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EARLY TERM DELIVERY IN WOMEN WITH PREGNANCY COMPLICATED BY DIABETES AND NEONATAL HYPOGLYCEMIA

Sávio Ferreira Camargo

Master's Programme in Health Sciences, Federal University of Rio Grande do Norte, prenatal fitness professional in Maternity Hospital-School Januário Cicco, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.

Jessione de Carvalho Lima Neto

Undergraduate student in Medicine, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.

Juliana Dantas de Araújo Santos Camargo

Master of Science in Demography, statistical analyst in Maternity Hospital-School Januário Cicco, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.

Maria da Conceição de Mesquita Cornetta

Doctor in obstetrics, Professor of the Department of tocogynecology of the Medicine Programme, Universidade Federal do Rio Grande do Norte, Natal, RN, Brazil.

Corresponding author:
Sávio Ferreira Camargo
saviocamargo@gmail.com

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ABSTRACT: The association between early term delivery (ETD) and neonatal hypoglycemia in women with diabetes in pregnancy (DP) is analyzed. 258 females (30.8 ± 6.4 years) with term delivery and diabetes in pregnancy participated in current study. Neonatal hypoglycemia was ≤ 45mg/dl in the first 24 hours of life. Gestational age at birth was established by ultrasonography. Sample was divided into (i) ETD females (n = 163) and (ii) females with non-early term delivery (n = 95). The Chi-Squared and Fisher's Exact tests and logistic regression were performed for association analysis at 5% significance level. Early term delivery and higher occurrence of neonatal hypoglycemia were associated (OR = 2.88; IC 95%: 1.19 – 6.96). Neonates born of females with diabetes during pregnancy and early term delivery had a higher incidence of hypoglycemia than their peers born in non-early term deliveries, which suggests a risk factor for early term delivery in females with pregnancy complicated by hyperglycemia.

KEY WORDS: Gestational diabetes; Neonatal hypoglycemia; Term birth.

PARTO A TERMO PRECOCE EM MULHERES COM GESTAÇÃO COMPLICADA POR DIABETES E HIPOGLICEMIA NEONATAL

RESUMO: Examinar a associação entre parto a termo precoce (PTP) e hipoglicemia neonatal em mulheres com hiperglicemia na gestação (HG). 258 mulheres (30,8 ± 6,4 anos) com parto a termo e HG participaram do estudo. A hipoglicemia neonatal foi estabelecida por registro inferior a 45 mg/dl nas primeiras 24 horas de vida. A idade gestacional no parto foi estabelecida por ultrassonografia. A amostra foi dividida em dois grupos: i) mulheres com PTP (n = 163); ii) mulheres com parto a termo não precoce (n = 95). Os testes Qui-quadrado e Exato de Fisher, além da regressão logística, foram utilizados para análise de associação. O nível de significância de 5% foi adotado. Houve associação entre PTP e maior ocorrência de hipoglicemia neonatal (RC = 2,88; IC 95%: 1,19–6,96). Neonatos de mulheres com HG e PTP apresentaram maior ocorrência de hipoglicemia que seus pares nascidos a termo não precoce, o que sugere um fator de risco do parto a termo precoce em mulheres com gestação complicada por hiperglicemia.

PALAVRAS-CHAVE: Hiperglicemia na gestação; Hipoglicemia neonatal; Parto a termo.

INTRODUCTION

When compared to full term delivery (between 39 weeks and 40 weeks and 6 days) and late term delivery (between 41 weeks and 41 weeks and 6 days)1, early term delivery (ETD) (between 37 weeks and 38 weeks and six days)1 has been associated with a higher neonatal morbidity rate coupled to high hospital costs, with possible long term negative repercussions, such as greater tendency for obesity/overweight, hyperlipidemia, diabetes mellitus type 2 and hospitalizations for endocrine-metabolic issues2,3. The hyperglycemic intrauterine space causes epigenetic changes in the offspring2–4. Assessment of such changes in genic expressions have not been sufficiently understood4–6.

The prevalence of hyperglycemia during pregnancy has always been high during the last decades, reaching 15.8% of neonatal pregnancies in 20197. The fetal hyperinsulin factor induced by maternal hyperglycemia increases the risk of neonatal hypoglycemia5,8–10, since the continuous glucose flow disappears and sharply reduces the energetic substrate available for the neonate10. It should be underpinned that neonatal hypoglycemia may cause neurologic deficits on a long term basis11,12. On the other hand, full and late term delivery, particularly in females with hyperglycemia during pregnancy, prevents neonatal hypoglycemia13, due to a greater degree of the fetal organism´s physiological maturation on birth2,3.

Previous studies have reported that non-early term delivery is associated with less prevalence rates of neonatal hypoglycemia2,14. However, there are only few studies that have analyzed the relationship between the different periods of full term and neonatal hypoglycemia in females with hyperglycemia during pregnancy15,16. Precisely this is the aim of current study, or rather, to investigate the association between pregnancy age at birth in females with neonatal hyper and hypoglycemia.

METHODOLOGY

STUDY DESIGN, BACKGROUND AND PARTICIPANTS

Current transversal study, following the STROBE declaration17, was undertaken in a university-maternity linked to the Universidade Federal do Rio Grande do Norte, between November 2017 and February 2019, after being approved by the local Committee for Ethics (protocol n. 73252017.3.0000.5292). Two hundred and fifty-eight puerperas with hyperglycemia during pregnancy were randomly selected (Figure 1). Recruitment occurred up to 48h after birth. Puerperas authorized the use of their data by signing the Free Consent Term and then interviewed. Inclusion criteria comprised (i) positive diagnosis for diabetes type 1, 2 or gestational diabetes mellitus (GDM) according to criteria by the World Health Organization published in 201816, which established that GDM may be diagnosed at any moment in pregnancy if at least one of the following indexes are fulfilled: (a) fasting plasma glucose 5.1–6.9 mmol/l (92–125 mg/dl); b) one hour plasma glucose ≥ 10.0 mmol/l (180 mg/dl) 1-h post 75g oral glucose load; c) 2h plasma glucose 8.5–11.0 mmol/l (153–199 mg/dl) 1-h post 75g oral glucose load; ii) full term birth. Exclusion criteria were: i) multiple pregnancy; ii) regular use of corticoids during pregnancy; iii) lack of data required to complete the collection tool.

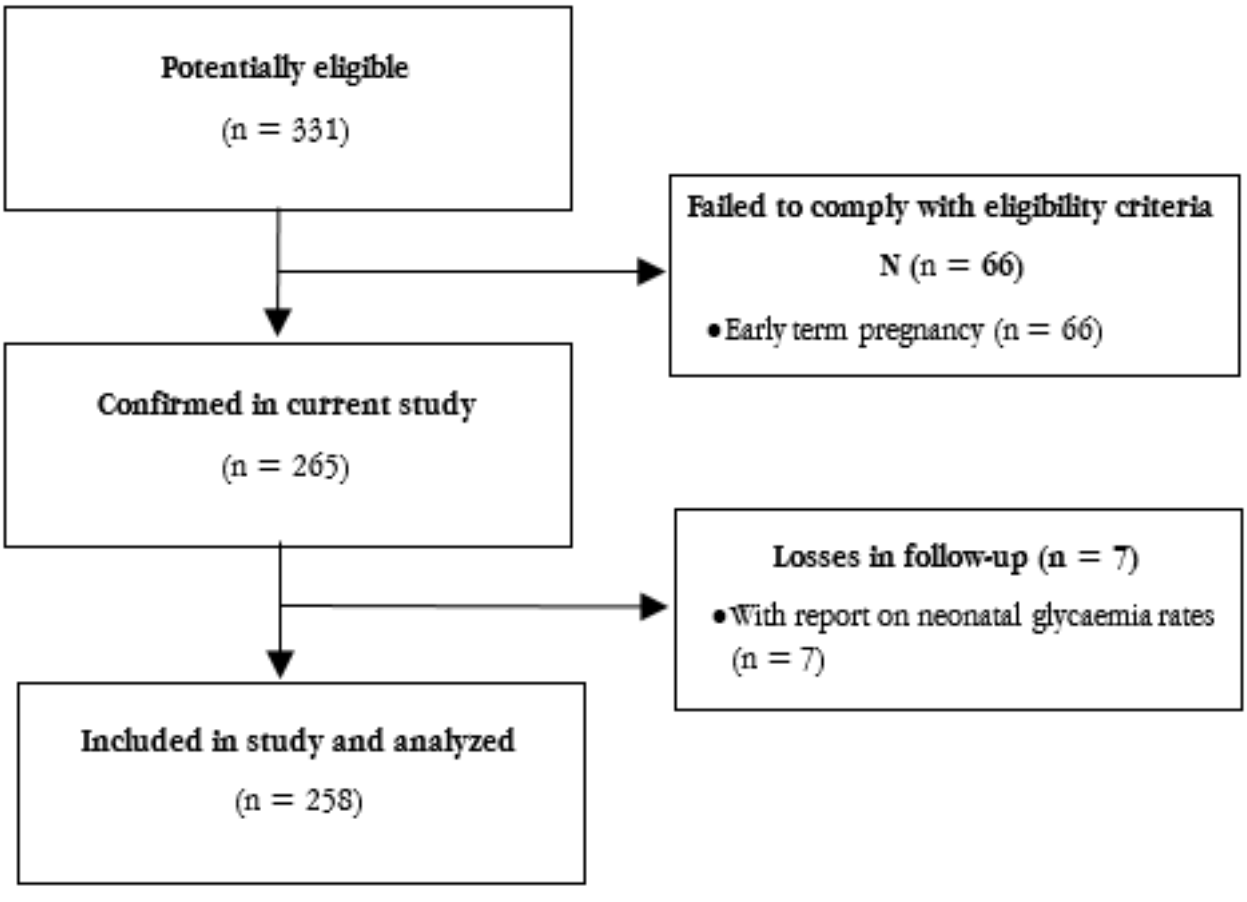

Figure 1. Flow chart of sample.

PROCEDURES

All participants underwent the following procedures: i) filling the form prepared by the main researcher, including mothers data: age, pre-natal follow-up, pre-pregnancy weight, height, previous pregnancies and births (interview); ii) data from clinical chart and pre-natal notebook on the diagnosis of diabetes, infections of the urinary tract, arterial hypertension, insulin therapy, gestational age (GA) at birth, type of birth, weight at birth, neonatal glycaemia, respiratory discomfiture and jaundice (up to a week after interview).

Body Mass Index (BMI) was calculated by dividing body weight (kg) by height squared (m). Pre-pregnancy weight was defined by index equal to or higher than 30[18]

GESTATIONAL AGE AT BIRTH

Gestational Age (GA) was determined by ultrasonography, following Henriques *et at*., 2019[19], based on the first test registered on the clinical chart. Participants´ classification was based on the definitions provided by the American College of Obstetricians and Gynecologists[1]: early-term delivery, between 37 and 38 weeks and 6 days; full-term delivery, between 39 and 40 weeks and 6 days; late-term delivery, between 41 weeks and 41 weeks and 6 days. Females were placed into two groups according to GA at full-term delivery: i) early-term, between 37 and 38 weeks and 6 days; ii) non-early term, comprising full term and late-term, between 39 and 41 week and 6 days.

NEONATAL HYPOGLYCEMIA

Neonatal hypoglycemia was tested by capillary glycaemia following guidelines on hypoglycemia established by the Brazilian Pediatric Society[20]. Classification of hypoglycemia (yes *vs* no) was determined by the occurrence of at least one report below deadline during the first 24h of life, following clinical protocol for the 2019 neonatal protocol of the Hospital de Clínicas of the Uni-

versidade Federal do Triângulo Mineiro (HC-UFTM)[21]. Deadline amounted to 45 mg/dl, following guidelines by the Brazilian Pediatric Society[20].

STATISTICAL ANALYSIS

Shapiro-Wilk´s test verified normality of continuous variables and was applied to each group: early-term delivery (yes *vs* no). The descriptive analysis of variables that evidenced normal distribution was performed by means and standard deviation (mean ± SD). Median and percentiles 25 and 75 were employed for variables without normal distribution in any group. In the case of categorical variables, analysis was undertaken by absolute and relative frequencies.

Test *t* for independent samples was employed for continuous variables with normality. Levene´s test verified homogeneity of variances. Mann-Whitney´s non-parametric test compared differences between distributions of variables with no normality. Chi-square test analyzed the association between full-term delivery period and categorical variables, such as pre-gestational obesity, diagnose for DM and type, maternal co-morbidities: infection of the urinary tract, chronic hypertension and gestational hypertension, insulin therapy, type of delivery and neonatal results (hypoglycemia, respiratory discomfiture, macrosomia and jaundice). In case cells of tables have expected frequencies lower than 5, Fisher´s exact test was employed. Phi (φ) coefficient was employed to analyze the association strength between the occurrence of early-term delivery and hypoglycemia. Associations between PTP and neonatal results in multivariate analysis were performed by logistic regression and results were given by ratio chances and their respective intervals at 95% confidence level (IC 95%). All multivariate models were adjusted for independent variables with $p<0.10$ in the bivariate analysis. A 5% level of significance was employed for all analyses and SPSS 25 (Statistical Package for the Social Sciences, Chicago, USA) was used.

RESULTS

Table 1 shows the characteristics of participants according to full-term delivery status (n = 258). There were differences among the groups early-term and non-early term delivery in the variables age, BMI (pre-gestational and end of gestation) and insulin therapy ($p < 0.05$).

Table 2 demonstrates the occurrence of negative neonatal results according to full term delivery status. The early-term delivery group had a greater occurrence of neonatal hypoglycemia ($p < 0.05$), with no statistically significant differences between groups in macrosomia, jaundice and respiratory discomfiture ($p > 0.05$).

There was a significant associated between early-term delivery and hypoglycemia, χ^2 (1) = 7.597, $p < 0.05$ (CR = 2.88; CI 95%: 1.19 – 6.96). Association was significant, $\varphi = 0.172$; $p < 0.05$, with small size effect (Table 2).

Table 1. Mothers´ and fetal factors of diabetic puerperas with early-term and non-early-term delivery (n = 258)

Variables	Early-term delivery		p
	Yes	No	
n, %	163 (63%)	95 (37%)	
GI, weeks	38.0 (37.2–38.2)	39.2 (39.0–40.0)	**< 0.001**
Age, years	31.78 ± 6.45	29.24 ± 6.01	**0.002**
BMI, kg/m^2			
Pre-gestational	33.0 (28.0 – 38.0)	29.5 (26.9 – 33.3)	**0.001**
End of gestation	36.0 (31.2 – 40.0)	33.2 (30.0 – 37.3)	**0.010**
pre-gestational obesity	109 (66.9%)	48 (51.1%)	**0.012**
Diagnosis DM, n (%)			
Pre-gestational	21 (12.9%)	13 (13.7%)	0.854
Gestational	142 (87.1%)	82 (86.3%)	
DM type, n (%)			
Gestational	136 (83.4%)	82 (86.3%)	0.396
Type I	3 (1.8%)	0 (0.0%)	
Type II	24 (14.7%)	13 (13.7%)	
Co-morbidity, n (%)			
Infection of the urinary tract	72 (44.2%)	42 (44.2%)	0.999
Chronic hypertension	27 (16.6%)	12 (12.6%)	0.395
Gestational hypertension	49 (30.1%)	23 (24.2%)	0.312
Insulin therapy	60 (36.8%)	21 (21.1%)	**0.008**
Type of delivery, n (%)			0.376
Caesarean	108 (66.3%)	68 (71.6%)	
Vaginal	55 (33.7%)	27 (28.4%)	
Weight at birth, g	3.449.74 ± 533.33	3.564.92 ± 525.21	0.109
Neonatal glycaemia, mg/dl	55 (48 – 63)	56 (50 – 62)	0.327

Continuous data are given in means ± SD.
Categorical data are given in absolute (n) and relative (%) frequency.
Rates in bold show significance $p < 0.05$.
Abbreviations: Gestational Age (GA); Body Mass Index (BMI); Diabetes Mellitus (DM); Standard deviation (SD).

Table 2. Main neonatal results of diabetic puerperas at full term or non-full term delivery

Variables	Total	Early-term		p[1]	Chance ratio (CR 95%)	Chance Ratio (CR 95%)
		Yes	No		Non-adjusted	Adjusted[2]
n, %[3]	258	163 (63%)	95 (37%)			
Hypoglycemia	40 (15.5%)	33 (20.2%)	7 (7.4%)	**0.006**[4]	3.19 (1.35 – 7.54)	2.88 (1.19 – 6.96)
Respiratory Discomfiture	60 (23.3%)	43 (26.4%)	17 (17.9%)	0.120	1.64 (0.88 – 3.09)	1.52 (0.79 – 2.92)
Macrosomia	52 (20.2%)	28 (17.2%)	24 (25.3%)	0.118	0.61 (0.33 – 1.14)	0.41 (0.20 – 0.81)
Jaundice	17 (6.6%)	13 (8.0%)	4 (4.2%)	0.240	1.97 (0.62 – 6.23)	1.30 (0.39 – 4.37)

[1] Significance of difference between groups by Pearson´s Chi-square test or Fisher´s Exact test.
[2] Logistic Regression adjusted to age, insulin therapy and maternal BMI at the end of gestation.
[3] Data given in absolute (n) and relative (%) frequency.
[4] $\varphi = 0.172$.
Rates in bold show significance at $p < 0.05$Abbreviations: Confidence Interval (CI).

DISCUSSION

There are only few researches on the association between negative health results and the period of term delivery in females with hyperglycemia during pregnancy[6]. The main result of current study was the identification of early-term neonates in females with hyperglycemia during pregnancy who had higher hypoglycemia rates than peers born in non-early term delivery (full or late).

The sample´s characterization revealed a significant difference between obesity groups and insulin therapy, with greater occurrence in early-term delivery group. Such results were expected since both variables are greatly associated with high concentration rates of maternal glycaemia[5,9,22]. In fact, main obstetrics guidelines indicate early delivery to decrease the possibility of intrauterine death[23,24].

Early-term delivery has been associated with high occurrence rates of negative neonatal health outcomes against full- and late-term deliveries in usual risk and in high-risk pregnancies[25–27]. Current findings suggest that the association extends to neonatal hypoglycemia in females with hyperglycemia during pregnancy. Or rather, non-early delivery provides a better chance in the status of health neonatal glycaemia than early-term delivery, due to a lower fetal maturity in early-term delivery. The above data may be an aid in the obstetric decision of elective delivery to provide, when possible, smaller chances of neonatal hypoglycemia.

The American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine (SMFM) recommend, in diabetes-complicated pregnancies, delivery prior to 39 weeks of gestation only in cases featuring pre-gestation diabetes with vascular complications, inadequate control of glucose or previous stillbirth[23]. In fact, elective delivery of premature or early-term pregnancies should be limited to situations where fetal or maternal risks are greater than possible neonatal issues due to insufficient fetal maturity as a whole[28]. Results reinforce the positive influence of non-early-term delivery for the clinical result of important perinatal outcome in females with hyperglycemia in pregnancy: neonatal hypoglycemia.

Neonatal hypoglycemia is a relatively common clinical fact, with a 5–15% occurrence in healthy newborns, of which 50% are asymptomatic[20]. It is actually a highly unfavorable outcome from the point of view of public health due to high morbimortality rates, with serious damage of the central nervous system, such as infarction of the middle brain artery and intra parenchymatose hemorrhages, which, in their turn, cause damage to the cognitive development, convulsions[29], brain paralysis and deafness[30]. However, it is an easily tracked situation with viable treatment[20,21], albeit basic in guidelines for medical care.

Clinical implications of current findings indicate that, in cases of early-term delivery, special care should be provided to neonatal hypoglycemia, with an early detection and treatment to avoid greater damages to children of diabetic mothers.

Limits of current study comprise the fact that generalization should be interpreted with caution due to the inclusion of sample recruited in a single reference center for females with hyperglycemia during pregnancy. Further, participants were not divided according to type of diabetes nor the level of glycaemia control during pregnancy was investigated. It may be recommended that further studies should be undertaken with these factors in view.

CONCLUSION

Newborns of females with hyperglycemia during pregnancy and early-term delivery provides higher occurrences of hypoglycemia than non-early delivery peers, indicating a risk factor of early-term delivery in females with hyperglycemia-complicated pregnancy. Results suggest that obstetric decision on the best moment for elective delivery in females with hyperglycemia should take into account the difference between periods of full term delivery to favor healthy neonatal glycaemia.

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