Profile of Pregnant Women with Gestational Diabetes Mellitus at Increased Risk for Large for Gestational Age Newborns

Perfil de gestantes com Diabetes Mellitus Gestacional com maior risco para recém-nascidos grandes para a idade gestacional

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Abstract

Objective Gestational diabetes mellitus (GDM) is associated with a higher risk of perinatal morbidity and mortality, and its main complication is the occurrence of large for gestational age (LGA) newborns. The present study aims to characterize pregnant women with GDM and to identify factors associated with the occurrence of LGA newborns in this population.

Methods A cross-sectional study was performed based on medical records of women whose prenatal care and delivery were performed at the Maternal and Child Unit of the Hospital Universitário of the Universidade Federal do Maranhão, state of Maranhão, Brazil. A total of 116 pregnant women diagnosed with GDM were included according to the criteria of the International Association of Diabetes and Pregnancy Study Groups (IADPSG).

Results The variables associated with LGA newborns after multivariate analysis were: obesity prior to pregnancy (OR = 11.6; 95% CI: 1.40–95.9), previous macrosomia (OR = 34.7; 95% CI: 4.08–295.3), high blood glucose levels in the 3rd trimester (OR = 2.67; 95% CI: 1.01–7.12) and combined change in the oral glucose tolerance test (OGTT) (fasting + postdextrose) (OR = 3.53; 95% CI: 1.25–14.2) = 1.17–10.6). Otherwise, insufficient weight gain during pregnancy reduced the risk for LGA newborns (OR = 0.04; 95% CI: 0.01–0.32).

Conclusion Obesity prior to pregnancy, previous macrosomia, high blood glucose levels in the 3rd trimester, and combined change in the OGTT were independent predictive factors for LGA newborns in pregnant women with GDM.

Resumo

Objetivo Diabetes mellitus gestacional (DMG) está associado a um maior risco de morbidade e mortalidade perinatais, e sua principal complicação é a ocorrência de...
Introduction

Gestational diabetes mellitus (GDM) is classically defined as glucose intolerance resulting in hyperglycemia of variable intensity, with onset or first recognition during pregnancy, which may or may not persist after childbirth.1

Gestational diabetes mellitus is usually diagnosed through provocative tests using glucose loads. In 2010, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) suggested a new diagnostic criteria based on the 75 g oral glucose tolerance test (75-g OGTT) – performed between 24 and 28 weeks of gestation, with plasma glucose measured at baseline (fasting), after 1 hour, and after 2 hours, wherein one altered measurement (fasting plasma glucose ≥ 92 mg/dL; 1 hour ≥ 180 mg/dL; 2 hour ≥ 153 mg/dL) is sufficient for the diagnosis of GDM.2 The American Diabetes Association (ADA) endorsed this diagnostic criteria in 2011, and 2 years later, the World Health Organization (WHO) revised and updated this criteria and introduced the recommendations of the IADPSG.3,4 Currently, the Brazilian Society of Diabetes and the Brazilian Federation of Gynecology and Obstetrics Associations, similar to the ADA and the WHO, use the same criteria for the diagnosis of GDM.5

The prevalence of GDM is quite variable, depending on the population under study and on the diagnostic criteria. According to the IADPSG criteria, the prevalence of GDM significantly increased by up to between 15 and 20%.2 In addition to being related to changes in the diagnostic criteria, this increase is also related to the increasing prevalence of obesity (body mass index [BMI] ≥ 30 kg/m²), which itself is a risk factor for the onset of GDM.6 The risk of developing GDM is estimated to be 2, 4, and 8 times greater in overweight, obese, and morbidly obese women, respectively, than in women of healthy weight.7 Thus, the higher the degree of maternal obesity, the greater the risk of developing GDM, primarily because of insulin resistance.7,8

Gestational diabetes mellitus is associated with a high risk of perinatal morbidity and mortality, and the main complication is macrosomia or large for gestational age (LGA) fetuses.9 Macrosomia is defined as birth weight > 4,000 g; however, this definition fails to consider gestational age (GA). Large for gestational age corresponds to birth weight ≥ 90th percentile for the corresponding GA.10 Fetal macrosomia is clinically relevant because it poses risks both for the mother as well as for the fetus. Maternal complications are often related to fetal-pelvic disproportion, prolonged labor, soft-tissue lacerations, high rates of cesarean section, postpartum hemorrhage, and placental rete-entions arising from uterine atony.9 It is also associated with perinatal morbidity and mortality: the fetal injuries most commonly associated with macrosomia and shoulder dystocia are fracture of the clavicle and damage to the nerves of the brachial plexus, which can produce Erb paralysis.11

The literature features substantial variations in factors that increase the probability of macrosomia with respect to the extent of the association between risk factors and excessive birth weight, with the true role of the several factors involved in the genesis of this complication remaining undefined. Fetal macrosomia is related to advanced maternal age, maternal diabetes and glucose intolerance, post-term pregnancy, excessive weight and obesity prior to pregnancy, male fetus, multiparity, excessive weight gain (EWG) during pregnancy, parental height, and an obstetric history of macrosomia.12,13

The most common and well-described pathogenic mechanism of accelerated fetal growth is related to maternal diabetes mellitus. In maternal hyperglycemia, excess glucose crosses the placenta and reaches the fetal circulation, thereby stimulating fetal insulin secretion. Hyperinsulinemia and excess glucose in utero favors insulin-sensitive tissue hypertrophy, promoting accelerated growth that may lead to macrosomia.14
To characterize the profile of pregnant women with GDM who are at a higher risk of presenting complications caused by excessive fetal growth, the present study seeks to identify risk factors associated with LGA newborns in this population.

Methods

A cross-sectional study was conducted at the Maternal and Child Unit of the Hospital Universitário of the Universidade Federal do Maranhão, state of Maranhão, Brazil, using information from medical records. The research protocol was approved in advance by the local Research Ethics Committee (opinion number: 1451033).

The present study included pregnant women with GDM diagnosed by OGTT using the IADPSG criteria, whose monitoring and delivery had taken place at the HUMI between January 2015 and December 2017. The exclusion criteria were: pregnant women with plasma glucose \( \geq 126 \text{ mg/dl} \) during the 1st trimester; previous diagnosis of chronic hypertension and collagen diseases; human immunodeficiency virus, hepatitis B or hepatitis C infection; newborns hospitalized in a neonatal intensive care unit (ICU); fetal malformation; and twin pregnancies. The data were collected from maternal and neonatal electronic medical records.

The variables studied were the following: maternal age in whole years, categorized as \(<35\) years old or \(\geq35\) years old; maternal height in centimeters; prepregnancy BMI estimated using the Quetelet index and classified according to the Food and Agriculture Organization (FAO)/WHO criteria; gestational weight gain (WG) estimated by the difference between maternal weight at delivery and the usual weight prior to the pregnancy reported at the 1st prenatal visit.\(^{15,16}\) Weight gain was classified according to the Institute of Medicine (IOM) criteria as insufficient (IWG), appropriate (AWG) and EWG.\(^{17}\) The investigation also included the following: a family history of diabetes among first-degree relatives; obstetric history, including parity, previous pregnancy with macrosomia, and a previous history of GDM; OGTT values upon diagnosis; and blood sugar levels throughout the 3rd trimester, using the arithmetic mean of capillary blood glucose levels while fasting and 2 hours after breakfast, routinely measured at every visit.

The studied characteristics of the newborns were the following: birthweight, gender, type of delivery, and GA. Birthweight was corrected for GA based on the recent recommendations suggested by the Intergrowth study, and it was used to analyze the calculated percentile values with the aid of this tool.\(^{18}\) Based on calculated percentile values, the newborns were classified as small for gestational age (SGA, weight \(<10^{th}\) percentile), appropriate for gestational age (AGA, 10\(^{th}\) percentile \(<\) weight \(<90^{th}\) percentile), or LGA (weight \(>90^{th}\) percentile).\(^{19}\) Macrosomia was defined as birth weight \(\geq4,000\) g, regardless of the GA.\(^{10}\)

Data were processed using the software PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA). Initially, a descriptive statistical analysis was performed by estimating frequency, mean, and standard deviation (SD). The normality of quantitative variables was tested using the Lilliefors test. Subsequently, analysis of variance (ANOVA) with the post-hoc Tukey test was used for the comparative analysis of numerical variables. The distribution of categorical variables was analyzed by using the chi-squared test or the Fisher exact test. Odds ratio (OR) and 95% confidence intervals (CIs) were used to assess the association with the LGA outcome. A multivariate logistic regression model was built to estimate the ORs adjusted for variables presenting a \(p\)-value \(<0.10\) in the bivariate analysis. Variables related to glycemia parameters were not adjusted to avoid multicollinearity. In addition, receiver operating characteristic (ROC) curves were analyzed to estimate the area under the curve (AUC), and a 95% CI was established to predict LGA newborns using OGTT levels (at 0, 60, and 120 minutes). The significance level adopted for all of the analyses was of 5%.

Results

In total, 116 pregnant women with GDM were included in the present study. The mean age was 32.7 \(\pm\) 6.4 (range: 18–44) years old; 41.1% of the women had a family history of diabetes among their first-degree relatives, and 25% were multiparous. The mean GA at delivery was 38.1 \(\pm\) 1.5 weeks, with a cesarean section rate of 75%. The overall occurrence of LGA newborns was of 25.9%.

With regard to prepregnancy BMI, 28% (32/116), 31% (35/116), and 43% (49/116) of the women had normal weight, were overweight, and were obese, respectively. Considering the IOM recommendations for WG during pregnancy, \(\sim\) 35% of the pregnant women had EWG, with a similar percentage being observed for WG in each prepregnancy BMI category (\(\sim\) Table 1). Large for gestational age newborns were more frequent in overweight and obese women. Macrosomia was only more frequent in the group of mothers who were obese before pregnancy (\(\sim\) Table 2). Only four women had SGA newborns and, of these, only one had insufficient WG during pregnancy.

The mean GA when OGTT was conducted was 25 weeks. At the time of the test, \(\sim\) 13% of the diagnoses were because of changes only in fasting plasma glucose, and 50.9% were because of changes in both fasting and post-dextrose load. The mean fasting plasma glucose level at the time of the test was higher in the group of pregnant women who were overweight and obese prior to the pregnancy (\(\sim\) Table 1).

With regard to treatment, \(\sim\) 43% of the pregnant women received only insulin as a medical therapy during pregnancy. Blood glucose levels were monitored during the 3rd trimester, and the mean fasting blood glucose level was higher in the group of women who were obese prior to the pregnancy (\(\sim\) Table 1).

The percentage of LGA newborns was statistically higher among women with overweight, with obesity, with a previous history of macrosomia, with high mean fasting blood glucose in the 3rd trimester, with changes in 3 OGTT measurements, and with a combined change in the OGTT (fasting + after dextrose load). In women with IWG during pregnancy, the percentage of LGA newborns was statistically lower. After the multivariate analysis, the following factors were associated with LGA newborns: obesity (OR = 11.6; 95% CI: 1.40–95.9), previous macrosomia (OR = 34.7; 95% CI: 4.08–295.3), high...
Table 1 Description of maternal and obstetric data according to pre-gestational body mass index

| Variables                  | Total n = 116 | Pre-gestational BMI | p-value |
|----------------------------|---------------|---------------------|---------|
|                            |               | Normal n = 32       | Overweight n = 35 | Obesity n = 49 |
| Age (years old)            | 32.7 ± 6.4    | 30.9 ± 7.1          | 33.6 ± 5.4      | 33.2 ± 6.3     | 0.158 |
| Height (cm)                | 156 ± 6       | 156 ± 7             | 155 ± 5        | 157 ± 5        | 0.178 |
| Multiparous (%)            | 25.0%         | 12.5%               | 20.0%          | 36.7%          | 0.101 |
| Weight gain (kg)           | 9.5 ± 6.9     | 12.9 ± 5.3          | 9.5 ± 6.4      | 7.3 ± 7.4**    | 0.001* |
| Categories of weight gain (%) |            |                     |                |                |       |
| Insufficient               | 33.6%         | 40.6%               | 37.1%          | 26.5%          | 0.731 |
| Appropriate                | 31.0%         | 28.1%               | 28.6%          | 34.7%          |       |
| Excessive                  | 35.4%         | 31.3%               | 34.3%          | 38.8%          |       |
| OGGT values (mg/dl)        |               |                     |                |                |       |
| Fasting                    | 95.6 ± 14.6   | 89.6 ± 12.0         | 98.2 ± 16.9**  | 97.6 ± 13.3**  | 0.021* |
| 60 minutes                 | 187.8 ± 34.5  | 184.7 ± 31.0        | 198.1 ± 42.2   | 183.0 ± 30.1   | 0.202 |
| 120 minutes                | 172.1 ± 35.1  | 160.4 ± 31.3        | 185.8 ± 36.4** | 169.7 ± 33.7   | 0.009* |
| Number of points changed in OGGT (%) |       |                     |                |                | 0.255 |
| 1 point                    | 37.1%         | 53.1%               | 28.6%          | 32.6%          |       |
| 2 points                   | 37.9%         | 31.3%               | 42.8%          | 38.8%          |       |
| 3 points                   | 25.0%         | 15.6%               | 28.6%          | 28.6%          |       |
| Categories changed in OGGT |               |                     |                |                | 0.084 |
| Only fasting               | 12.9%         | 18.7%               | 5.7%           | 14.3%          |       |
| Only after dextrose load   | 36.2%         | 50.0%               | 34.3%          | 28.6%          |       |
| Fasting and after dextrose load | 50.9%   | 31.3%               | 60.0%          | 57.1%          |       |
| Insulin therapy (%)        | 43.1%         | 28.1%               | 54.3%          | 44.9%          | 0.091 |
| Mean fasting blood glucose during 3rd trimester (mg/dl) | 90.8 ± 15.3 | 85.1 ± 12.0 | 91.8 ± 17.1 | 93.8 ± 15.2** | 0.048* |
| Delivery (%)               |               |                     |                |                | 0.991 |
| Normal                     | 25.0%         | 25.0%               | 25.7%          | 24.5%          |       |
| Cesarean                   | 75.0%         | 75.0%               | 74.3%          | 75.5%          |       |

Abbreviations: BMI, body mass index; OGGT, oral glucose tolerance test.
* Statistically significant differences among BMI categories (p < 0.05).
** Statistically significant difference compared with the normal BMI group (p < 0.05).

Table 2 Description of newborn data according to pregestational maternal body mass index

| Variables            | Total n = 116 | Pregestational BMI | p-value |
|----------------------|---------------|--------------------|---------|
|                      |               | Normal n = 32      | Overweight n = 35 | Obesity n = 49 |
| Gender (%)           |               |                    |                |                | 0.538 |
| Male                 | 47.4%         | 53.1%              | 40.0%          | 49.0%          |       |
| Female               | 52.6%         | 46.9%              | 60.0%          | 51.0%          |       |
| Post-term pregnancy (%) | 12.9%        | 15.6%              | 8.5%           | 14.3%          | 0.645 |
| GA at birth (weeks)  | 38.1 ± 1.5    | 38.3 ± 1.3         | 37.5 ± 1.9     | 38.2 ± 1.1     | 0.072 |
| Weight at birth (g)  | 3342 ± 534    | 3092 ± 348         | 3319 ± 592     | 3523 ± 530**   | 0.001* |
| Macrosomia (%)       | 11.2%         | 0%                 | 14.3%          | 16.3%**        | 0.037* |
| LGA (%)              | 25.9%         | 3.1%               | 28.6%**        | 38.8%**        | 0.001* |

Abbreviations: BMI, body mass index; GA, gestational age; LGA, large for gestational age.
* Statistically significant differences among BMI categories (p < 0.05).
** Statistically significant differences compared with the normal BMI group (p < 0.05).
mean fasting blood glucose in the 3rd trimester (OR = 4.23; 95% CI: 1.25–14.2), and combined change in the OGTT (fasting + after the dextrose load) (OR = 3.53; 95% CI: 1.17–10.6).

Insufficient WG reduced the risk for LGA newborns even after adjustment (OR = 0.04; 95% CI: 0.01–0.32) (Table 3).

The prediction of the occurrence of LGA newborns was estimated using plasma glucose values from the OGTT at 0, 60, and 120 minutes (Fig. 1). The data show an area under the curve (AUC) of 0.647 (0.552–0.735) at 0 minutes, of 0.525 (0.413–0.634) at 60 minutes, and of 0.661 (0.567–0.747) at 120 minutes, thus demonstrating that at 0 and 120 minutes were the times that best predicted the occurrence of LGA newborns (p < 0.05).

Discussion

In the present study, the incidence of LGA newborns was of 25.9%; in the literature, this incidence varies from 15 to 45%.

Several studies have shown the influence of prepregnancy BMI, as well as of weight gain during pregnancy, on fetal weight. Obesity is currently one of the major public health problems. Table 3 presents the crude and adjusted odds ratios of developing large for gestational age offspring.

**Table 3 Crude and adjusted odds ratios of developing large for gestational age offspring**

| Variables                                    | LGA (Percentile >90) |
|----------------------------------------------|----------------------|
| %                                            | Crude OR (95% CI)    | p-value | Adjusted OR (95% CI) | p-value |
| Previous macrosomia                          |                      |         |                      |         |
| No                                           | 17.5                 | Ref.    | Ref.                 | Ref.    |
| Yes                                          | 92.3                 | 56.7 (6.92–463.8) | < 0.001* | 34.7 (4.08–295.3) | 0.001*  |
| Pregestational BMI                           |                      |         |                      |         |
| Normal                                       | 3.1                  | Ref.    | Ref.                 | Ref.    |
| Overweight                                   | 28.6                 | 12.4 (1.48–103.5) | 0.006*  | 6.53 (0.62–68.5)  | 0.117   |
| Obesity                                      | 38.8                 | 19.6 (2.41–155.9) | < 0.001* | 11.6 (1.40–95.9)  | 0.023*  |
| Categories of weight gain                    |                      |         |                      |         |
| Insufficient                                 | 7.7                  | 0.11 (0.03–0.45)  | < 0.001* | 0.04 (0.01–0.32)  | 0.001*  |
| Appropriate                                  | 41.7                 | Ref.    | Ref.                 | Ref.    |
| Excessive                                    | 29.3                 | 0.57 (0.22–1.48)  | 0.368    | 0.39 (0.11–1.37)  | 0.142   |
| Number of points changed in OGTT (%)         |                      |         |                      |         |
| 1 point                                      | 16.3                 | Ref.    | Ref.                 | Ref.    |
| 2 points                                     | 27.3                 | 1.92 (0.67–5.49)  | 0.327    | 1.05 (0.29–3.75)  | 0.932   |
| 3 points                                     | 37.9                 | 3.14 (1.04–9.47)  | 0.037*   | 1.86 (0.38–9.03)  | 0.440   |
| Categories changed in OGTT                  |                      |         |                      |         |
| Only fasting                                 | 13.3                 | 0.92 (0.16–5.16)  | 1.000    | 1.11 (0.16–7.38)  | 0.912   |
| Only after dextrose load                     | 14.3                 | Ref.    | Ref.                 | Ref.    |
| Fasting and after dextrose load              | 37.3                 | 3.56 (1.29–9.82)  | 0.020*   | 3.53 (1.17–10.60) | 0.024*  |
| Mean fasting blood glucose during 3rd trimester (mg/dl) |    |                      |         |                      |         |
| > 95 mg/dL                                   | 41.7                 | 3.07 (1.25–7.53)  | 0.022*   | 2.67 (1.01–7.12)  | 0.048*  |
| < 95 mg/dL                                   | 18.8                 | Ref.    | Ref.                 | Ref.    |

Abbreviations: BMI, body mass index; CI, confidence interval; LGA, large for gestational age; OGTT, oral glucose tolerance test; OR, odds ratio. * Statistically significant differences in the prevalence of LGA (p < 0.05). Adjustment of the OR for pregestational BMI variables, previous macrosomia, weight gain categories, fasting blood glucose during the 3rd trimester, number of altered points and categories of OGTT.
health problems, and its prevalence has been increasing among women of reproductive age. Obesity during preg-
nancy is associated with an increased risk of gestational hyper-
tension, preeclampsia, fetal macrosomia, and with the need
for cesarean section, in addition to the risk of developing
gDM. Among Brazilian pregnant women, a BMI > 25 kg/m² was related to an increased risk of fetal macrosomia and
gDM.

Excessive birthweight is more frequent among obese
mothers, regardless of the association with diabetes. Mat-
ternal obesity is associated with reduced sensitivity to insu-
lin and consequent hyperinsulinemia, which, incremented
by high levels of triglycerides, favor excessive fetal growth,
regardless of plasma glucose levels. Some authors state that
maternal obesity is the leading factor for the occurrence of
LGA newborns. Black et al reported a 21.6% frequency of
LGA newborns among overweight or obese pregnant women
without GDM, a percentage that rose to 23.3% when the
factors obesity and GDM were combined, whereas the fre-
cuency of LGA newborns among women with normal weight
and GDM was only 2.9%.

It is estimated that between 65 and 75% of the women with
GDM are also overweight or obese. In our sample, 72.4% of
the women with GDM were overweight or obese before the
pregnancy, and the percentage of LGA newborns was higher
among these women, with obesity being an independent risk
factor for LGA newborns after the adjusted analysis.

The risk for LGA newborns also appears to increase when
WG is considered regardless of prior BMI. Miao et al found
a higher incidence of macrosomia among pregnant women
with EWG, as did Alberico et al, who observed that EWG
during pregnancy was significantly associated with macros-
omia, with a 2.6-fold higher risk in comparison with the
recommended WG. Mastella et al found that EWG
during pregnancy was an independent risk factor for LGA
newborns, and that WG during the 3rd trimester was also
associated with LGA newborns. In the present study, EWG was
not a risk factor for the birth of LGA newborns. The limited
sample and possible errors in the self-reported prepregnancy
weight may have altered the amount of gained weight.

Although the IOM guidelines for gestational WG are not
specific for pregnant women with GDM, they are often applied
to them. It is unknown whether the IOM recommendations are
appropriate for pregnant women at increased risk of adverse
outcomes, or if adjusting these guidelines for women with
GDM could improve perinatal outcomes. It can be assumed
that women with GDM require more stringent WG recom-
mendations because of the association of EWG and hypergly-
cemia and their potentially additive effects that lead to adverse
outcomes, such as LGA newborns.

Miao et al found that IWG decreased the risk for LGA
newborns. This study also showed that WG below that rec-
ommended by the IOM was a protective factor for the outcome
of LGA newborns, but it is necessary to consider the small
sample and the limited statistical power of this analysis.

Additionally, Mastella et al found that both AWG and
IWG decreased the risk for LGA newborns in pregnant
women with GDM. On the other hand, Vesco et al noted
that WG below recommendations decreases LGA newborns,
but increases the risk of SGA newborns. Furthermore, Wong
et al showed that EWG was a predictive factor for LGA
newborns; however, they noted that changing the IOM
criteria to more stringent WG recommendations would not
improve perinatal outcomes, including the percentage of
macrosomic and LGA newborns.

With the increase of maternal obesity, development of
lifestyle interventions may have the potential to improve
adverse reproductive outcomes. Wolff et al showed that a
simple goal-setting and support program, directed toward a
dietary-induced limitation of WG in obese pregnancy,
achieved very positive results, including a significant reduc-
tion in the fasting serum insulin concentration. In addition,
preconceptional counseling of the overweight and obese
woman, as well as lifestyle changes, may have the potential
to improve adverse reproductive outcomes. However, a
meta-analysis that evaluated different dietary interventions
in women with GDM did not observe reduction of LGA
newborns among the groups studied.

A previous history of macrosomia is often a risk factor for
LGA newborns. In the present sample, a history of macro-
somia was a risk factor for LGA newborns. Heiskanen et al
in a study comparing 886 pregnancies with macrosomic fetuses
with 26,075 pregnancies with AGA fetuses, found a 3.1-fold
higher risk of recurrence of macrosomia. Nkwabong et al
also showed that a history of fetal macrosomia is a significant
risk factor for the recurrence of macrosomia in subsequent
pregnancies. Although a history of macrosomia is a nonmo-
difiable factor, it serves as a marker of major metabolic changes
during pregnancy and, in these cases, health care providers
should pay attention to potentially influential factors for
excessive fetal growth that can be controlled.

With regard to blood glucose levels in the 3rd trimester,
high fasting glucose level was an independent risk factor for
LGA newborns. Legardeur et al observed that fasting blood
sugar ≥ 95 mg/dL doubled the risk for fetal macrosomia.
Thus, adequate glycemic control throughout the pregnancy,
through diet and/or insulin therapy, especially in the 3rd
trimester, should be intense to reduce risks.

The occurrence of LGA newborns was significantly higher
in the group of women with combined change in the OGTT
(fasting + after the dextrose load), even after the multivari-
one analysis. Brankica et al found that the combination of
fasting blood glucose and blood glucose 1 hour after the
glucose load in the OGTT was a predictor of occurrence of LGA
newborns. Pregnant women exhibiting this combination
may be considered at increased risk because of the fact
that they have two distinct changes, altered fasting glucose
and glucose intolerance, which suggests impairment in two
different metabolic pathways associated with the disease,
dysfunction of pancreatic β cells and insulin resistance.

In the present study, the ROC curve analysis showed that
plasma glucose 2 hours after the glucose load in the OGTT
was a better predictor for LGA newborns. Silva et al have also
identified high levels of plasma glucose at the 2-hour mea-
surement in the OGTT as one of the major independent risk
factors for LGA newborns. Brankica et al and Ouzilleau

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et al found high levels of fasting blood glucose to be better predictors, whereas Mello et al showed that 1-hour blood glucose was the factor most closely associated with LGA newborns.

**Conclusion**

The present study with pregnant women diagnosed with GDM showed that maternal prepregnancy obesity, history of macrosomia, combined change in the OGTT (fasting + after dextrose load), and high-fasting glycemic mean during the 3rd trimester were independent predictive factors for LGA newborns. Weight gain below that recommended by the IOM seems to be a protective factor for the occurrence of LGA newborns, and the need for specific recommendations for pregnant women with GDM may be suggested. However, more studies, with larger numbers of participants, are necessary to validate this finding. Maternal prepregnancy obesity and high-fasting glycemic mean in the 3rd trimester are modifiable factors, so preventive measures or therapeutic intervention can be implemented to minimize these risk factors. In general, retrospective studies present limitations related to the data obtained. Nonetheless, the present study highlights factors associated with LGA newborns of pregnant women with GDM in Brazil, which may be useful in the management of these patients during pregnancy and in preventing complications for the mothers and for the fetuses.

**Collaborations**

All of the authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

**Conflicts of Interests**

The authors have no conflicts of interests to declare.

**References**

1. Metzger BE, Coustan DR. Summary and recommendations of the fourth international workshop - Conference on gestational Diabetes Mellitus. The Organizing Committee. Diabetes Care 1998;21(Suppl 2):B161–B167
2. Metzger BE, Gabbe SG, Persson B, et al; International Association of Diabetes and Pregnancy Study Groups Consensus Panel. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycaemia in pregnancy. Diabetes Care 2010;33(03):676–682. doi: 10.2337/dc09-1848
3. American Diabetes Association. Standards of medical care in diabetes–2011. Diabetes Care 2011;34(Suppl 1):S11–S61. doi: 10.2337/dc11-5011
4. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy: a World Health Organization Guideline. Diabetes Res Clin Pract 2014;103(03):341–363. doi: 10.1016/j.diabres.2013.10.012
5. Oliveira JEP, Montenegro RM Junior, Vencio S. Avaliação e tratamento do diabetes mellitus gestacional. In: Oliveira JEP, Montenegro Junior RM, Vencio S, Orgs. Diretrizes da Sociedade Brasileira de Diabetes 2017–2018. São Paulo, SP: Clannad; 2017:217–222
6. Siega-Riz AM, King JC; American Dietetic Association; American Society of Nutrition. Position of the American Dietetic Association and American Society of Nutrition: Position of the American Dietetic Association and American Society of Nutrition for gestational diabetes mellitus. J Am Diet Assoc 2009;109(05):918–927. doi: 10.1016/j.jada.2009.09.006
7. Metzger BE, Coustan DR. Summary and recommendations of the fourth international workshop - Conference on gestational Diabetes Mellitus. Diabetes Care 2007;30(08):2070–2076. doi: 10.2337/dc06-2559a
8. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care 2007;30(08):2070–2076. doi: 10.2337/dc06-2559a
9. Huda SS, Brodie LE, Sattar N. Obesity in pregnancy: prevalence and metabolic consequences. Semin Fetal Neonatal Med 2010;15(02):70–76. doi: 10.1016/j.siny.2009.09.006
10. Mitanchez D, Yzydorczyk C, Simeoni U. What neonatal complications should the pediatrician be aware of in case of maternal gestational diabetes? World J Diabetes 2015;6(05):734–743. doi: 10.4239/wjd.v6.i5.734
11. Battaglia FC, Luchchenco LO. A practical classification of newborn infants by weight and gestational age. J Pediatr 1967;71(02):159–163. doi: 10.1016/S0022-3476(67)80066-0
12. American College of Obstetricians and Gynecologists’ Committee on Practice Bulletins—Obstetrics Practice Bulletin No. 173: fetal macrosomia. Obstet Gynecol 2016;128: e195–e209. doi: 10.1097/ AOG.0000000000001767
13. Melo ASO, Assunção PCS, Gondim SSR, et al. Estado nutricional materno, ganho de peso gestacional e peso ao nascer. Rev Bras Epidemiol 2007;10:249–257. doi: 10.1590/S1415-790X2007000000012
14. Braga CR, Santos FA, Silva EG, Hirakawa HS, Fernandes AAH, Calderon IMP. Relação do ganho de peso, antes e durante a gravidez, com a macrosomia fetal em gestações complicadas pelo diabetes gestacional e hiperglicemia leve. Nutrire Rev Soc Bras Aliment Nutrire 2011;36(01):85–98
15. Braga CR, Santos FA, Silva EG, Hirakawa HS, Fernandes AAH, Calderon IMP. Relação do ganho de peso, antes e durante a gravidez, com a macrosemia fetal em gestações complicadas pelo diabetes gestacional e hiperglicemia leve. Nutrire Rev Soc Bras Aliment Nutrire 2011;36(01):85–98
16. DiCianni G, Miccoli R, Volpe L, Lencioni C, Del Prato S. Intermediate metabolism in normal pregnancy and in gestational diabetes. Diabetes Metab Res Rev 2003;19(04):259–270. doi: 10.1002/dmrr.390
17. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Gestação de Alto Risco: Manual Técnico. 5° ed. Brasília, DF: Editora do Ministério da Saúde; 2012. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/manual_tecnico_gestacao_alto_risco.pdf. Accessed March 10, 2017
18. WHO Expert Committee on Physical Status: the Use and Interpretation of Anthropometry: report of a WHO Expert Committee. Technical report series; 854. Geneva, 1995. Available from: https://apps.who.int/iris/bitstream/handle/10665/37003/WHO_TRS_854.pdf?sequence=1. Accessed February 12, 2017
19. Rasmussen KM, Yaktine AL; Institute of Medicine and National Research Council. Weight Gain During Pregnancy: Reexamining the Guidelines. Washington, DC: The National Academies Press; 2009. Available from: https://www.nap.edu/read/12584/chapter/1. Accessed April 10, 2017
20. Villar J, Cheikh Ismail I, Victora CG, et al; International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st). International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014; 384(9946):857–868. doi: 10.1016/S0140-6736(14)60932-6
21. Silva JC, Bertini AM, Ribeiro TE, de Carvalho LS, Melo MM, Barreto Neto L. [Factors related to the presence of large for gestational age newborns in pregnant women with gestational diabetes mellitus]. Rev Bras Ginecol Obstet 2009;31(01):5–9. doi: 10.1590/S0100-720320090000100002
22. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab 2015;66:14–20. doi: 10.1590/0140-67361460932-6
23. HAPO Study Cooperative Research Group. Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) Study: associations with maternal body mass index. BJOG 2010;117(05):575–584. doi: 10.1111/j.1471-0528.2009.02486.x
22 Badon SE, Dyer AR, Josefson JL; HAPO Study Cooperative Research Group. Gestational weight gain and neonatal adiposity in the Hyperglycemia and Adverse Pregnancy Outcome study-North American region. Obesity (Silver Spring) 2014;22(07):1731–1738. Doi: 10.1002/oby.20742

23 Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care 2013;36(01):56–62. Doi: 10.2337/dc12-0741

24 Ehrenberg HM, Mercer BM, Catalano PM. The influence of obesity and diabetes on the prevalence of macrosomia. Am J Obstet Gynecol 2004;191(03):964–968. Doi: 10.1016/j.ajog.2004.05.052

25 Miao M, Dai M, Zhang Y, Sun F, Guo X, Sun G. Influence of maternal overweight, obesity and gestational weight gain on the perinatal outcomes in women with gestational diabetes mellitus. Sci Rep 2017;7(01):305. Doi: 10.1038/s41598-017-00441-z

26 Alberico S, Montico M, Barresi V, et al; Multicentre Study Group on Mode of Delivery in Friuli Venezia Giulia. The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. BMC Pregnancy Childbirth 2014;14:23. Doi: 10.1186/1471-2393-14-23

27 Mastella LS, Weinert LS, Gnielka V, et al. Influence of maternal weight gain on birth weight: a gestational diabetes cohort. Arch Endocrinol Metab 2018;62(01):55–63. Doi: 10.20945/2359-399700000009

28 Vesco KK, Sharma AJ, Dietz PM, et al. Newborn size among obese women with weight gain outside the 2009 Institute of Medicine recommendation. Obstet Gynecol 2011;117(04):812–818. Doi: 10.1097/AOG.0b013e3182113ae4

29 Wong T, Barnes RA, Ross GP, Cheung NW, Flack JR. Are the Institute of Medicine weight gain targets applicable in women with gestational diabetes mellitus? Diabetologia 2017;60(03):416–423. Doi: 10.1007/s00125-016-4173-3

30 Wolff S, Legarth J, Vangsgaard K, Toubro S, Astrup A. A randomized trial of the effects of dietary counseling on gestational weight gain and glucose metabolism in obese pregnant women. Int J Obes 2008;32(03):495–501. Doi: 10.1038/sj.ijo.0803710

31 Han S, Middleton P, Shepherd E, Van Ryswyk E, Crowther CA. Different types of dietary advice for women with gestational diabetes mellitus. Cochrane Database Syst Rev 2017;2:CD009275. Doi: 10.1002/14651858.cd009275.pub3

32 Heiskanen N, Raatikainen K, Heinonen S. Fetal macrosomia—a continuing obstetric challenge. Biol Neonate 2006;90(02):98–103. Doi: 10.1159/000092042

33 Nkwabong E, Nzalli Tangho GR. Risk factors for macrosomia. J Obstet Gynaecol India 2015;65(04):226–229. Doi: 10.1007/s13224-014-0586-4

34 Legardeur H, Girard G, Journy N, Ressencourt V, Durand-Zaleski I, Mandelbrot L. Factors predictive of macrosomia in pregnancies with a positive oral glucose challenge test: importance of fasting plasma glucose. Diabetes Metab 2014;40(01):43–48. Doi: 10.1016/j.diabet.2013.01.008

35 Brankica K, Valentina VN, Slagjana SK, Sasha JM. Maternal 75-g OGTT glucose levels as predictive factors for large-for-gestational age newborns in women with gestational diabetes mellitus. Arch Endocrinol Metab 2016;60(01):36–41. Doi: 10.1590/2359-39970000126

36 Tripathy D, Carlsson M, Almgren P, et al. Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia Study. Diabetes 2000;49(06):975–980. Doi: 10.2337/diabetes.49.6.975

37 Ouzilleau C, Roy MA, Leblanc L, Carpenterier A, Maheux P. An observational study comparing 2-hour 75-g oral glucose tolerance with fasting plasma glucose in pregnant women: both poorly predictive of birth weight. CMAJ 2003;168(04):403–409

38 Mello G, Parretti E, Cioni R, et al. The 75-gram glucose load in pregnancy: relation between glucose levels and anthropometric characteristics of infants born to women with normal glucose metabolism. Diabetes Care 2003;26(04):1206–1210. Doi: 10.2337/diacare.26.4.1206