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Predicting macrosomic newborns using postprandial glycemia of pregnancy in diabetic women

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Summary

Purpose: To determine the mean two-hour postprandial (2hPP) blood glucose level and to analyze the maternal variables that can predict macrosomic or large for gestational age (LGA) newborns in diabetic mothers such as the type of diabetes mellitus, pre-gestational body mass index (BMI), previous macrosomic newborn, and parity. *Materials and Methods:* A prospective, longitudinal study was conducted with 200 pregnant women who had either gestational (103) or pre-gestational (97) diabetes. The mean 2hPP blood glucose levels, which were obtained by capillary glycemia, were calculated for all pregnant women >24 weeks gestation and divided into three groups: group 1 ≤100 mg/dl, group 2 100–120 mg/dl, and group 3 ≥120 mg/dl. The analysis of variance (ANOVA) was used to investigate the differences between groups for the occurrence of macrosomia or LGA. The receiver operator characteristics (ROC) curve was used to identify the significant cutoff point for the mean level of 2hPP blood glucose. *Results:* Pre-gestational BMI and previous macrosomia were associated with the occurrence of newborns with weight alterations of 32.8% and 35.7%, respectively ($p < 0.001$). However, other independent variables such as multiparity, lipid profile (total cholesterol and triglycerides, both isolated and associated), and type of diabetes were assessed both isolated and grouped. The best cutoff point for 2hPP blood glucose was >109 mg/dl, with a sensitivity of 81%, specificity of 40%, positive predictive value of 27.8%, and negative predictive value of 88.1%. *Conclusion:* Macrosomic and LGA were associated with maternal 2hPP blood glucose values > 109 mg/dl between 24 and 34 weeks gestation.

Key words: Gestational diabetes; Postprandial glycemia; Macrosomia; Large for gestational age.

Introduction

Maternal hyperglycemia is associated with increased fetal and neonatal morbidity [1]. Macrosomic and large for gestational age (LGA) infants are still observed, even though diabetic pregnant women's follow-up is carefully performed during prenatal care [2, 3]. Macrosomia is usually defined as a birth weight > 90th percentile for gestational age or > 4,000 grams [4], with their frequency ranging from 20% in pregnant women with gestational diabetes to ≥ 35% in pregnant women with pre-existing diabetes (type 1 and 2) in comparison to 12% of newborns in normal pregnant women [5]. In addition to hyperglycemia, other risk factors as maternal obesity, gestational age at delivery, pre-gestational body mass index (BMI), maternal height, hypertension, cigarette smoking, maternal age, parity, excessive weight gain during pregnancy, macrosomia in previous delivery, and maternal triglycerides levels may influence fetal growth [6].

Fetal macrosomia is associated with maternal and neonatal complications. The main maternal complications are the following: increased cesarean delivery rate, uterine atony, and puerperal hysterectomy, with a consequent greater need for blood transfusion [7, 8]. During labor, macrosomia increases the risk of asphyxia and shoulder dystocia, which can lead to long-term sequelae [8, 9]. In the neonatal period, complications such as hypoglycemia, hyperbilirubinemia, hypocalcemia, and respiratory distress syndrome are common among macrosomic fetuses [10, 11]. In addition, there is a high prevalence of obesity, insulin resistance, and type 2 diabetes mellitus in adult offspring of women with gestational diabetes, type 1 diabetes mellitus, macrosomic, and large for gestational age infants [12, 13].

Veciana *et al.* [14] compared the efficacy of postprandial and preprandial monitoring in achieving glycemic control in women with gestational diabetes. They have shown that adjustment of insulin therapy in women with gestational diabetes according to the results of postprandial, rather than preprandial, blood glucose values improves glycemic control and decreases the risk of neonatal hypoglycemia, macrosomia, and cesarean delivery rate. The values that resulted in fewer maternal-fetal complications were < 88

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Table 1. — *Maternal and perinatal characteristics of the study groups according to the mean 2hPP blood glucose.*

	Mean 2hPP blood glucose (mg/dl)			
	≤100 Group 1 (n=45)	100–120 Group 2 (n=148)	>120 Group 3 (n=7)	*p*
Maternal age, weeks (mean)	30.30 ± 6.75	30.81 ± 6.43	30.71 ± 6.45	0.877*
Blood glucose, mg/dl (mean)	93.3 ± 5.04	111.1 ± 5.62	147.7 ± 6.2	0.0012*
Glycemia, mg/dl (median) 95% CI	94 (91 to 97)	112 (110 to 114)	141 (133.3 to 151)	0.0077*
Parity (mean)	1.18 ± 1.27	1.74 ± 1.48	1.80 ± 1.60	0.050†
History of DM in the family	20 (44.4%)	42 (57.5%)	49 (62.0%)	0.160§
Pregestational BMI, kg/m^2 (mean)	27.11 ± 5.11	25.90 ± 5.06	27.10 ± 5.80	0.320*
Insulin therapy, UI/kg/day	15 (33.3%)	64 (87.7%)	77 (93.9%)	< 0.001§
Gestational age at delivery, weeks (mean)	37.49 ± 2.43	37.73 ± 1.39	36.68 ± 2.84	0.014*
Cesarean section	24 (60.0%)	49 (67.1%)	58 (70.7%)	0.469§
Newborn weight, grams (mean)	3283.00 ± 130.42	3,311.18 ± 118.61	3,466.26 ± 145.56	0.847*
Sex of newborn	F 24/M 21	F 62/M 86	F 3/M 4	-
Type 2 DM	6	50	4	-
Type 1 DM	3	31	3	-
Gestational DM	36	67	0	-

95% CI: 95% confidence interval; BMI: body mass index; DM: diabetes mellitus; F: female; M: male
**Analysis of variance (ANOVA); †Kruskal–Wallis non-parametric test; §Chi-squared test*

mg/dl and < 115 mg/dl for fasting blood glucose and two-hour postprandial (2hPP) blood glucose, respectively [15]. Hutcheon *et al.* [16] reported a significant correlation between 2hPP blood glucose and birth weight in different pregnant women and a weak correlation in different pregnancies of the same woman.

This study aimed to predict the incidence of macrosomic or LGA infants based on the mean 2hPP blood glucose levels in second- and third-trimester pregnancies.

Materials and Methods

This was a prospective, longitudinal study that evaluated pregnant women with gestational or pre-gestational diabetes (type 1 or 2) and who had at least three 2hPP blood glucose measurements in the second and third trimesters of their pregnancy (24 and 34 weeks, respectively). This study was approved by the Ethics Committee of the Federal University of São Paulo (UNIFESP) and the women who agreed to participate signed an informed consent form.

Glucose levels were assessed in separate prenatal care consultations. The mean interval between appointments was two weeks until the 30th week and weekly thereafter until delivery. The inclusion criterion was women with at least three prenatal care consultations who delivered in this service. The exclusion criteria were failure of prenatal care follow-up, multiple pregnancies, fetuses with malformations, and newborns weighing < 2,500 grams.

To assess the impact of glycemic control, a reference value of up to 120 mg/dl (6.66 mmol/l) was determined as the normality upper limit for 2hPP blood glucose [16, 17]. Based on these values, cases were divided into three groups: group 1 ≤100 mg/dl (5.55 mmol/l), group 2 100–120 mg/dl (5.55–6.66 mmol/l), and group 3 > 120 mg/dl (6.66 mmol/l).

Maternal blood glucose was measured using a glucometer capable of detecting blood glucose in the range of 10–600 mg/dl (0.6–33.3 mmol/l). For this measurement, lancets and test strips were used. Normal fasting blood glucose values ranged from 70 to 105 mg/dl (3.89–5.83 mmol/l). Pregnant women were instructed to feed at lunch with similar food which was consumed at their homes and new 2hPP blood glucose was measured.

After delivery, the mean 2hPP blood glucose in the second and third trimesters of pregnancy were correlated to weight of newborns, who were classified as LGA if their weight was ≥ 90th percentile for gestational age and as macrosomic if weight was ≥ 4,000 grams, regardless of gestational age ≥ 90th percentile [18]. Other variables considered to influence fetal growth were multiparity (≥1 previous delivery), pre-gestational BMI, history of macrosomia, type of diabetes (type 1, 2, or gestational diabetes), and lipid profile (total cholesterol and triglycerides). The lipid profile was considered to be altered when cholesterol was > 200 mg/dl and triglycerides > 180 mg/dl.

The data were compiled into an Excel 2003 spreadsheet and analyzed using SPSS version 15.0. The mean and median of glycemic groups, with their respective standard deviations (SD) and confidence intervals (CI) of 95% were calculated. The analysis of variance (ANOVA) was used to identify whether there was a statistically significant difference between the groups for the occurrence of macrosomia or LGA; this was complemented by the nonparametric Kruskal–Wallis and chi-square (X^2) tests. A receiver operator characteristics (ROC) curve was created to determine the sensitivity, specificity, positive predictive value, and negative predictive value for the cutoff point of the assessed blood glucose levels, including all patients in this analysis. The variables considered as influencing fetal growth were assessed both isolated and grouped using multivariate analysis to obtain an association with the response variable (macrosomia or LGA). In all analyses, the significance level was set at $p < 0.05$.

Results

Initially, 215 pregnant women were selected. However, 15 were excluded due to failure of follow-up. Therefore, 200 pregnant women were analyzed (103 with gestational diabetes and 97 with pre-gestational diabetes) for the final statistical analysis.

The maternal age ranged from 13 to 46 (mean 30.6 ± 6.5) years. There were 11 (5.5%) patients younger than 20 years,

Table 2. — *Incidence of macrosomic or LGA infants based on the mean 2hPP blood glucose levels, type of diabetes, parity, start of specialized prenatal care, maternal cholesterol and triglycerides level, pregestational BMI, and previous macrosomia.*

	Macrosomia or LGA		Total	p^*
	Yes n=37	No n=163		
Mean 2hPP				0.218
≤ 120 mg/dl	18 (15.2%)	100 (84.7%)	118 (100.0%)	
> 120 mg/dl	19 (23.2%)	63 (76.8%)	82 (100.0%)	
DM type				0.147
Gestational DM	15 (14.6%)	88 (85.4%)	103 (100.0%)	
Type 1 DM	6 (16.2%)	31 (83.8%)	37 (100.0%)	
Type 2 DM	16 (26.7%)	44 (73.3%)	60 (100.0%)	
Parity				0.570
Primiparous	11 (17.4%)	42 (82.8%)	53 (100.0%)	
> 1 delivery	25 (20.8%)	120 (79.2%)	145 (100.0%)	
Start of specialized prenatal care				0.722
< 26 weeks	24 (17.9%)	110 (82.1%)	134 (100.0%)	
> 26 weeks	13 (20.0%)	52 (80.0%)	65 (100.0%)	
Cholesterol				0.839
Normal (≤ 200 mg/dl)	14 (19.2%)	59 (80.8%)	73 (100.0%)†	
Altered (> 200 mg/dl)	17 (20.5%)	66 (79.5%)	83 (100.0%)	
Triglycerides				0.416
Normal (≤ 180 mg/dl)	16 (17.8%)	74 (82.2%)	90 (100.0%)§	
Altered (> 180 mg/dl)	15 (23.1%)	50 (76.9%)	65 (100.0%)	
Pregestational BMI				<0.001
Normal (≤ 30 kg/m^2)	18 (12.7%)	124 (87.3%)	142 (100.0%)	
Altered (> 30 kg/m^2)	19 (32.8%)	39 (67.2%)	58 (100.0%)	
Previous macrosomia				<0.001
No	17 (11.8%)	127 (88.2%)	144 (100.0%)	
Yes	20 (35.7%)	36 (64.3%)	56 (100.0%)	

LGA: large for gestational age; 2hPP: 2-hour postprandial blood glucose; DM: diabetes mellitus; BMI: body mass index
*Chi-squared test; †156/200 pregnant women who realized the cholesterol blood analysis; §155/200 pregnant women who realized the triglycerides blood analysis

134 (67.0%) between the ages of 20 and 35 years, and 55 (27.5%) patients older than 35 years . Regarding ethnicity, 121 (60.5%) and 79 (39.5%) patients were classified as white and non-white, respectively. Concerning the number of pregnancies, 157 (79.3%) were multigravidas and 41 (20.7%) were primigravidas.

Table 1 shows the maternal and perinatal characteristics of the three groups assessed in relation to 2hPP blood glucose levels. Significant differences were observed between groups 1, 2, and 3 in relation to mean gestational age at delivery (37.49, 37.73, and 36.68 weeks, respectively; p = 0.014) and insulin therapy (15 UI/kg/day, 64 UI/kg/day, and 77 UI/kg/day, respectively; $p < 0.001$). The weight of the newborns ranged from 2,545 to 4,965 (3370.0 ± 504.6) grams. The macrosomia rate was 11.3%, which corresponded to 19 newborns. The LGA rate was 10.8%, which corresponded to 37 newborns. Therefore, the rate of macrosomia and LGA combined was 22.1%.

Table 2 shows that there were no statistically significant difference between the groups for the occurrence of macrosomia or LGA with regard to the mean 2hPP blood glucose values (p = 0.218), type of diabetes (p = 0.147), parity (p = 0.570), start of specialized prenatal care (p = 0.722), maternal cholesterol levels (p = 0.839), and maternal triglycerides (p = 0.416). However, for pre-gestational BMI (> 30 kg/m^2) and previous macrosomia (birth weight ≥ 4,000 grams), all three groups had a higher percentage of cases with macrosomia or LGA than the normal group ($p <$ 0.001).

Considering only the newborns with a birth weight ≥ 2,500 grams (166 patients), there were 37 newborns classified as LGA and 129 classified as adequate for gestational age and/or small for gestational age. According to the ROC curve, the cutoff point with the best counterbalance between sensitivity and specificity to identify the occurrence of LGA was a mean 2hPP blood glucose level of >109 mg/dl (sensitivity 81.0%, specificity 40.0%, positive predictive value 27.8%, and negative predictive value 88.1%) (Figure 1 and Table 3).

Discussion

The prevalence of gestational diabetes is influenced by several factors, such as the characteristic of studied population and the diagnostic tests employed. The prevalence of gestational diabetes in Northern Europe ranges from 0.6% in the Netherlands to 3.6% in Denmark. In the US, 7.0% of all pregnancies are complicated by gestational di-

Table 3. — *Counterbalance between sensitivity and specificity for mean 2hPP glucose and diagnosis of LGA infants.*

Glycemia (mg/dl)	Sensitivity	95% CI	Specificity	95% CI	+LR	-LR	+PV	-PV
>100	89.19	74.6–96.9	28.46	20.9–37.0	1.25	0.38	26.2	90.2
>101	89.19	74.6–96.9	31.54	23.7–40.3	1.30	0.34	27.0	91.1
>102	83.78	68.0–93.8	33.08	25.1–41.9	1.25	0.49	26.3	87.8
>103	83.78	68.0–93.8	34.62	26.5–43.5	1.28	0.47	26.7	88.2
>104	83.78	68.0–93.8	35.38	27.2–44.2	1.30	0.46	27.0	88.5
>105	83.78	68.0–93.8	37.69	29.3–46.6	1.34	0.43	27.7	89.1
>106	83.78	68.0–93.8	38.46	30.1–47.4	1.36	0.42	27.9	89.3
>107 *	83.78	68.0–93.8	39.23	30.8–48.2	1.38	0.41	28.2	89.5
>108	81.08	64.8–92.0	39.23	30.8–48.2	1.33	0.48	27.5	87.9
>109 **	81.08	64.8–92.0	40.00	31.5–49.0	1.35	0.47	27.8	88.1
>110	78.38	61.8–90.1	43.08	34.4–52.0	1.38	0.50	28.2	87.5
>111	75.68	58.8–88.2	44.62	35.9–53.6	1.37	0.55	28.0	86.6
>112	67.57	50.2–82.0	46.92	38.1–55.9	1.27	0.69	26.6	83.6
>113	64.86	47.5–79.8	48.46	39.6–57.4	1.26	0.73	26.4	82.9
>114	56.76	39.5–72.9	51.54	42.6–60.4	1.17	0.84	25.0	80.7

** Significant value as determined by the program; ** Value defined as the best counterbalance point*
95% CI: 95% confidence interval; + LR: positive likelihood ratio; -LR: negative likelihood ratio; PV +: positive predictive value; -PV: negative predictive value

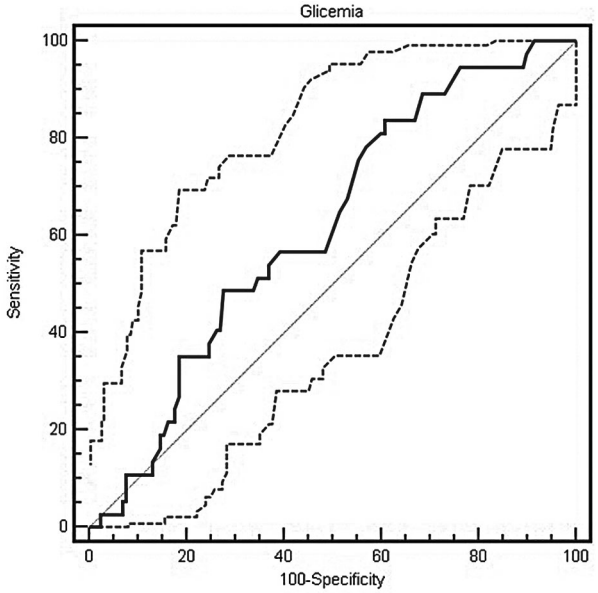

Figure 1. — ROC curve showing the association of mean 2hPP glucose levels and the occurrence of LGA in newborns with birth weight ≥ 2,500 grams.

abetes [19]. Gestational diabetes prevalence is 2.4 times higher using the most recent International Association of Diabetes in Pregnancy Study Group (IADPSG) criteria compared to the World Health Organization (WHO) 1999 criteria. Using the new criteria, gestational diabetes prevalence ranges from 9.0% to 26.0% in the 15 centers that participated in the hyperglycemia and adverse pregnancy outcome (HAPO) study, which was a large international observational study [20]. Perinatal mortality associated with gestational or pre-gestational diabetes has decreased significantly in recent decades. However, perinatal morbidity has remained constant [21].

Recently, a randomized controlled trial assessed 418 women to compare induction of labour *vs.* expectant management in suspected LGA pregnancies [22]. The authors have shown that induction of labour at 37-39 weeks gestation for suspected LGA fetuses is associated with reduced risk of shoulder dystocia and morbidity compared to expectant management. Induction of labour does not increase the risk of cesarean delivery and improves the likelihood of spontaneous vaginal delivery [22]. This evidence reinforces the need for new strategies to improve antenatal identification of LGA infants.

Maternal hyperglycemia in early pregnancy does not produce fetal hyperinsulinemia, as the fetal pancreas does not secrete insulin before the second trimester [23]. The second and third trimesters of pregnancy appear to be the period when high glucose levels lead to important changes in fetal growth [24, 25]. Because of this, the purpose of this study was to predict the rate of macrosomic and LGA infants based on 2hPP blood glucose in the second and third trimester of pregnancy.

The exclusion of newborns < 2500 grams occurred because of fetuses with an estimated birth weight that was < 5th percentile for gestational age from pregnant women with type 1 diabetes mellitus may be related with advanced vascular disease. Placental insufficiency is usually followed by pre-eclampsia, fetal growth restriction, and beyond acute distress during the delivery, which is followed by secondary polycitemia in the newborn. This condition is an independent factor for acute distress during delivery, which is independent of maternal glycemic control [26]. Different from Langer *et al.* [27] findings, which reported low glycemia < 86 mg/dl (group 1), mean glycemia between 87 and 104 mg/dl (group 2), and high glycemia > 105 mg/dl (group 3), the present results showed that group 1 had a

higher rate of small for gestational age (SGA) newborns (20.0%). However group 2 showed a rate 21 times higher for LGA newborns than group 1. Group 3 showed a rate two times higher for LGA newborns than group 1, however without statistical difference regarding the group 2.

In this study, parity was not significant for the detection of macrosomic newborns. This finding differs from the study by Adesina and Olayemi [27] who reported that parity, maternal weight at the end of gestation (≥ 90 kg), and pregnancy duration were related to the occurrence of macrosomia in the current pregnancy. In concordance with previous studies [27, 28], the present authors found that macrosomia in the previous pregnancy was a significant parameter for the prediction of macrosomia or LGA in the current pregnancy. Richardson and Trotman [28] evaluated retrospectively, 316 macrosomic newborns and 316 controls. They observed that macrosomia in a previous pregnancy was the main risk factor for macrosomia in the current pregnancy (a six-fold increase).

Regarding pre-gestational BMI, the present study found a higher incidence of LGA or macrosomic newborns in the group with abnormal BMI (>30 kg/m^2). Similar results were also observed by Schaefer-Graf *et al.* [29], who reported that pre-gestational BMI was associated with increased fetal growth in the last trimester of pregnancy. In addition, Hutcheon *et al.* [16] reported that BMI was the pre-gestational factor most related to the occurrence of macrosomic infants of diabetic mothers.

In the present study, there were no significant correlations between mean 2hPP blood glucose levels > 120 mg/dl and the occurrence of LGA or macrosomia. Legardeur *et al.* [30] retrospectively evaluated 1,268 pregnancies with the positive oral glucose tolerance test (OGTT). Macrosomia risk did not differ between patients with gestational diabetes with normal plasma glucose and non-diabetics. However, the risk of macrosomia significantly increased in cases of fasting plasma glucose ≥ 95 mg/dl, regardless of the postprandial blood glucose level. Similarly, González-Quintero *et al.* [31] reported that poor glycemic control, defined as mean fasting blood glucose > 95 mg/dl, 1hPP blood glucose >140 mg/dl, or 2hPP blood glucose >120 mg/dl, was associated with a third of neonates with adverse perinatal outcomes such as macrosomia, LGA, hypoglycemia, jaundice, and stillbirth. According to Brankica *et al.* [32], fasting glucose levels and one-hour OGTT glucose levels showed statistically significant predictability for LGA newborns in gestational diabetes pregnant women.

In the present study, mean 2hPP blood glucose level > 109 mg/dl (sensitivity 81.0%, specificity 40.0%, positive predictive value 27.8%, and negative predictive value 88.1%) was the best cutoff point for predicting the occurrence of LGA or macrosomia. In a study by El-Halwagy *et al.* [33] with 281 diabetic women, the best cutoff point for predicting macrosomic newborns (1hPP blood glucose > 135 mg/dl) had a sensitivity of 72.7%, specificity of 82.8%, positive predictive value of 46.8%, and negative predictive value of 93.7%. The present authors prioritized sensitivity in the present study because when they reduced it, they failed to diagnose an increasing number of newborns with birth weight alterations. Despite the low specificity, a high negative predictive value indicates that in the presence of a negative test, a large number of newborns will not be LGA or macrosomic.

The concentration of all lipoprotein fractions increases during pregnancy. Triglycerides increase 2.5-fold over pre-pregnancy levels. In diabetic pregnant women, the available data indicate that triglyceride concentrations were increased and HDL cholesterol concentrations were decreased with reference to lipoproteins in non-diabetic, pregnant women [34]. In the present study, the authors chose to make an adjustment of 20% in the maximum level of triglyceride (180 mg/dl) because the main objective was the prediction of LGA or macrosomic newborns. According to Wen-Yuan *et al.* [35], the best cutoff to predict LGA was 309 mg/dl (3.53 mmol/l). They described that the level of triglycerides in the end of pregnancy was an independent and significant marker to gestational diabetes mellitus, pre-eclampsia, LGA, and decreased risk to SGA newborns in a Chinese population.

Limiting factors of this study were the heterogeneity of the groups regarding the types of diabetes mellitus and the correlation between good maternal glycemic control and adequate for gestational age newborns using a small number of participants. The variable gestational gain weight was initially a searched variable, however the authors decided to exclude it because of the great difficulty to identify the pre-gestational weight in the studied group. Many pregnant women did not know to refer their weight in the begging of prenatal care or their weight in the previous pregnancy. Furthermore, the highest number of pregnant women began their prenatal care in the second trimester of pregnancy.

Conclusion

In summary, maternal 2hPP blood glucose levels > 109 mg/dl were associated with a considerable number of newborns with weight alterations. However, this parameter alone cannot predict macrosomic or LGA newborns. The group with a mean glycemic 2hPP between 100 and 120 mg/dl requires more studies to establish an ideal cutoff to avoid adverse perinatal outcomes.

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