ORIGINAL RESEARCH

GLYCEMIA IN NEWBORNS OF HYPERTENSIVE MOTHERS ACCORDING TO MATERNAL TREATMENT

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PURPOSE: To evaluate the evolution of glycemic levels in newborns of hypertensive mothers according to maternal treatment.

METHODS: Prospective randomized study, including 93 newborns of mothers treated with isradipine (n = 39), atenolol (n = 40), or low sodium diet (control group – n=14). Glycemia was determined at birth (mother and newborn by the oxidase glucose method) and in the 1st, 3rd, 6th, 12th, and 24th hours after birth (newborn by a test strip method). The evolution of glycemia was analyzed in each group (Friedman test). The groups were compared regarding glycemia (Kruskall-Wallis test), and linear regression models were constructed for the analyses (independent variable = maternal glycemia; dependent variables = umbilical cord, 3rd, and 6th hour glycemia).

RESULTS: There were no statistically significant differences among the mean blood glucose levels of the 3 groups in any of the assessments. There was a correlation between maternal and umbilical cord blood glucose in the isradipine (r = 0.61; *P* <.05) and control (r = 0.84; *P* <.05) groups. Regarding glycemia levels of the mothers and newborns in the third and sixth hours postpartum, this correlation was present only in the control group (maternal x third hour: r = 0.65; *P* <.05; maternal x sixth hour: r = 0.68; *P* <.05). There were no correlations in the atenolol group. Hypoglycemia was detected in 51.3% of the isradipine group, 60% of the atenolol group, and 35.7% of the control group, and it was more frequent in the first hour postpartum in all groups.

CONCLUSIONS: The results suggest a similar effect of the 3 types of treatment upon newborn glycemia. The correlation analysis suggests that isradipine could have effects upon newborn glycemia only after birth (correlation only in umbilical cord blood), whereas atenolol could act earlier (there was no correlation at any moment). The results also point to the need for glycemic control from the first hour postpartum of newborns of hypertensive mothers whether they have or have not undergone treatment with antihypertensive drugs.

KEY WORDS: **Hypertension. Pregnancy. Glycemia. Hypoglycemia.**

Hypertension during gestation may be considered not only a disorder but also a maternal response to an underlying disease. It is usually the first signal of a placental dysfunction, and therefore it may be used as a risk predictor.[1,2]

The elevation of blood pressure in gestation that is a consequence of a pre-existent arterial hypertension or preeclampsia is associated with severe fetal-maternal risks. For the mother, there is the risk of eclampsia, HELLP syndrome with multiple organ failure, cerebral hemorrhage, and death. For the fetus, there is an increasing risk of an intrauterine growth restriction, premature birth, abruptio placenta, and fetal death.[1-3]

However, since antihypertensive treatment may reduce the need for interrupting gestation, fetal maturity may be obtained, with a reduction of neonatal loss as a consequence.[1,4]

There are several drugs that act upon blood pressure control, with different responses. Some exert central action, oth-

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ers alter cardiac output, others affect peripheral vascular resistance, and others inhibit angiotensin-converting enzyme.[1]

Some treatment modalities seem to be favorable, although other drugs have undesirable side effects. Atenolol, a beta-blocker, is a drug used to control the blood pressure levels during gestation, mainly in the patient who has an elevated cardiac output. However, there are reports of abnormalities in the fetal heart rate when this drug is used. The use of beta-blockers in gestation is also associated with hypoglycemia, bradycardia, and hypotension in some newborns.[1,5]

Among the treatment modalities, isradipine is a dihydropyridine calcium antagonist that acts as a calcium channel blocker (classified as a drug that acts upon peripheral vascular resistance). Isradipene has been found to be well-tolerated, free from side effects upon the uteroplacental circulation and the fetal hemodynamics, presenting a low tocolytic effect, reducing blood pressure in non-proteinuric hypertensive women.[6,7,8,9]

Considering these characteristics of isradipine, a study was developed with the aim of evaluating its effects on the evolution of glycemia levels in newborns of pregnant women who have arterial hypertension , comparing it to the use of atenolol and with situations where the blood pressure control was done without using antihypertensive medications.

Test Population and Methodology

Test population

The test population comprised 93 newborns admitted in the Nursery Annex to the Maternity, Neonatal Pediatrics Service, Children's Institute "Prof. Pedro de Alcântara", Faculty of Medicine, University of São Paulo (BAM), from 06/01/1994 to 03/19/1997, who fulfilled the following inclusion criteria:

1) Newborn of a mother with arterial hypertension defined as a diastolic blood pressure (Korotkoff phase 4) equal to or higher than 90 mmHg, measured on the left arm at the heart level, after at least 10 minutes of resting, seated, or in dorsal decubitus position with adequate cuff on 2 occasions at intervals of a minimum of 6 hours;

2) The maternal hypertension diagnosis was specific hypertensive disease of pregnancy (SHDP) or chronic arterial hypertension (CAH) and superimposed SHDP, treated with isradipine, atenolol, or without antihypertensive medication with only a low sodium diet (noting that the pregnant women who received drugs also were prescribed a low sodium diet);

3) The mother had been undergoing the treatment for at least 2 weeks before the delivery (a previous study with pregnant women showed a statistically significant reduction in the blood pressure levels in a week after the beginning of the use of drugs.[10] Also, the group that received only the diet intervention must have been on the low sodium diet for a minimum period of 2 weeks);

4) The newborn was a result of a singleton pregnancy;

5) The pregnant woman had given post-information consent.

Exclusion criteria:

1) The mother had a previous fetal loss, especially without explanation;

2) The mother had another pathology, such as cardiopathy, hepatopathy, hemopathy, diabetes, or pneumopathy;

3) The mother had been taking other medications that could interfere with the metabolism of carbohydrates in the newborn.

The study was approved by the Ethics Committee in Research of the Institution.

Methodology

This was a randomized, longitudinal, prospective study comparing 3 groups of patients according to the type of maternal treatment:

Group 1: 39 newborns of hypertensive mothers treated with isradipine (5 mg twice a day);

Group 2: 40 newborns of hypertensive mothers treated with atenolol (50 mg twice a day);

Control group: 14 newborns of mothers whose hypertension was controlled with diet only.

Study Design

All newborns included in the study were evaluated at birth through the use of the Apgar score at the first and fifth minutes postpartum, and birth weight in relationship to gestational age was evaluated according to Ramos intrauterine growth curve.[11]

Glycemia was determined at birth in the mother and in the newborn (through venous blood assessment of the umbilical cord) and then successively in the newborn in the 1st, 3rd, 6th, 12th, and 24th hours postpartum. Immediately after collection, the blood sample was sent to the laboratory for analysis.

The glucose oxidase method was used for the maternal and newborn glycemias at birth, and the Dextrostix® strip method test (analyzed by the same Glucometer® machine throughout the study) for the 1st, 3rd, 6th, 12th, and 24th hour samples from the newborn.

The newborns were preferentially breastfed, and in cases where this was not possible, were fed with a formula for term newborns after the first 6 hours postpartum.

Hypoglycemia was considered to be blood glycemia values less than 40 mg/dL.

Statistical analysis

The 3 groups were analyzed among themselves, at every time point of assessment by analysis of variance (ANOVA), in which the Kruskal-Wallis test (one-way ANOVA test) was used. The evolution of glycemic levels was evaluated by

the Friedman repeated measure test (one-way ANOVA test) in each group.

Linear regression models were constructed for the glycemic concentrations, considering maternal glycemia as an independent variable; dependent variables were the glycemias of the umbilical cord and of the newborn in the third and sixth hours postpartum.

Fisher's exact test was used for comparing the proportions.

The significance level was set as $P < 05$.

RESULTS

Ninety-three newborns that fulfilled the inclusion criteria were included in the study. However, only the newborns with usable test results were included in the statistical evaluation.

There was no difference among the groups regarding gestational age, weight, classification, Apgar, sex, color, and type of delivery. (Table 1)

Differences related to the glycemic levels of the mother and the newborn were not observed among the groups, and there were no differences among the glycemic levels regarding any of the determinations at any time point for any group as shown in Table 2.

Figure 1 shows the evolution of glycemic levels with time in each group.

Figures 2 and 3 show the correlation between the maternal and umbilical cord glycemias in the isradipine group and in the control group respectively.

The glycemic values in each group according to the assessment time point are listed in Table 3.

The hypoglycemic episodes that occurred during the first 24 hours postpartum are shown in Figure 4, and the distribution of these episodes per group is shown in Figure 5.

Figure 6 shows the number of newborns with hypoglycemia in each of the groups.

DISCUSSION

Several cardiovascular and hematologic effects due to the use of

Table 1 - Characteristics of the newborn.

	Isradipine	Atenolol	Control	Test (Kuskal-Wallis)
GESTATIONAL AGE	n = 39	n = 40	n = 14	$\chi^2_2 = 1.79$
μ (weeks/days) ± sd(days)	37/3 ± 13.2	37/3 ± 15.2	38/6 ± 13.6	(ns)
WEIGHT	n = 39	n = 40	n = 14	$\chi^2_2 = 3.78$
μ(kg) ± sd	2.91 ± 0.7	2.63 ± 0.6	2.97 ± 0.6	(ns)
CLASSIFICATION	n = 39	n = 40	n = 13	$\chi^2_2 = 0.71$
AIG - n (%)	33 (84.6)	31 (77.5)	12 (85.7)	(ns)
PIG -n (%)	3 (7.7)	8 (20)	2 (14.3)	
GIG -n (%)	3 (7.7)	1 (2.5)	0	
μ ± sd	13.0 ± 17.3	13.3 ± 15.7	4.7 ± 6.4	
APGAR first. MINUTE	n = 36	n = 40	n = 14	$\chi^2_2 = 1.00$
0-3 - n (%)	2 (5.6)	2 (5.0)	-	(ns)
4-6 - n (%)	1 (2.8)	2 (5.0)	2 (14.3)	
7-10 - n (%)	33 (91.7)	36 (90.0)	12 (85.7)	
μ ± sd	7.8 ± 1.8	8.0 ± 1.6	7.9 (± 1.4)	
APGAR fifth. MINUTE	n = 39	n = 40	n = 14	$\chi^2_2 = 2.25$
7 - n (%)	-	1 (2.5)	-	(ns)
8 - n (%)	2 (5.1)	3 (7.5)	-	
9 - n (%)	30 (76.9)	23 (57.5)	10 (71.4)	
10 - n (%)	7 (17.9)	13 (32.5)	4 (28.6)	
μ ± sd	9.1 ± 0.5	9.2 ± 0.7	9.3 ± 0.5	
SEX	n = 39	n = 40	n = 14	$\chi^2_2 = 0.10$
Male-n (%)	21 (53.8)	22 (55.0)	7 (50.0)	(ns)
Female-n (%)	18 (46.2)	18 (45.0)	7 (50.0)	
COLOR	n = 39	n = 39	n = 14	(white vs black
White-n (%)	10 (25.6)	14 (35.9)	7 (50.0)	+ dark)
Black-n (%)	6 (15.4)	6 (15.4)	1 (7.1)	$\chi^2_2 = 2.88$
Dark-n (%)	23 (59.0)	19 (48.7)	6 (42.9)	(ns)
TYPE OF DELIVERY	n = 39	n = 40	n = 14	(normal ±
Cesarean-n (%)	28 (71.8)	30 (75.0)	8 (57.1)	forceps vs
Forceps-n (%)	5 (12.8)	4 (10.0)	2 (14.3)	cesarean)
Normal-n (%)	6 (15.4)	6 (15.0)	4 (28.6)	$\chi^2_2 = 1.63$ (ns)

Table 2 - Maternal and newborn glycemic levels (mg/dL).

	Isradipine	Atenolol	Control	Test (Kruskal-Wallis)
Maternal glycemia	n = 37	n = 33	n = 13	$\chi^2_2 = 0.95$
μ ± sd	104.1 ± 42.2	110.9 ± 43.2	114.0 ± 33.8	(ns)
Umbilical Cord glycemia	n = 38	n = 38	n = 12	$\chi^2_2 = 4.01$
μ ± sd	80.5 ± 32.3	78.9 ± 30.7	97.4 ± 31.7	(ns)
Glycemia 1st h (newborn)	n = 35	n = 36	n = 9	$\chi^2_2 = 1.47$
μ ± sd	45.0 ± 23.1	37.6 ± 13.3	53.9 ± 18.0	(ns)
Glycemia 3rd h (newborn)	n = 36	n = 37	n = 11	$\chi^2_2 = 2.95$
μ ± sd	56.0 ± 24.8	53.4 ± 22.7	68.5 ± 39.6	(ns)
Glycemia 6th h (newborn)	n = 34	n = 36	n = 13	$\chi^2_2 = 1.86$
μ ± sd	58.8 ± 25.2	55.9 ± 22.3	52.0 ± 15.8	(ns)
Glycemia 12th h (newborn)	n = 37	n = 39	n = 12	$\chi^2_2 = 2.19$
μ ± sd	61.4 ± 24.9	55.7 ± 22.8	53.3 ± 18.1	(ns)
Glycemia 24th h (newborn)	n = 36	n = 38	n = 14	$\chi^2_2 = 1.65$
μ ± sd	64.0 ± 19.7	66.6 ± 22.4	53.1 ± 14.1	(ns)
Friedman Test	$\chi^2_5 = 25.51$ (P <.001)	$\chi^2_5 = 48.40$ (P <.001)	$\chi^2_5 = 18.89$ (P <.01)	

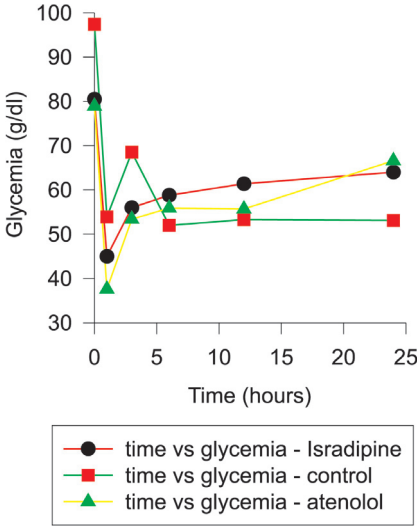


Figure 1 - Evolution of glycemia during the study.

isradipine have been published in the medical literature.[12,13,14,15,16] The drug has been shown to have a good antihypertensive effect in patients who have nonproteinuric hypertension during gestation without modifying placental circulation,[6,7,8,9] and its efficiency and good tolerance in patients who have essential hypertension has been demonstrated.[17] However, concerns about the effects on the fetus have been raised, since isradipine can pass through the placenta, although the concentration has been found to be low in the fetus.[18] Despite these concerns, calcium channel blockers have been described as safe drugs and free of side effects to the fetus when used during gestation to control arterial hypertension.[1,19] But data is scarce concerning the possible hypoglycemic effect on the fetus of isradipine, a new generation calcium channel blocker.

The present study demonstrates that all treatments were safe regarding the evolution of glycemic levels, since there was no difference between the treated and the control groups for any assessment (Table 2).

As for the glycemia evolution with time in each study group, a statistically significant difference was verified among the groups at several times of glycemic determination (isradipine: *P*

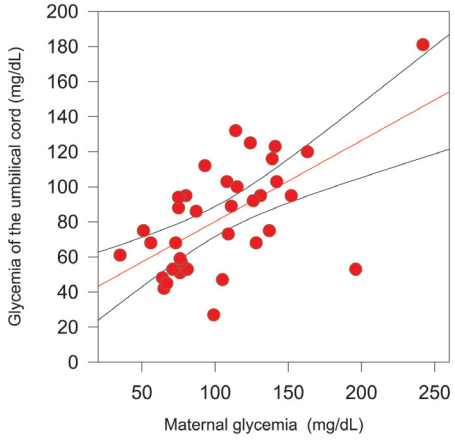


Figure 2 - Correlation between maternal and the umbilical cord glycemia in the isradipine group.

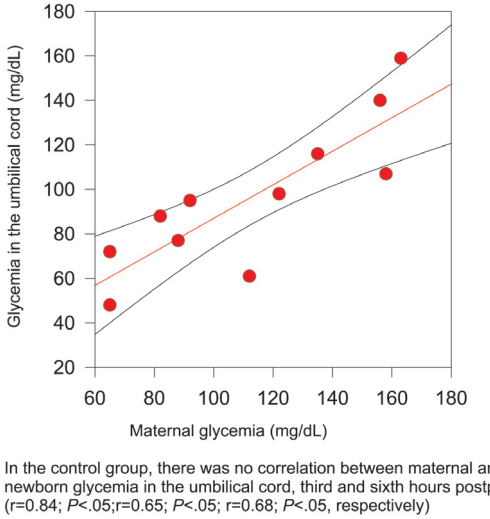
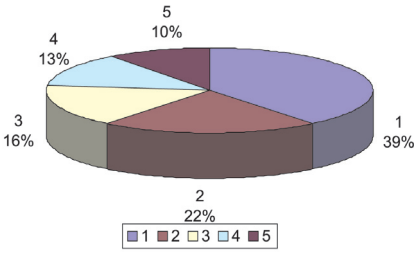


Figure 3 - Correlation between maternal and the umbilical cord glycemia in the control group.

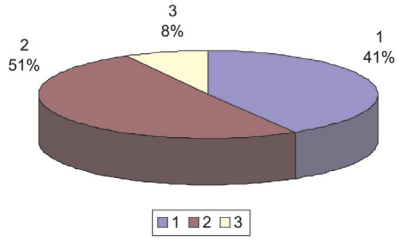
Table 3 - Hypoglycemia episodes in each of the groups, according to the assessment time point.

	1st hour	3rd hour	6th hour	12nd hour	24th hour	Total
ISRADIPINE	15	8	5	3	5	36
ATENOLOL	17	10	8	6	3	44
CONTROL	2	1	1	2	1	7
Total	34	19	14	11	9	87



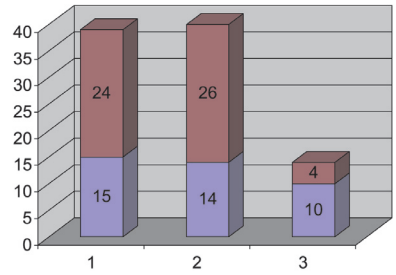
1- 1st hour postpartum (34 episodes)
2- 3rd hour postpartum (19 episodes)
3- 6th hour postpartum (14 episodes)
4- 12th hour postpartum (11 episodes)
5- 24th hour postpartum (9 episodes)
Total = 87 hypoglycemic episodes in the 3 groups

Figure 4 - Hypoglycemic episodes according to lifetime.



1- Isradipine group: 36 hypoglycemic episodes
2- Atenolol group: 44 hypoglycemic episodes
3- Control group: 7 hypoglycemic episodes
Total = 87 hypoglycemic episodes in the 3 groups

Figure 5 - Hypoglycemic episodes distributions per groups.



1- Isradipine (n = 39): 24 newborns (61.5%)
2- Atenolol group (n = 40): 26 newborns (65%)
3- Control group (n = 14): 4 newborns (28.5%)
Total: 54 out of 93 newborns had hypoglycemia

Hypoglycemia occurrence in the groups:
- Isradipine x Atenolol: $P = .818$
- Isradipine x Control: $P = .060$
- Atenolol x Control: $P < .05$

Figure 6 - Number of newborns with hypoglycemia in each one of the groups.

<.001; atenolol: P <.001; control; P <.01; Table 2). This finding is to be expected, beginning with the difference observed between the maternal glycemia and the umbilical cord, since fetal plasma glucose levels at birth have been reported to be two thirds of maternal levels.[20]

Moreover, the evolution of glycemic levels during the consecutive time points of this study in each group is consistent with the published data, which show a reduction of the plasma glucose concentration after birth, reaching a nadir around 1 hour postpartum followed by elevation and stabilizing of levels between 2 and 4 hours after birth,[20,21] as it may be observed on Table 2 and in Figure 1. The 3 groups presented similar patterns, having no significant differences among themselves at each time point of the assessments (Table 2).

In 1992, Kalhan[20] referred to a linear relationship between maternal and fetal glycemia, which is also evident in the present study, since there was correlation between maternal and umbilical cord glycemias in the isradipine and control groups (Figures 2 and 3). In the control group, there was also a correlation between glycemia levels in the mother and in the newborn at the third and sixth hours postpartum, suggesting that there is a tendency for maintaining the glycemia at normal levels for a longer time, in spite of the drop during the first hours postpartum. This finding differs from that of the isradipine group, where a correlation of glycemia levels was found only between the maternal and umbilical cord blood. In the atenolol group, there was no correlation of glycemia levels at any time between the mother and newborn. This finding may suggest that atenolol has an earlier effect upon newborn glycemia than isradipine does.

This observation, associated with the presence of correlation at all time points of assessment in the control group, suggests that isradipine may have an early effect upon newborn glycemia, although a bit later than that of atenolol.

The observation of more frequent hypoglycemic episodes in the first and third hours postpartum in all groups (Figure 4, Table 3), agrees with the well-known evolution of the glycemic levels of the newborn during the first hours after birth.[20]

There were more hypoglycemic episodes in newborns of the atenolol group than in the isradipine group, although this was not statistically significant (P = .818). However, the occurrence of hypoglycemia was significantly higher in the atenolol group compared with the control group, which indicates its effects upon the newborn glycemia. As for the isradipine group compared with the control group, there was a trend of the occurrence of hypoglycemia, suggesting a mild effect upon the newborn glycemia (Figures 5 and 6).

The occurrence of hypoglycemia also in newborns of mothers whose hypertension was controlled with diet only is consistent with the knowledge of the effects of hypertensive disease on the fetal glycemia. These effects include the reduction of uteroplacental circulation, resulting in hypoxemia that stimulates hormonal and circulatory effects with the redistribution of the fetal blood flow and stimulation of glycolysis (Pasteur effect), resulting in an increase of triphosphate adenosine (ATP) and lactic acid, in addition to causing hypoglycemia.[2] Besides that, data that suggest a similarity between

specific hypertensive disease of pregnancy and the resistance to insulin syndrome are increasing in the medical literature: hyperinsulinemia, low levels of high density lipoproteins (HDL) and elevated levels of triglyceride.[23]

After the analysis of these results, some conclusions and consequent recommendations could be made:

- Different antihypertensive treatment schemes used in pregnant women (diet, isradipine, and atenolol) have similar effects upon mean values of glycemia in the newborn;
- The correlation analysis suggests that isradipine may have later and milder effects upon the glycemia, since the correlation was obtained only in umbilical cord, while atenolol may act earlier, since there was no correlation in any time point;
- The results reinforce the need for glycemic control from the first hour postpartum in newborns of hypertensive mothers whether or not they are undergoing drug treatment.

RESUMO

DARCIE S e col. Glicemia no recém-nascido de mãe hipertensa de acordo com a terapêutica materna. **Rev. Hosp. Clín. Fac. Med. S. Paulo 59**(5):244-250, 2004.

OBJETIVO: Avaliar o comportamento da glicemia em recém-nascidos (RN) de mães hipertensas conforme o tratamento materno.

MÉTODOS: Estudo prospectivo, randomizado, incluindo 93 RN de mães tratadas com isradipina(n=39), atenolol (n=40) ou dieta - controle (n=14). Determinou-se a glicemia ao nascimento (mãe e RN, pela glicose oxidase) e na 1ª., 3ª., 6ª., 12ª. e 24ª. horas (RN, por fita reagente). A evolução da glicemia, em cada grupo, foi analisada (Teste de Friedman). Os grupos foram comparados, quanto às glicemias, em cada momento (Teste de Kruskall-Wallis) e foram ajustados modelos de regressão linear para as glicemias (variável independente = glicemia materna; variáveis dependentes = glicemias de cordão, 3ª. e 6ª. horas).

RESULTADOS: Não houve diferença estatisticamente significante entre as glicemias médias dos 3 grupos, em qualquer uma das coletas. Houve correlação entre as glicemias materna e de cordão umbilical nos grupos isradipina ($r = 0,61$; $p<0,05$) e controle ($r = 0,84$; $p<0,05$); entre as glicemias materna e 3ª. e 6ª. horas, houve apenas no grupo controle (materna X 3ª.hora: $r = 0,65$; $p<0,05$; materna X 6a.hora: $r = 0,68$; $p<0,05$). Não houve correlação em nenhum momento no grupo atenolol. Detectou-se hipoglicemia em 51,3% (Isradipina), 60% (Atenolol) e 35,7% (Controle), mais freqüentemente na 1ª. hora de vida, em todos os grupos.

CONCLUSÕES: Os resultados sugerem efeito semelhante dos 3 tipos de terapêutica sobre a glicemia do RN. As análises de correlação sugerem que a isradipina possa ter efeitos sobre a glicemia somente após o nascimento (correlação apenas em cordão umbilical), enquanto o atenolol, possa atuar mais precocemente (não se correlacionou em nenhum momento). Também reforçam a necessidade de controle glicêmico desde a 1ª. hora de vida em RN de mães hipertensas, submetidas ou não a tratamento medicamentoso.

UNITERMOS: **Hipertensão. Gestação. Glicemia. Hipoglicemia.**

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