Original Article

Clinical conditions and metabolic profile of preterm newborns from birth to six months of corrected age

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RESUMO

The survival of preterm newborns and low weight has shown the metabolic changes throughout their lives. The objective is to correlate if the clinical conditions of the preterm newborn (PTNB) at birth, during admission and after discharge from the Neonatal Intensive Care Unit, influence their metabolic profile at six months of Corrected Age. It is a prospective cohort study with 37 PTNB. The statistical analysis was descriptive and inferential. When correlating the clinical conditions at birth, during admission and at follow-up with the PTNB metabolic profile, the necrotizing enterocolitis (p=0.006) and late sepsis (p= 0.02) presented a significant statistical difference in the insulin concentration. The glycemic profile in the presence of comorbidities stayed normal and the lipidic profile gradually increased. The PTNB of this study constitutes a group at risk for the development of metabolic syndrome and cardiovascular diseases, due to lipidic and insulin changes found.

Descriptors: Infant, Premature; Pediatric Nursing; Intensive Care Units, Neonatal; Continuity of Patient Care; Metabolic Syndrome.

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INTRODUCTION

Worldwide, 15 million babies are prematurely born per year; Brazil appears in the 10th position with 279,000 premature births annually. From 2011 to 2012, the Brazilian rate of premature births was 11.5%, varying from 10.4% to 13% between the different regions of the country. In the South region, the location of the city where this study was developed, premature births comprehend 11.2% of total births[1]. Resulting from the percentage of premature births, there is the survival increment of Preterm Newborns (PTNB) with increasingly lower Gestational Age (GA) and lower weight at birth.

Additionally, prematurity brings consequence to families and society in general, due to the social and financial cost that is difficult to measure, as well as, having repercussions for the child's health both at admission in the Neonatal Intensive Care Unit (NICU) and throughout his life after hospital discharge.

The PTNB suffers the influence of intrauterine maternal nutritional and metabolic factors, the clinical conditions during the gestational period and, at birth starts to be affected by actions of the extrauterine environment in their physiological and emotional behavior. During the post-natal period, the baby is subjected to many complications, including what has been studied in the last decades, the association between prematurity and the development of diseases as hypertension, glucose intolerance, and dyslipidemias during childhood, adolescence and also adulthood[2].

Evidence point that the relationship of the premature birth and weight gain of children in the first weeks is directly associated to the increase of childhood overweight and obesity from five years of age, as well as, changes in blood pressure, plasmatic insulin, and leptin in adolescents[3-4]. However, studies that correlate the clinical conditions and the metabolic profile of PTNB at birth and during follow-up after hospital discharge in Brazil are still a scientific literature gap.

Considering that Brazil faces an epidemiological transition period, including the increase of non-communicable chronic disease which require lengthy treatments[5] and, consequently, with the increase in illness and mortality of the population; it becomes necessary to conduct research to identify in populations at risk, for example, the preterm and low weight baby, factors that can be markers for non-communicable chronic diseases. Thus, contributing to the reduction in the number of adults with chronic health conditions that impact the family and individual health, as well as the health system. The nurse, as a member of both the multi-professional team in the accompaniment ambulatories and the primary health attention, can contribute to this assessment during the nursing appointments of PTNB in the follow-up after hospital discharge.

Therefore, it is questioned if the clinical conditions of the PTNB at birth can influence the metabolic condition at six months of Corrected Age (CA), during admission and after discharge from NICU. Therefore, the objective is to establish the relationship of clinical conditions of the PTNB at birth, during admission and, after NICU discharge with the metabolic profile at six months of corrected age.

METHODS

A prospective cohort study, part of the research project "Prematurity repercussions: maternal stress and metabolic programming", approved in the Universal Notice 014/2014, CNPq. It was conducted from June 2015 to August 2016 in the NICU of a university hospital of Paraná and the follow-up outpatient clinic of the referred hospital.

The Ethics Committee of the State University of the West of Paraná (CEP – UNIOESTE) assessed the present study, approved in the protocol nº 385.370 respecting the resolution 466/2012 ruling the Research with Human Beings.

All PTNB who were admitted in the NICU from June 2015 to March 2016 and who returned for the follow-up in the high-risk outpatient clinic until August 2016 composed the population. They met the inclusion criteria: to be premature up to 36 weeks and six days of gestational age; without congenital anomalies. Those who died during the admission or follow-up period or who did not come to the return consultation in the ambulatory were excluded. Thus, 37 PTNB composed the study sample.

The recruitment of participants was done with the puerperal woman in the maternity, who was contacted between 24 to 48 hours after delivery by one of the researchers, explaining about the study. With the acceptance to participate and signature of the Free and Informed Consent Term, the collection of documental data and samples of the biochemical material was started. This material was obtained from the leftovers of the blood samples of the routine collections from the obstetric center unit (mother) and NICU (PTNB). The NICU nurse scheduled the return of PTNB in the outpatient clinic in the discharge from the unit. The appointment was conducted by the research team at the six months of CA, contemplating the mother's interview and the PTNB's clinical assessment, with sample collections of the material to conduct biochemical exams from this period.

The biochemical exams obtained at birth, discharge from NICU, and follow-up outpatient clinic were insulin, glucose, total cholesterol and plasmatic triglycerides. The dry chemistry method was used to read the exams, by the quantitative measurement of its concentration in the serum using the Chemical Systems VITROS 250/350/950/5,1 FS and 4600 and the Integrated system VITROS 5600 (s/d). The insulin dosages were conducted using the electrochemiluminescence method and presented in international units (uUI/mL).

The analyzed variables referred to three moments:

- **Birth***:* weight, Gestational Age (GA), gender, weight at birth and GA relationship, lipidic, glycemic and insulin profiles.

The classification regarding the prematurity level refers to less than 28 weeks of GA (extreme prematurity); from 28 to 31 weeks (very premature) and 32 to 36 weeks and six days (moderate and late premature) [6]. To classify the adequacy of weight at birth, the Fenton and Kim curve was used[7], specific for the premature population, classifying them as: Small for Gestational Age (SGA – those below the 10th percentile), Large for Gestational Age (LGA – those above the 90th percentile) and Adequate for Gestational Age (AGA – between the 10th and 90th percentiles).

- **Hospital discharge***:* Lipidic, glycemic and insulin profiles and the comorbidities in the NICU admission period.
- **Six months of CA:** Lipidic, glycemic and insulin profiles and comorbidities presented after hospital discharge, obtained by the medical diagnosis.

The analyzed comorbidities referred to: respiratory distress syndrome, early and late sepsis, necrotizing enterocolitis (NEC), periventricular hemorrhage, leukomalacia, ventriculomegaly, Bronchopulmonary dysplasia (BPD) and Retinopathy of Prematurity (ROP). The treatments during admission were the use of oxygen therapy, blood transfusion and laser treatment for retinopathy of prematurity.

There are no specific reference values for PTNB for the biochemical exams analyzed in this study. Therefore, the results of the plasmatic parameters for glucose, cholesterol, and triglycerides were compared to the reference data of the Brazilian Diabetes Society[8] and the Brazilian Consensus for the normalization of the laboratory determination of the lipidic profile[9]. The insulin values were based on the reference of the laboratory where the exam was processed.

The data were entered in the program Microsoft Excel for Windows 2010 in duplicity. The descriptive statistical analysis was used to characterize the sample and the metabolic profile using absolute and relative frequencies, mean and standard deviation. Inferential statistics were applied to correlate the clinical variables of the PTNB and their metabolic profile where the distribution pattern of residuals was conducted using the Shapiro-Wilk's test, and the homogeneity of the variances was assessed using the Cochran's test. Once the data met such assumptions, the factorial ANOVA test for repeated measures was applied, followed by the LSD-Fisher's test. All analyses were conducted in the statistical program STATISTICA 7.0®.

Analyses could not be performed for the comorbidities: respiratory distress syndrome, severe leukomalacia, ventriculomegaly, because of an insufficient number of patients with or without the diseases or treatment use.

RESULTS

During the study period 47 PTNB were born. Eight died in the early neonatal period and two in the late neonatal period, so, they were excluded from the present study. The final sample was composed of 37 PTNB followed from birth until six months of CA in the outpatient clinic. The sample characterization is presented for birth variables, corresponding to gender, weight, weight at birth/GA relationship and GA (Table 1).

Table 1: Characteristics of PTNB accompanied regarding their birth data (n=37). Cascavel, PR, Brazil. 2016.

Variables	AF	RF (%)
Gender		
Male	18	48.60%
Female	19	51.30%
Weight		
≤ 1,000g	4	10.80%
1,000 to 1,499g	15	40.50%
1,500 to ≥ 2,500g	18	48.60%
Weight/GA ratio		
Small for Gestational Age	4	10.80%
Adequate for Gestational Age	32	86.50%
Large for Gestational Age	1	2.0%
GA		
< 28 weeks	4	10.80%
28-31 weeks	15	40.50%
32-36 weeks	18	48.60%

Footnotes: AF: Absolute Frequency; RF: Relative Frequency; GA: Gestational Age

The PTNB did not have a sex predominance, being balanced between females (N=19/51.3%) and males (n=18/48.6%), and in its majority weighting less than 1,500 grams at birth (n=19/51.3%) and most being (n=32/86.5%) classified as AGA regarding the adequacy of weight at birth, that is, above the 10th percentile of the reference curve. About the GA, 18 (48.6%) were very premature, with mean GA at birth of 31 (±5.8) weeks. The

admission time meets the classification of the prematurity level found, once the mean admission time of 21 (±14.6) days agrees with very premature and moderate premature PTNB (Table 1).

Table 2 presented the main identified comorbidities and treatments during admission.

Table 2: Description of comorbidities and treatments during PTNB admission in the NICU (n=37). Cascavel, PR, Brazil. 2016

Variables	AF	RF(%)
Necrotizing enterocolitis		
Yes	8	21.60%
No	29	78.40%
Respiratory distress syndrome		
Yes	36	97.30%
No	1	2.70%
Periventricular hemorrhage		
Yes	2	5.40%
No	35	94.60%
Early sepsis		
Yes	27	72.90%
No	10	27.00%
Late sepsis		
Yes	16	43.20%
No	21	56.70%
Retinopathy of prematurity (ROP)		
Yes	6	16.20%
No	31	83.80%
ROP laser treatment		
Yes	1	2.70%
No	36	97.30%
Bronchopulmonary dysplasia		
Yes	6	16.20%
No	31	83.80%
O_2 dependence at discharge		
Yes	11	29.70%
No	26	70.30%

Footnotes: AF: Absolute Frequency; RF: Relative Frequency; GA: Gestational Age

The main comorbidities during the admission period were the respiratory syndrome distress (n=36/97.3%), early sepsis (n=27/72.9%), late sepsis (n=16/43.2%). Within the treatments to which PTNB was submitted, the oxygen therapy at NICU discharge prevailed (n=11/29.7%) (Table 2).

In Table 3, the metabolic profile through the plasmatic parameters for total cholesterol, triglycerides, insulin and glucose from birth to six months of CA of the PTNB are presented.

The metabolic profile of the studied PTNB shows that glycemia was stable at admission to NICU until six months of CA without a significant statistical difference (p=0.639). However, as seen in Table 3, the 5epidic (p=<0.0001) and insulin profile (p=0.048) presented significant statistical difference for the periods assessed. The insulin presented reduction at birth until the sixth month of CA. In the 5epidic profile, both the total cholesterol and triglyceride demonstrated a gradual increase from admission to six months of CA.

Additionally, in the description of the studied sample in the three assessment periods, the majority of PTNB presented insulin concentration according to the reference values. About the glycemic profile, despite 15 newborns (40.5%) had hypoglycemia at NICU admission, these values increased throughout the follow-up, and at

NICU discharge, 17 (46.0%) and at six months of CA, most preterm babies (28/76.0%) had a normal glycemic index. Regarding the 6epidic profile, both at admission and discharge of NICU, a significant part of PTNB had adequate values of triglycerides and total cholesterol. At six months of CA, 20 (54.0%) of PTNB presented an increase in the serum levels of triglycerides, most with levels of ≥130 mg/dl, characterizing triglyceridemia. The cholesterol, therefore, stayed at normal levels for most PTNB (n=23/62.0%).

Table 3: Plasmatic parameters of the lipidic, glycemic and insulin profiles of PTNB at birth, discharge and at six months of Corrected Age (n=37). Cascavel, PR, Brazil. 2016.

Variables	Mean (SD)	Min-Max	p-value
Glycemia (mg/dL)			
Admission	83.11 (±8.20)	20-285	
Discharge	80.25 (±4.62)	20-164	0.639
6 months	87.53 (±2.41)	64-132	
Triglycerides (mg/dL)			
Admission	45.36 (±4.72)[a]	16-139	
Discharge	87.17 (+6.0)[b]	34-178	<0.0001
6 months	153.7 (+13.2)[c]	46-338	
Total Cholesterol (mg/dL)			
Admission	77.97 (±4.13)[c]	25-130	
Discharge	114.83 (±5.8)[b]	64-215	<0.0001
6 months	136.94 (±5.7)[a]	83-240	
Insulin (uIU/mL)			
Admission	11.1 (+2.5)[b]	0.81-83	
Discharge	7.0 (+1.45)[ab]	0.36-45	0.048
6 months	5.0 (±0.66)[a]	1.2-16	

Footnotes:

- **SD**: Standard Deviation
- * When the means were statistically different in the three assessment periods, analyzed through the ANOVA test represented in the table by the junction of the letters ab;
- ** When there was no statistical difference between the means verified by the variance test (ANOVA) in the three assessment periods, considering the SD, represented in the table by the letters a;b= b or c, alone.
- **Used reference values:** Glycemia 80-126mg/dL (postprandial); Triglycerides <85mg/dL (no fasting); Total Cholesterol <170mg/dL (no fasting) ; Insulin 2.6 to 24.9 uUI/mL.

The correlation of variables about the comorbidities presented by the PTNB and their biochemical profile during the follow-up are presented in Table 4.

Only the insulin presented a significant statistical difference in the presence of the morbidities NEC (p= 0.006) and late sepsis (p= 0.02), in the assessed periods (Table 4). For the PTNB who developed NEC, the insulin had higher mean at NICU admission (21.6 ± 26.8). Similarly, in the correlation with late sepsis, the high levels of serum insulin at admission (17.6 ± 19.7) decreased to very low values at the following moments. About the presence of ROP, BPD and early sepsis, the insulin values were stable with a decrease since admission (Table 4).

The treatments to which PTNB were submitted and the biochemical profile are described in Table 5.

The blood transfusion and use of oxygen did not influence the lipidic, glycemic and insulin profiles of PTNB (p= >0.05). When analyzing the glucose values alone, they presented stability in all periods studied, independently of the treatment used. The insulin values decreased at the admission moment, and they were stable from the discharge until the sixth month (Table 5).

Triglycerides and cholesterol levels tend to increase over time in the two groups of patients, that is, among those who did and did not receive the treatments, as well as, in the presence or not of comorbidities (Table 4 and 5).

Table 4: Descriptive statistics (mean ± standard deviation) and correlation of the 7epidic, glycemic and insulin profiles related to the comorbidities NEC, ROP, early and late sepsis, and BPD during admission, discharge and at six months of PTNB (n=37). Cascavel, PR, Brazil. 2016

	NEC	Glucose	Triglycerides	Total Cholesterol	Insulin
Admission	Yes	103.4±85.5	43.4±39.9^{a}	76.8±26.2^{b}	21.6±26.8^{b}
	No	77.3±33.0	46.0±25.0^{a}	78.3±24.8^{b}	8.1±7.8^{a}
Discharge	Yes	79.1±25.9	80.2±29.7^{ab}	106.1±27.0^{a}	4.4±3.5^{a}
	No	80.6±28.6	89.1±37.9^{b}	117.3±37.2^{a}	7.8± .6^{a}
6 months	Yes	94.5±9.8	138.4±85.1^{c}	117.2±20.6^{ac}	4.1±2.2^{a}
	No	85.5±12.3	158.1±78.5^{c}	142.6±35.6^{c}	5.2±4.4^{a}
	Early sepsis	**Glucose**	**Triglycerides**	**Total Cholesterol**	**Insulin**
Admission	Yes	79.6±39.1	46.0±29.8^{a}	72.3±19.4^{b}	9.4±9.6^{ab}
	No	93.5±73.9	43.5±24.7^{a}	94.9±32.1^{ab}	16.1±25.3^{b}
Discharge	Yes	83.5±24.6	89.9±38.0^{a}	113.7±37.5^{a}	7.3±9.4^{a}
	No	70.3±35.3	79.0±29.9^{ab}	118.1±28.5^{ac}	6.0±6.4^{a}
6 months	Yes	86.1±12.0	151.7±81.8^{c}	133.8±36.2^{cd}	5.5±4.2^{a}
	No	91.9±20.5	159.8±75.0^{c}	146.4±27.2^{d}	3.6±2.8^{a}
	Late sepsis	**Glucose**	**Triglycerides**	**Total Cholesterol**	**Insulin**
Admission	Yes	88.7±64.2	49.9±28.5^{ab}	77.9±23.0^{a}	17.6±19.7^{b}
	No	78.6±4.0	41.7±28.3^{a}	78.0±26.7^{a}	5.8±6.4^{a}
Discharge	Yes	81.0±33.6	90.2±38.4^{c}	106.3±37.8^{b}	7.9±11.6^{a}
	No	79.7±22.8	84.7±34.9^{bc}	121.6±32.2^{bc}	6.3±5.6^{a}
6 months	Yes	86.0±18.2	170.0± 0.5^{d}	132.4±25.4^{cd}	4.5±3.3^{a}
	No	88.8±10.9	140.6±68.4^{d}	140.5±40.2^{d}	5.3±4.5^{a}
	BPD	**Glucose**	**Triglycerides**	**Total Cholesterol**	**Insulin**
Admission	Yes	75.2±36.4	72.3±30.4^{ac}	66.0±12.1^{c}	10.7±9.8^{ab}
	No	84.7±51.7	40.0±25.0^{c}	80.4±26.0^{c}	11.2±16.0^{b}
Discharge	Yes	91.8±43.2	122.2±46.0^{ab}	113.5±55.1^{ab}	12.6±16.9^{ab}
	No	78.0±24.0	80.2±30.0^{a}	115.1±31.0^{a}	5.9±5.9^{ab}
6 months	Yes	77.2±10.0	177.0±93.6^{b}	142.2±28.1^{ab}	3.3±2.7^{ab}
	No	89.6±14.4	149.0±77.0^{b}	136.0±35.7^{b}	5.3±4.1^{a}
	ROP	**Glucose**	**Triglycerides**	**Total Cholesterol**	**Insulin**
Admission	Yes	80.2±49.9	44.2±27.4^{a}	80.6±26.2^{b}	10.9±16.0^{b}
	No	97.8±47.2	51.2±34.8^{ab}	64.8±7.4^{b}	12.0±9.0^{ab}
Discharge	Yes	78.0±24.7	82.1±29.6^{bc}	114.4±31.4^{c}	6.2±6.0^{ab}
	No	91.3±40.7	112.5±55.7^{cd}	117.2±54.0^{ac}	11.3±17.1^{ab}
6 months	Yes	88.6±15.0	146.4±74.3^{de}	135.6±35.2^{a}	4.9±4.0^{a}
	No	82.3±11.2	190.2±99.8^{e}	143.7±31.2^{a}	5.5±4.5^{ab}

Footnotes:

- NEC – Necrotizing enterocolitis;
- ROP – Retinopathy of prematurity;
- BPD – Bronchopulmonary dysplasia.
- * When the means were statistically different in the three analyzed periods, obtained through the ANOVA test and represented in the table by the combination of letters ab; bc; cd; de;
- ** When there was no statistically significant difference between the means in the three analyzed periods, verified by the test of variance (ANOVA) and represented in the table by the letters a; b; c; d; e, alone.
- **Used reference values:** Glycemia 80-126mg/dL (postprandial); Triglycerides <85mg/dL (no fasting); Total Cholesterol <170mg/dL (no fasting) ; Insulin 2.6 to 24.9 uUI/mL.

Table 5: Descriptive statistics (mean ± standard deviation) of the variables related to oxygen at discharge and blood transfusion at admission, discharge and at six months of PTNB associated with the glycemic, lipidic and insulin profiles (n=37). Cascavel, PR, Brazil. 2016.

	Discharge O^2	Glucose	Triglycerides	Total Cholesterol	Insulin
Admission	Yes	87.8±42.0	57.6±29.3^{ab}	73.1±14.7^{b}	14.2±11.7^{b}
	No	81.0±52.7	40.0±26.7^{a}	80.1±28.1^{b}	9.7±16.2^{ab}
Discharge	Yes	91.4±30.9	105.4±39.3^{cd}	121.0±43.6^{ac}	10.5±13.3^{ab}
	No	75.3±25.3	79.1±32.1^{bc}	112.1±31.3^{c}	5.5±5.3^{a}
6 months	Yes	81.0±8.9	137.0±74.7^{de}	140.2±41.1^{a}	4.5±3.3^{a}
	No	90.4±15.6	161.0±81.5^{e}	135.5±31.6^{a}	5.2±4.3^{a}
	BT	**Glucose**	**Triglycerides**	**Total Cholesterol**	**Insulin**
Admission	Yes	78.6±52.7	35.4±14.6^{a}	84.0±27.5^{b}	10.4±16.8^{ab}
	No	91.2±43.2	63.0±37.8^{ab}	67.4±14.5^{b}	12.3±11.4^{b}
Discharge	Yes	74.5±25.2	76.4±29.2^{bc}	115.0±32.8^{a}	5.3±5.4^{ab}
	No	90.5±29.9	106.2±40.2^{cd}	114.6±40.3^{a}	10.1±12.3^{ab}
6 months	Yes	90.2±15.9	158.8±75.6^{e}	139.6±36.1^{c}	4.8±4.2^{a}
	No	82.8±10.5	144.6±87.6^{de}	132.3±31.5^{ac}	5.3±3.8^{ab}

Footnotes:

- O^2 – oxygen use at discharge from NICU
- BT – blood transfusion.
- * When the means were statistically different in the three periods analyzed through the ANOVA test and represented in the table by the combination of the letter: ab; ac; bc; cd; de;
- ** When the means were not statistically significant in the three analyzed periods and represented in the table by the letters a; b; c; d; or e, alone.
- **Used reference values:** Glycemia 80-126mg/dL (postprandial); Triglycerides <85mg/dL (no fasting); Total Cholesterol <170mg/dL (no fasting) ; Insulin 2.6 to 24.9 uUI/mL.

DISCUSSION

About the characterization of studied PTNB, similar data was found in other national studies[10-11]. The glycemic profile identified in the PTNB is mentioned in the literature as expected, that is, neonatal concentrations of glucose decrease after birth, once right after birth, the response of hormones that regulate the glucose levels in the blood is less sensitive due to the immaturity of the cyclic adenosine monophosphate, a second messenger related to the glucose metabolism. Besides, PTNB has less ability to store the glycogen than term newborns. Therefore, post-natal hypoglycemia is common between PTNB[12].

Studies about the lipidic, glycemic and insulin profiles of PTNB are not common in the literature, and there are no standardized values for this group. It is common to find low glycemic rates with values of 30 mg/dl in healthy newborns for one to two hours after birth. About the hypoglycemia definition, there is no consensus in the literature, and it is frequently defined as glycemia >125 mg/dL (6.9 mmol/L) or plasmatic glucose >150 mg/dL (8.3 mmol/L). However, these levels are frequently observed during glucose infusions in newborns, especially in extreme preterm and might not indicate the morbidity, which does not require therapeutic intervention[13]. Because glucose in the maturation mechanism stimulates insulin secretion, the mean glucose concentration in newborns without health complications occurs around 72 hours of life, when it starts to be similar to older children[14].

Reference insulin values in adults would be 2.6 to 24.9 UI/ml[15], according to the standardization of the analysis method from the laboratory that conducted the insulin exam. Hyperinsulinemia occurs when the values are above 15 mU/mL in children[16]. The first defense of the neonate organism is the suppression of the insulin

secretion when the plasmatic glucose concentration lowers to below the normal post-absorptive mean of 85 mg/dL[14].

For this reason, insulin concentration values in PTNB started to drop during follow-up, to keep the plasmatic glucose concentration stable. This study considers that the higher insulin concentration in the NICU admission can result from the glucocorticoid before labor, commonly used to stimulate the pulmonary maturation of the PTNB at birth. A study[17] identified higher insulin levels in small babies for the gestational age when compared to the ones adequate to the gestational age.

In the present study, the lipidic profile of PTNB demonstrated a gradual increase from the admission to six months of CA. In a study[18] conducted with PTNB of 28 to 37 weeks and term newborn, using the blood sample from the cord, the researchers found increased Low-Density Lipoproteins (LDL) cholesterol rate, comparing to term newborns. Another accompaniment investigation[19] observed that PTNB had increased triglycerides in the first year of life, compared to term newborns.

The prematurity has been associated with the development of a few health commitments as the glucose intolerance, dyslipidemias, and hypertension, both in children and in adults[2]. Corroborating with this affirmation, research[20] indicates that high levels of triglycerides in PTNB increase the risk of developing future cardiovascular diseases. Still, a study developed in India found that the lipidic profiles in newborns have higher levels in comparison to babies born in other parts of the world, demonstrating a total cholesterol rate of 103.92 ± 47.79 and triglycerides of 187.62 ± 144.44 mg/dl[21], an approximate data from our study.

The isolated analysis of the mean levels of triglycerides in PTBN late sepsis, BPD and the PTNB without ROP, the mean was higher compared to the indicated reference values[9] where for the age between zero and nine years is considered a high-value cholesterol > 170 mg/dl no fasting, > 75 mg/dl fasting and, > 85 mg/dl no fasting for triglycerides. Because there are no reference values for PTNB, there was a need to use reference values of children and adolescents aged two to 19 years and, in this analysis, the PTNB at six months of corrected age presented triglycerides and cholesterol results higher than the reference used. Thus, they can be comprehended as groups at risk for the development of Metabolic Syndrome (MS) and cardiovascular diseases, once triglycerides and cholesterol values are high at six months of CA[4,19].

PTNB, especially the ones with very-low weight at birth and extremely premature received the parenteral nutrition as one of the treatments at NICU, which contributes to triglyceridemia[22]. A study points out that higher doses of amino acids during hospitalization can lead to early metabolic disorders, with higher values in lactant who are born extremely premature[23]. However, studies addressing the lipidic profile of premature babies are recent, what indicates the need to develop more than one research in this field.

The insulin had a distinct behavior in the cases of late sepsis and NEC, both morbidities resulting from infectious processes. In these cases, the invasive microorganisms threatens homeostasis. As a reaction, the organism tries to establish a complex response where many neuroendocrine and inflammatory mediators are involved, being hyperglycemia an essential characteristic of the acute changes that occur during this response, besides being an answer to the insulin resistance, which impedes the glucose to be part of the Krebs cycle. This process results in changes in the metabolism of carbohydrates, within them the peripheral resistance to insulin, increased hepatic glycogenolysis, aiming to redirect the supply of energy to vital organs[24].

With a basis in the physiological process of the response to infections, it is possible to explain the distinct behavior of the insulin concentration when conducted between PTNB with and without NEC or sepsis, where it was observed higher concentration in PTNB with this issue. Therefore, during the admission period in the NICU, the team can include the insulin dosage as routine for PTNB who developed NEC and late sepsis, to conduct treatments to reduce this increase. About early sepsis, there was no positive correlation with the change of the insulin profile.

The limitations of this study are: the sample size and the short follow-up period, indicating the need to follow PTNB during the first years of life, including the assessments of the metabolic profile to confirm the findings of this study.

CONCLUSIONS

When correlating the variables comorbidities and received treatments with the biochemical profile throughout the follow-up, among PTNB who had some comorbidity and who were submitted to blood transfusion and the use of oxygen in the discharge from NICU with those who were not under these conditions, it was identified that the triglycerides and cholesterol levels tend to increase over time. The plasmatic glucose concentration presented a tendency for stability in PTNB in all studied periods, submitted or not to treatments.

The NEC and late sepsis were the comorbidities that presented a significant statistical difference in the insulin levels, which can suggest that the insulin increment might constitute an early marker of sepsis. From this knowledge, it is possible to add the insulin control as routine in the NICU, besides the rigorous glycemic control in PTNB by the nursing before the development of these comorbidities, especially, in the sepsis case, once the hyperglycemia results from the insulin resistance, indicating the need for intervention.

From this study, it was possible to classify the PTNB as having a potential risk for the development of metabolic complications and cardiovascular diseases in the late phases of life, due to lipidic and insulin changes found. Thus, efforts should be made to accompany such neonates since birth until the follow-up, recognizing early the metabolic changes and proposing interventions to reduce the risk of developing complications at adult age.

The results of this study contribute to alert the health team for the need of glycemic control, assessment of the lipidic and insulin profile and use of amino acids in high concentration to manage the PTNB both during admission and follow-up after the hospital discharge, when it is essential to avoid glycemic and lipidic overload that might contribute to long-term changes. Considering the results of this study, it is urgent to develop more studies with the PTNB population to obtain reference values for this group, once the values are for older children and adolescents in the literature.

REFERENCES

1. Leal MD, Esteves-Pereira AP, Nakamura-Pereira M, Torres JA, Theme-Filha M, Domingues RM, et al. Prevalence and risk factors related to preterm birth in Brazil. Reprod Health [Internet]. 2016 [cited 2018 dec 05];13(Suppl 3):127. Available from: https://doi.org/10.1186/s12978-016-0230-0.

2. Marciniak A, Patro-Małysza J, Kimber-Trojnar Ż, Marciniak B, Oleszczuk J, Leszczyńska-Gorzelak B. Fetal programming of the metabolic syndrome. Taiwan J Obstet Gynecol [Internet]. 2017 [cited 2018 dec 05];56(2):133-8. Available from: https://doi.org/10.1016/j.tjog.2017.01.001.

3. Ribeiro AM, Lima MC, Lira PIC, Silva GAP. Baixo peso ao nascer e obesidade: associação causal ou casual? Rev Paul Pediatr [Internet]. 2015 [cited 2018 dec 05];33(3):340-8. Available from: https://doi.org/10.1016/j.rpped.2014.09.007.

4. Huang YT, Lin HY, Wang CH, Su BH, Lin CC. Association of preterm birth and small for gestational age with metabolic outcomes in children and adolescents: A population-based cohort study from Taiwan. Pediatr Neonatol [Internet]. 2018 [cited 2018 dec 05];59(2):147-153. Available from: https://doi.org/10.1016/j.pedneo.2017.07.007.
5. Oliveira MA, Luiza VL, Tavares NU, Mengue SS, Arrais PS, Farias MR, et al. Access to medicines for chronic diseases in Brazil: a multidimensional approach. Rev Saude Publica. 2016 [cited 2018 dec 05];50(suppl 2):6s. Available from: https://doi.org/10.1590/S1518-8787.2016050006161.
6. Executive Summary. New Dir Youth Dev [Internet]. 2013 [cited 2018 dec 05];2013(137):11-4. Available from: https://doi.org/10.1002/yd.20044.
7. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. BMC Pediatr [Internet]. 2013 [cited 2018 dec 05];13:59. Available from: https://doi.org/10.1186/1471-2431-13-59.
8. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes (2015-2016) [Internet]. Rio de Janeiro: A.C. Farmacêutica, 2016 [cited 2018 dec 05]. Available from: https://www.diabetes.org.br/profissionais/images/docs/DIRETRIZES-SBD-2015-2016.pdf.
9. Sociedade Brasileira de Análises Clinícas. Consenso Brasileiro para a Normatização da Determinação Laboratorial do Perfil Lipídico [Internet]. 10 dez. 2016 [cited 2018 dec 05]. Available from: http://www.sbac.org.br/acompanhamento-politico/consenso-brasileiro-para-a-normatizacao-da-determinacao-laboratorial-do-perfil-lipidico/.
10. Rover MMS, Viera CS, Silveira RC, Guimarães ATB, Grassiolli S. Risk factors associated with growth failure in the follow-up of very low birth weight newborns. J Pediatr (Rio J) [Internet]. 2016 [cited 2018 dec 05];92(3):307-13. Available from: https://doi.org/10.1016/j.jped.2015.09.006.
11. Rover MDMS, Viera CS, Toso BRGO, Grassiolli S, Bugs BM. Growth of very low birth weight preterm until 12 months of corrected age. J Hum Growth Dev [Internet]. 2015 [cited 2018 dec 05];25(3):351-6. Available from: https://doi.org/10.7322/jhgd.90228.
12. Yoon JY, Chung HR, Choi CW, Yang SW, Kim BII, Shin CH. Blood glucose levels within 7 days after birth in preterm infants according to gestational age. Ann Pediatr Endocrinol Metab [Internet]. 2015 [cited 2018 dec 05];20(4):213-9. Available from: https://doi.org/10.6065/apem.2015.20.4.213.
13. Szymońska I, Jagła M, Starzec K, Hrnciar K, Kwinta P. The incidence of hyperglycaemia in very low birth weight preterm newborns. Results of a continuous glucose monitoring study--preliminary report. Dev Period Med [Internet]. 2015 [cited 2018 dec 05];XIX(3 Pt 1):305-12. Available from: http://medwiekurozwoj.pl/articles/2015-3-1-9.pdf.
14. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr [Internet]. 2015 [cited 2018 dec 05];167(2):238-45. Available from: https://doi.org/10.1016/j.jpeds.2015.03.057.
15. Biovel. Laboratório Biovel Análises e Pesquisas Clínicas - Home [Internet]. [cited 2018 dec 05]. Available from: https://www.biovel.com.br/#exames.
16. Kostovski M, Simeonovski V, Mironska K, Tasic V, Gucev Z, Metabolic profiles in obese children and adolescents with insulin resistance. Open Access Maced J Med Sci [Internet]. 2018 [cited 2018 dec 05];6(3):511-8. Available from: https://doi.org/10.3889/oamjms.2018.097.
17. Payal V, Jora R, Sharma P, Gupta PK, Gupta M. Premature birth and insulin resistance in infancy: A prospective cohort study. Indian J Endocrinol Metab [Internet]. 2016 [cited 2018 dec 05];20(4):497-505. Available from: https://doi.org/10.4103/2230-8210.183470.
18. Li L, Hua J, Jian-Ping H, Yan L. Association between the Lipid Levels and Single Nucleotide Polymorphisms of ABCA1, APOE and HMGCR Genes in Subjects with Spontaneous Preterm Delivery. PLoS One [Internet]. 2015 [cited 2018 dec 05];10(8):e0135785. Available from:: https://doi.org/10.1371/journal.pone.0135785.
19. de Jong M, Cranendonk A, van Weissenbruch MM. Components of the metabolic syndrome in early childhood in very-low-birth-weight infants and term small and appropriate for gestational age infants. Pediatr Res [Internet]. 2015 [cited 2018 dec 05];78(4):457-61. Available from: https://doi.org/10.1038/pr.2015.118.
20. Tank S, Jain SK. Altered cord blood lipid profile, insulin resistance & growth restriction during the perinatal period & its potential role in the risk of developing cardiovascular disease later in life. Indian J Med Res [Internet]. 2016 [cited 2018 dec 05];144(2):151-3. Available from: https://doi.org/10.4103/0971-5916.195021.
21. Ramaraj SM, Bharath AP, Sanjay KM. Lipid profile in neonates and its relation with birth weight and gestational age. Indian J Pediatr [Internet]. 2015 [cited 2018 dec 05];82(4):375-7. Available from: https://doi.org/10.1007/s12098-014-1661-7.
22. Raman M, Almutairdi A, Mulesa L, Alberda C, Beattie C, Gramlich L. Parenteral Nutrition and Lipids. Nutrients [Internet]. 2017 [cited 2018 dec 05];9(4):388. Available from: https://doi.org/10.3390/nu9040388.
23. Lee BS. Nutritional strategy of early amino acid administration in very low birth weight infants. Korean J Pediatr [Internet]. 2015 [cited 2018 dec 05];58(3):77-83. Available from: https://doi.org/10.3345/kjp.2015.58.3.77.
24. Hellström A, Ley D, Hansen-Pupp I, Hallberg B, Löfqvist C, van Marter L, et al. Insulin-like growth factor 1 has multisystem effects on foetal and preterm infant development. Acta Paediatr [Internet]. 2016 [cited 2018 dec 05];105(6):576-86. Available from: https://doi.org/10.1111/apa.13350.