight was performed, using Group 1 as a reference level, based on two criteria: OR>1 and 95% CI , statistically significant. At this stage, a new investigation of potential modifying covariables was performed using the likelihood ratio test with an alpha of 5%. Potential confounding covariables were identified using the proportional difference greater than 10%, and the epidemiological relevance of these factors in the association under study were also considered. Finally, multiple linear regression was used to verify the effect of glycated hemoglobin on birth weight, taking the exposure, as well as outcome as continuous variables and adopting as confounder covariables, those with epidemiological importance in the topic. Linear regression (LR) coefficient, with its respective 95% confidence interval, was estimated to investigate the variation in birth weight in grams with the addition of each unit (1%) of HbA1c.

Results

The final sample included 1,142 participants, 329 in the LBW case group (mothers of live neonates with weights <2,500 g) and 813 in the control group (mothers of neonates with weights ≥ 2,500 g). In the case group the mean of the glycated hemoglobin was 5.33% (± 0.5), whereas in the control group this measure was 5.30% (± 0.5). The average age of the case group was 22.1 years old (± 7.8), ranging from 10 to 44 years old. The average age of the control group was 23.6 years old (± 7), ranging from 10 to 46 years old.

The overall participant characteristics per group (cases and controls) are described in (Table 1). The groups were relatively homogeneous relative to most characteristics, with the exception of age (p<0.001).

The group of cases had a higher frequency of women younger than 35 years old compared with the control group (Table 1).

Characteristics	CASES* (329)	CONTROLS** (813)	P***
	n (%)	n (%)	
Maternal age			
10-35 years old	299 (90.9)	748 (92.0)	
>35 years old	30 (9.1)	65 (8.0)	<0.01
Maternal educational level			
>4 years of formal schooling	40 (12.2)	117 (14.4)	0.32
≤ 4 years of formal schooling	289 (87.8)	696 (85.6)	
Family income			
≥ 1 or more times the equivalent of the minimum wage	206 (62.6)	540 (66.4)	
<1 time the equivalent of the minimum wage	123 (37.4)	273 (33.6)	0.22
Maternal occupation during pregnancy			
Paid job	164 (49.8)	393 (48.3)	
Homemaker/student/unemployed	165 (50.2)	420 (51.7)	0.64
Marital status			
Married/stable union	173 (52.6)	470 (57.8)	
Single/widowed/divorced	156 (47.4)	343 (42.2)	0.1
Maternal race/skin colour			
Brown/Black	286 (86.9)	689 (84.7)	
White/Asian	43 (13.1)	124 (15.3)	0.34
Household density			
≤ 4 individuals	198 (60.2)	484 (59.5)	
>4 individuals	131 (39.8)	329 (40.5)	0.83
*Mothers of live neonates with weights <2,500 g			
**Mothers of live neonates with weights ≥ 2,500 g			
***P = p-value, significance level ≤ 0.05			

Table 1: Maternal sociodemographic characteristics corresponding to cases and controls, Pernambuco/Bahia, Brazil (n=1,142).

Relative to reproductive history, lifestyle, prenatal care, and state of health (Table 2), some covariates exhibited significant between-group differences. The case group exhibited a higher frequency of women with a body mass index ≤ 18.5 (28.9% vs. 15.50%; p<0.001), prematurity (27.7% vs. 21.8%; p<0.03), and high-risk pregnancy (28% vs. 22.5%; p<0.05) compared with the control group. In turn, the control group exhibited a higher frequency of primiparous women compared with the case group (57.3% vs. 42.9%; p<0.001).

In the crude association analysis, a significant association was not found between elevated glycated haemoglobin and LBW considering the groups defined in accordance with HbA1c cut-off points, i.e., Group 1 (<5.6%), Group 2 (≥ 5.6% and <6.5%), Group 3 (≥ 6.5% and <7.0%) and Group 4 (≥ 7.0%) (Table 3). Group 1 (HbA1c <5.6%) was considered as the reference. Neither confounding nor modifying covariables were detected in the stratified analysis.

A logistic regression analysis confirmed the absence of a confound or modification between the analysed covariables. Based on the available and relevant literature, the following covariables were retained in the final model: maternal age, arterial hypertension, smoking during pregnancy, primiparity, body mass index before pregnancy, number of prenatal care visits, and maternal occupation during pregnancy. Adjusting for these covariables, almost no change was produced compared with the crude data analysis (i.e., they were not significant (Table 3).

Characteristics	CASES* (329)	CONTROLS** (813)	P***
	n (%)	n (%)	
Primiparity			
No	188 (57.2)	347 (42.7)	<0.01
Yes	141 (42.8)	466 (57.3)	
History of LBW neonates			
Yes	27 (8.2)	69 (8.5)	0.87
No	302 (91.8)	744 (91.5)	
History of preterm neonates			
Yes	16 (4.9)	58 (7.2)	0.15
No	313 (95.1)	755 (92.9)	
Smoking during pregnancy			
Yes	23 (7)	53 (6.5)	0.77
No	306 (93.0)	760 (93.5)	
Drinking during pregnancy			
Yes	33 (10.1)	104 (12.8)	0.19
No	296 (89.9)	709 (87.2)	
Number of prenatal care visits			
<6 visits	192 (58.4)	520 (64.0)	0.07
≥ 6 visits	137 (41.6)	293 (36.0)	
Urinary tract infection			
Yes	127 (38.6)	346 (42.6)	0.21
No	202 (61.4)	467 (57.4)	
Arterial hypertension			
Yes	57 (17.3)	120 (14.8)	0.27
No	272 (82.7)	693 (85.2)	
Preeclampsia			
Yes	11 (3.3)	29 (3.6)	0.85
No	318 (96.7)	784 (96.4)	
Body mass index before pregnancy			
>18.5	234 (71.1)	687 (84.5)	<0.01
≤ 18.5	95 (28.9)	126 (15.5)	
Prematurity			
<37 weeks	91 (27.7)	177 (21.8)	0.03
≥ 37 weeks	238 (72.3)	636 (78.2)	
High-risk pregnancy			

Yes	92 (28.0)	183 (22.5)	0.05
No	327 (72.0)	630 (77.5)	
*Mothers of live neonates with weights <2,500 g			
**Mothers of live neonates with weights ≥ 2,500 g			
***P=p-value, significance level ≤ 0.05			

Table 2: Maternal reproductive, lifestyle, and gestational health characteristics corresponding to cases and controls, Pernambuco/Bahia, Brazil (n=1,142).

Levels				
HbA1c%	**ORcrude (95% CI)**	**P***	**ORadjusted** (95% CI)**	**P***
Group 2#				
(≥ 5.6 and <6.5)	0.90 (0.65-1.25)	0.52	0.83 (0.59-1.16)	0.29
Group 3&				
(≥ 6.5 and <7.0)	0.25(0.31-1.23)	0.18	0.27(0.34-1.26)	0.21
Group 4				
(≥ 7.0)	2.07(0.63-6.84)	0.23	2.39(0.70-8.19)	0.16
*P=p-value, significance level ≤ 0.05				
**Adjusted for maternal age, arterial hypertension, smoking during pregnancy, primiparity, body mass index before pregnancy, number of prenatal care visits, delivery type, and maternal occupation during pregnancy				
#Women with HbA1c ≥ 6.5% were excluded				
&Women with HbA1c ≥ 7.0% were excluded				

Table 3: Odds ratios (OR) and 95% CI, crude and adjusted, associated with high glycated haemoglobin (HbA1c%) levels and LBW, Pernambuco/Bahia, Brazil (n=1,142).

After adjusting for confounders, women of Group 2 (ORadjusted: 0.83 95% CI: 0.59-1.16) and Group 3 (ORadjusted: 0.27 95% CI: 0.34-1.26) showed a negative association between high glycemic level and low birth weight. Finally, for Group 4, the chance of the outcome considered was 2.39 times greater than in the comparison group-Group 1 (ORadjusted: 2.39 IC95%: 0.70-8.19). Although there was no significant association for either group.

When using only a cutoff point for the glycated hemoglobin level (HbA1c ≥ 6.5%), there was no association between exposure and outcome under study (OR: 1.03 95% CI: 0.36-2.95) (Table 4).

Model	**LR Coefficient**	**95% CI**
Crude	132.84	(39.75-225.93)
Adjusted*	177.63	(77.85-277.41)
*P=p value: significance level ≤ 0.05		
**Adjusted by maternal age, arterial hypertension, smoking during pregnancy, primiparity, body mass index before pregnancy, number of prenatal care visits, and maternal occupation during pregnancy.		

Table 4: Association between maternal HbA1c level and birth weight, using linear regression (n = 1142). Juazeiro-BA and Petrolina-PE, Brazil, 2012.

Linear regression analysis showed that for every 1% added of HbA1c, there was an increase, on average, of 132.84 g (95% CI: 39.75-225.93) in the birth weight of the newborn. When adjustment for the confounders considered was performed, it was estimated that for each 1% of HbA1c that was elevated there was an average increase of 177.63 g (95% CI: 77.85-277.41) in birth weight.

Discussion

According to the findings of the present study, from the logistic regression, no association was found between high maternal glycated haemoglobin levels and LBW. The results did not show an association between the various levels of elevated maternal glycated haemoglobin and LBW even after adjusting for confounds such as maternal age, smoking during pregnancy, body mass index before pregnancy, arterial hypertension, number of prenatal care visits, and maternal occupation during pregnancy. However, for postpartum women with a higher level of glycated hemoglobin (Group IV), there was an increase in the epidemiological measurement that should be disregarded, in principle, since the number of women was lower when compared to the other groups. Thus, the confidence interval presented was wider, reflecting imprecision of this finding.

These findings of no association corroborate the results from other studies, including classic studies that found that elevated glycaemia during pregnancy is associated with higher birth weight, rather than the risk of LBW9-12. However, the results of the present study differ from others that suggested that both macrosomia and intrauterine growth restriction occur as a function of glycaemia variation, with the latter condition potentially leading to LBW [5-7,13,14,18,19].

When the main variables were considered as continuous, linear regression analysis was used to evaluate the association between HbA1C values and birth weight, this study showed a rise in birth weight, directly proportional to the increase in glycemic level. These data corroborate the results of the study entitled Hyperglycemia and Adverse Results in Pregnancy [8], in which the authors also evidenced this progressive increase in birth weight, in addition to other effects, such as: fetal hypoglycemia, increased C-peptide and shoulder dystocias [8]. All of these findings were directly proportional to the maternal glucose level.

The lack of an association between elevated glycaemia and LBW might be because the intrauterine environment and an excessive supply of glucose, which serves as the main energy source for foetal growth, increases birth weight. This phenomenon might lead to the exaggerated development of the foetus, causing macrosomia and undesirable events in extrauterine life such as hypoglycaemia, hypocalcaemia, cardiomyopathy, shoulder dystocia with consequent brachial plexus injury, and hypoxia [20].

All of the results described here should be considered with caution because of the methodological strategies adopted. For instance, the choice of HbA1c as marker of glycaemia and its cut-off points are disputed in the literature [16,17]. Although the measurement of HbA1c has certain advantages over conventional methods (e.g., eliminating the need for fasting before sample collection and reflecting an average blood sugar level of 8 to 10 weeks) [21,22], its application with regard to pregnancy remains somewhat criticised.

Ferritin and folic acid as well as vitamins B6 and B12 might influence HbA1c [16]. In addition, the measurement of HbA1c might be modified by bleeding during delivery, which might not be reported or not duly registered in the medical records of healthcare facilities.

However, relevant and recent multicentre studies addressing the control and prevention of gestational diabetes did measure HbA1c levels [8,16,22] because HbA1c reflects retrospective alterations of glycaemic control. Given the lack of data on the previous state, HbA1c can be used to represent the previous and recent glycaemic profiles of individuals [22].

A recent study of glycaemia during pregnancy conducted in Japan suggested a reference range for HbA1c during pregnancy of 4.5-5.7% [16]. The authors also recommended the changes that are occurring more broadly in this field such as universal screening for diabetes during pregnancy and the use of lower reference blood glucose values for disease diagnosis. This trend developed primarily based on the results of the Hyperglycemia and Adverse Pregnancy Outcome study8, resulting in the International Association of the Diabetes and Pregnancy Studies Group (IADPSG) considering a glycaemia level ≥ 92 mg/dl as gestational diabetes [23].

The present retrospective study was unable to classify participants' glycaemic profiles as pre-gestational or gestational diabetes, even though one of the exclusion criteria was self-reported diabetes before pregnancy because the investigators did not have access to the blood glucose levels at the onset of pregnancy. Some of the participants might have been unaware that they had pre-gestational hyperglycaemia. This uncertainty becomes even more significant when one considers that, according to IADPSG recommendations, HbA1c levels over 6.5% should be viewed as pre-gestational diabetes [23].

Another limitation of the present study might derive from the lack of monitoring of the participants' weight gain during pregnancy. The pattern of weight gain during this stage of life directly influences foetal development. Insufficient weight gain might be associated with a predisposition towards intrauterine weight restriction, whereas excess weight is related to occurrence of macrosomia [24]. Finally, another methodological difficulty of this investigation refers to the non-representativeness of the sample for the universe of pregnant women in the municipalities investigated, since the study was hospital based with a convenience sample. This sample aspect implies in the reduction of the external validity of the research, since its results cannot be generalized to other localities, without due care. These characteristics could have biased the measurements as a result of the presence of unmeasured confounders.

No association was found between elevated maternal glycated haemoglobin and LBW. Although the findings do not reveal maternal hyperglycemia as a risk factor for low birth weight, signaling that the effect of the exposure studied is macrosomia, contributes to the consolidation of the previous hypothesis and contrary to that one verified in this study [25].

Conclusion

Thus, this work confirms the need for greater glycemic monitoring [26], from the beginning of gestation, for a woman whose fetus has been suspected of macrosomic growth, in order to reduce the innumerable complications associated with this fetal event, which do not increase risks only for newborns , but also maternal complications.

Conflict of Interest

The authors declare no conflict of interest in preparing this article.

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