

# Hypertension and maternal urinary tract infection and the metabolic conditions of preterm infants

*Hipertensão e infecção do trato urinário maternas e condições metabólicas em prematuros*  
*Hipertensión e infección del tracto urinario en madres y condiciones metabólicas de prematuros*

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## ABSTRACT

**Objective:** The present study evaluated the anthropometric and metabolic profiles of preterm infants (PT) born from mothers with urinary tract infections (UTI) and mothers with hypertensive disorders (HD). **Method:** This was a longitudinal prospective study conducted between May 2015 and August 2016. First, 59 mothers with premature birth were included; after excluding 29 mothers, two subgroups were created: UTI-mothers (n=12) and HD-mothers (n=18). The anthropometric and metabolic variables of mothers and their respective PT were analyzed at birth and at 6 months of corrected age (CA). **Results:** Plasma triglyceride levels were higher among HD-mothers and their respective PT in comparison with UTI-mothers and their PT at 6 m of CA. **Conclusion:** Plasma triglyceride level is an important metabolic biomarker in HD-mothers resulting in higher triglyceride levels among PT at the CA of 6 m, suggesting an early programming effect of maternal hypertension.

**Descriptors:** Premature Birth; Hypertension; Urinary Infection; Metabolic Programming; Mothers.

## RESUMO

**Objetivo:** No presente estudo foram avaliados os perfis antropométricos e metabólicos de prematuros (PT) nascidos de mães com Infecção do trato Urinário (ITU) e mães com Desordens Hipertensivas (DH). **Método:** Este é um estudo longitudinal-prospectivo realizado entre Maio de 2015 a Agosto de 2016. Inicialmente, 59 mães com parto prematuro foram incluídas; após 29 exclusões as mães foram subdivididas em dois grupos: mães-ITU (n=12) e mães-DH (n=18). As variáveis antropométricas e metabólicas foram analisadas nas mães e nos seus respectivos PT ao nascimento e aos 6 meses de Idade Corrigida (IC). **Resultados:** Os níveis de triglicérides plasmáticos foram maiores em mães-DH, bem como, em seus respectivos PT, quando comparados às mães-ITU e seus PT aos 6 m IC. **Conclusão:** Os níveis dos triglicérides plasmáticos são um importante biomarcador metabólico in mães-DH resultando em elevados valores de triglicérides in PT aos 6 m de IC; sugerindo precoce efeito programador da hipertensão maternal.

**Descritores:** Parto Prematuro; Hipertensão; Infecção Urinária; Programação Metabólica; Mães.

## RESUMEN

**Objetivo:** El estudio evaluó los perfiles antropométricos y metabólicos de prematuros (PT) nacidos de madres con infección del tracto urinario (ITU) y de madres con desórdenes hipertensivos (DH). **Método:** Estudio longitudinal-prospectivo, realizado entre mayo de 2015 y agosto de 2016. Inicialmente fueron incluídas 59 madres con partos prematuros; luego de 29 exclusiones, fueron separadas en dos grupos: madres-ITU (n=12) y madres-DH (n=18). Las variables antropométricas y metabólicas fueron analizadas en las madres y en sus PT al nacimiento y a los 6 meses de edad corregida (EC). **Resultados:** Los niveles de triglicéridos plasmáticos fueron mayores en madres-DH y en sus PT, en comparación con las madres-ITU y sus PT a los 6 meses de EC. **Conclusión:** Los niveles de triglicéridos plasmáticos constituyen un importante biomarcador metabólico en madres-DH, determinando valores elevados de triglicéridos en PT de 6 meses de EC, sugiriendo de modo precoz un efecto programador de hipertensión maternal.

**Descritores:** Parto Prematuro; Hipertensión; Infección Urinaria; Programación Metabólica; Madres.

## INTRODUCTION

Preterm (PT) birth is defined as birth occurring at fewer than 37 weeks' gestational age<sup>(1)</sup>. According to the World Health Organization (WHO)<sup>(2)</sup>, approximately 15 million infants are born prematurely every year worldwide<sup>(3)</sup>. Several studies have reported an increase in the incidence of PT births in the last two decades in several countries, including in some regions in Brazil<sup>(1,4)</sup>. It is well established that PT infants present greater mortality and morbidity rates, in the early stages of life, and also tend to present lifelong health complications<sup>(5)</sup>.

The etiology of PT birth is not completely clear and various maternal risk factors, such as urinary tract infections, multiple births, hypertension, smoking, and low socioeconomic condition can explain part of PT births, especially when linked with genetic factors<sup>(5)</sup>. Among the known causes of PT birth, the presence of urinary tract infections (UTI) and hypertensive disorders (HD) during pregnancy are considered two important risk factors for prematurity<sup>(6-8)</sup>.

The presence of UTI during pregnancy increases inflammatory responses in maternal and fetal tissues, a process intimately associated with elevated maternal and neonatal risk, including PT birth<sup>(9)</sup>. In this direction, it is estimated that approximately half of PT births that occur spontaneously are associated with intrauterine infection, which triggers maternal and fetal inflammatory reactions, stimulating uterine contractions and consequently, PT birth<sup>(10)</sup>. Furthermore, the presence of maternal UTI increases the risk of systemic inflammation in very PT newborns<sup>(11)</sup>. Last, babies who are born from mothers who had a UTI during pregnancy seem to present an increased risk for developing a variety of lifelong health disorders, such as neural and cognitive problems and asthma<sup>(11-12)</sup>.

Similarly, HD represent the most common medical complication during pregnancy and is an important risk factor for PT birth<sup>(13)</sup>. Women diagnosed with preeclampsia or chronic hypertension, in addition to women who are retrospectively diagnosed with temporary gestational hypertension are categorized as having HD; all these conditions are associated with significant implications for the long-term health of both mothers and infants<sup>(13)</sup>. For example, children of mothers with preeclampsia present a greater risk of developing hypertension, lipid disorders and a higher body mass index (BMI)

Prematurity is an independent risk factor for metabolic programming, since PT births are related to the development of chronic diseases in adult life. Metabolic programming is defined as hormonal and/or nutritional alterations that occur in very early life stages, such as pregnancy and lactation, which permanently alter the metabolism and physiology of an organism with effects lasting into adulthood<sup>(13-15)</sup>. Thus, adults who were born PT present a higher risk for obesity, metabolic syndromes, and a higher incidence of diabetes and cardiovascular diseases<sup>(13)</sup>. Interestingly, up to the present, no studies have compared PT infants born from mothers with UTI with infants born from mothers with HD.

## OBJECTIVE

To evaluate and compare the anthropometric and metabolic profiles of PT infants born of mothers with UTI versus PT infants born of mothers with HD, both at birth and at 6 months of corrected age.

## METHOD

### Ethical aspects

The present study was approved by the Research Ethics Committee of the State University of West Paraná (Unioeste), under process no. 1,134,712 and informed consent forms were signed by mothers or adult legal guardians after agreeing to participate in the survey.

### Study design, setting and period

This was a longitudinal prospective study comparing mothers with HD and mothers with UTI during pregnancy and the anthropometric and metabolic profiles of their PT infants at birth and 6 months of CA. The study was carried out between May (2015) and August (2016). The study setting was the Neonatal Intensive Care Unit (NICU) of a maternity hospital in the South of Brazil, a reference for high-risk pregnancies.

### Sample, inclusion and exclusion criteria

At first, 59 mothers with premature births were considered eligible (<37 weeks' gestational age). Exclusion criteria were as follows: PT infants with congenital birth defects; those who had been hospitalized in the NICU for less than seven days or who died during the hospital stay, in addition to those who were lost in follow-up or whose blood samples were not collected or were insufficient for biochemical analysis. Mothers who refused to participate or who did not collect blood samples were also excluded. Mothers with other pathologies (n=23) or who presented HD and UTI simultaneously (n=6) were excluded from the sample.

### Experimental design and protocols

After birth, a trained nurse carried out interviews with mothers and the data were gathered using a single open-ended and pre-coded questionnaire exclusively prepared to address the following domains: maternal age (years); ethnicity (white or nonwhite) and maternal schooling (years). When necessary, data were also gathered from the electronic patient charts available at the unit or from the woman's prenatal card. Weight gain ( $\Delta$ ) during pregnancy was based on the body weight (kg) registered before pregnancy and at the last prenatal appointment. The women's height ( $m^2$ ) was also collected to calculate their body mass index ( $BMI = \text{body weight (Kg)}/\text{height (m}^2\text{)}$ ), which was classified into <18.5, 18.5–23.99, 24–27.99,  $\geq 28$  as per WHO recommendations<sup>(2)</sup>. All the mothers in the sample (n=59) reported some health comorbidity during pregnancy such as diabetes, toxoplasmosis, HIV or syphilis; however, HD and UTI were the most common. Thus, considering the inclusion and exclusion criteria presented above, two experimental groups of mothers were formed, UTI-mothers (n=12) and HD-mothers (n=18) and their respective infants, UTI-mother PTs (n=21) and HD-mother PTs (n=12). The PTs in each group of mothers were assessed at birth and at 6 m CA; according to the flow chart presented in Figure 1. Presence of UTI or HD during pregnancy was based

on the self-report of mothers; a reliable method as shown in various studies<sup>(16-18)</sup>. Thus, the HD-mother group included those who reported any of the following situations during pregnancy: hypertension, gestational hypertension, preeclampsia, superimposed preeclampsia, or chronic hypertension; according to criteria established by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy<sup>(19)</sup>. The UTI-mother group included those who presented vaginal or cervical infection, or bladder or kidney infection<sup>(11)</sup>. Gestational age (GA) was calculated based on the date of the last menstrual period. The anthropometric data collected from PT infants were body weight (g); length (cm) and head circumference (HC, cm), which were recorded at birth and 6 m of CA. Body weight was obtained at birth (infants naked and lying on their backs) and at 6 m of CA was evaluated with a digital weighing scale (10-g subdivisions). At both assessments, HC was measured using a nonelastic metric tape (1-cm wide; 0.1-cm subdivisions) placing the tape on the greatest occipital-frontal circumference over the occipital and the brow region. Length at birth was measured using an infantometer, placing the newborn in supine position over a vertical surface to obtain full knee extension and the measurement was made from the top of the head to the heel. Similar procedures were used to take measurements at 6 m of CA. Two consecutive measurements for each variable and the mean of the two measurements was recorded.

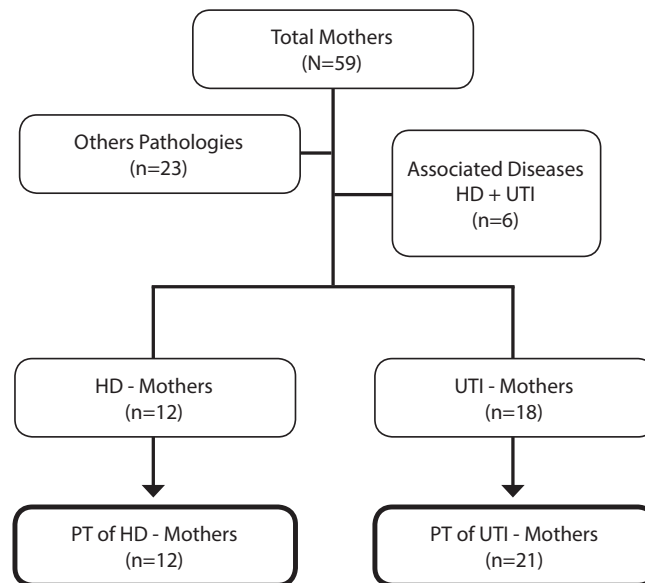
### Blood-based metabolic biomarkers

To determine the metabolic profile of the mothers and their respective PT infants, blood samples were collected to assess plasma biochemical parameters. All samples were collected without fasting. Blood samples were taken from the heels of PT infants 72 hours after admission to NICU; approximately 600 µL of blood were collected. Venous blood samples were also taken from mothers (approximately 1mL) at 72h postpartum and from the PT at 6 m of CA. The blood samples were collected in heparin tubes. The plasma was centrifuged at 1500xg for 15min at 4°C within 2h and stored in a freezer at -80°C until the time of analysis. The separated plasma was used to analyze glucose, triglycerides, total cholesterol and insulin; all biochemical analyses were carried out twice. The blood samples were processed at the maternity's clinical laboratory by a professional pharmacist. Glucose, triglycerides and total cholesterol were measured using a dry-chemical method in an automatic analyzer (Vitros 4600; Ortho Clinical Diagnostics), and the results were expressed in mg/dL. Plasma insulin (µU/mL) was analyzed using electrochemical luminescence in an automatic analyzer (UniCelDxl 800; Beckman Coulter), with Access Ultrasensitive Insulin immunoassays system (Beckman Coulter). The delta (Δ) of the plasma variables of PT infants was obtained by calculating the difference between the values at birth and the values at 6 m of CA.

### Results and statistical analysis

The quantitative variables were expressed as mean ± standard error of the mean (SEM) and statistically assessed using unpaired

t-test or Mann-Whitney's test as indicated by the Shapiro-Wilk test of normality conducted previously. The qualitative variables were presented in terms of frequency and assessed using a chi-squared test. Statistical analyses were performed using the R software program, version 3.3.2 (Since Pumpkin Patch), and level of significance was set at  $p < 0.05$  in all the analyses.



Note: PT = preterm; UTI = urinary tract infections; HD = hypertensive disorders.

Figure 1 - Flowchart of Experimental Design, Cascavel, Paraná, Brazil, 2016

## RESULTS

As shown in Table 1, HD mothers and UTI mothers presented similar mean age and pre-pregnancy body weight. Furthermore, both groups of mothers presented similar ethnic distribution, BMI classification and years of schooling. Figure 2 shows weight gain and plasma metabolic profile of HD- and UTI-mothers. Body weight gain (2A), glucose (2B), total cholesterol (2D) and insulin (2E) were similar for both groups of mothers. However, the UTI-mothers presented lower plasma concentration triglycerides when compared to the HD-mothers 2C;  $p < 0.05$ ).

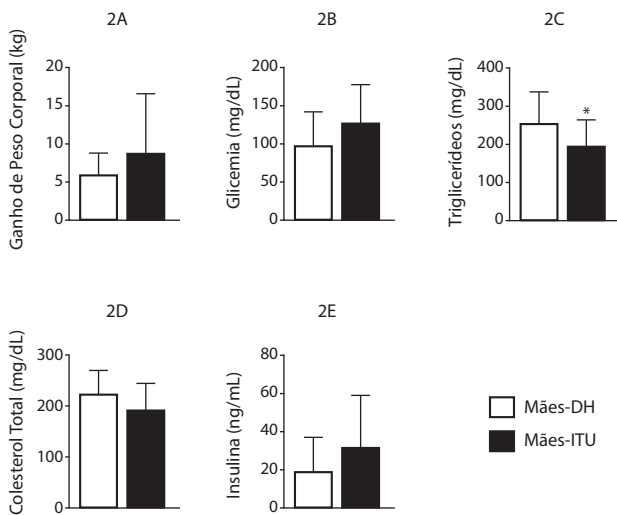
Comparison between the PT infants of HD-mothers and the PT infants of UTI-mothers are shown in Table 2. Birth body weight, length, and HC were similar between the two groups of PT infants at birth. At 6m, the PT infants of UTI mothers presented greater body weight in comparison with those from HD-mothers ( $p < 0.05$ ). Mean gestational age and frequency of sexes were similar among the PT groups.

Figure 3 presents the comparison between the blood plasma levels in PT infants born to HD-mothers and UTI-mothers. Plasma concentrations of glucose (Fig. 3A-C); insulin (3D-F) and total cholesterol (3J-K) were similar between the PT infants born of mothers with HD and UTI. On the other hand, similar to that observed among mothers, at 6 m of CA, PT infants of HD-mothers presented triglyceride levels (Fig. 3H) higher than those of PT infants of UTI-mothers ( $p < 0.05$ ); also resulting in a greater delta (Fig. 3I).

**Table 1** - Maternal anthropometric and sociodemographic characteristics, Cascavel, Paraná, Brazil, 2016

	HD-Mothers (n=12)	UTI-Mothers (n=18)	p value
Age (years)	26.92 ± 5.334	24.72 ± 5.432	0.283
Body Weight# (Kg)	70.34 ± 16.89	60.43 ± 12.36	0.073
<b>n (%)</b>			
BMI#			
Underweight	0	2 (11.11)	0.345*
Normal	4 (33.33)	10 (55.60)	
Overweight	5 (41.67)	4 (22.22)	
Obese	3 (25.00)	2 (11.11)	
Ethnicity			
White	11 (91.67)	16 (88.89)	0.804
Nonwhite	1 (8.33)	2 (11.11)	
Maternal schooling			
Zero – 4 years	0	2 (11.11)	0.335*
Five – 9 years	1 (8.33)	4 (22.22)	
Ten or more years	11 (91.67)	12 (66.67)	

Note: #Body weight and BMI were obtained pre-pregnancy. BMI classification was based on the WHO classification<sup>21</sup>. \*Monte Carlo Permutational Test; UTI = urinary tract infections; HD = hypertensive disorders.



Note: Data are mean ± SEM; HD-Mothers (n=12) and UTI-Mothers (n=18). Body weight gain (Figure 2A) was obtained by subtracting pre-pregnancy weight from body weight at the last prenatal measurement. Plasma biochemistry parameters for Glucose (2B); Triglycerides (2C); Total Cholesterol (2D) and Insulin (2E) were evaluated up to 72h after birth; UTI = urinary tract infections; HD = hypertensive disorders.

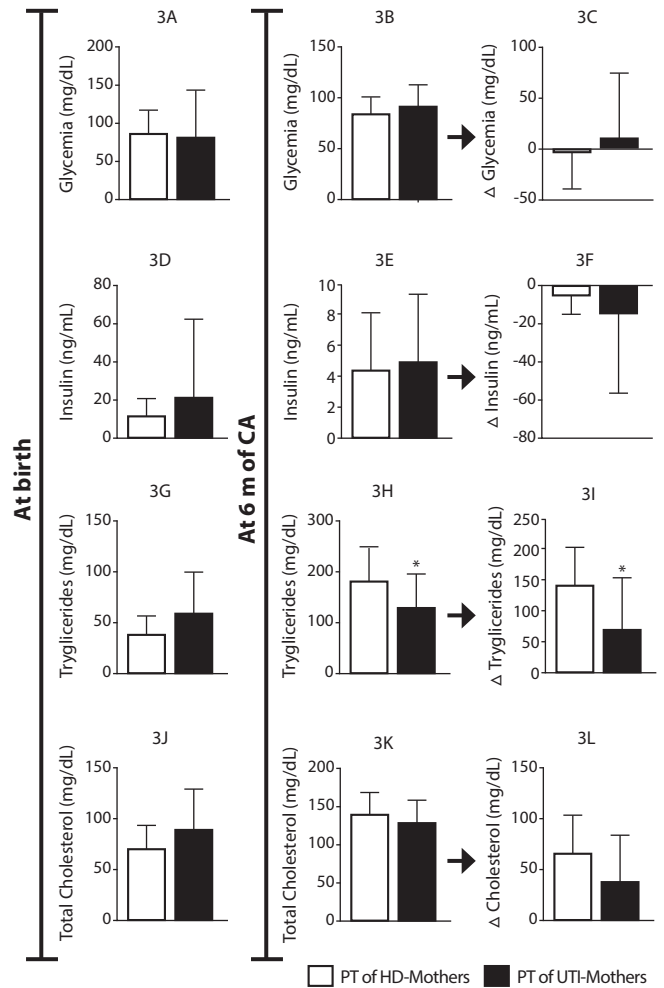
**Figure 2** - Maternal body weight gain and metabolic plasma parameters, Cascavel, Paraná, Brazil, 2016

**Table 2** – Preterm infant characteristics, Cascavel, Paraná, Brazil, 2016

	PT of HD-Mothers (n=12)	PT of UTI-Mothers (n=21)	p value
Body weight* (g)			
At birth	1373 ± 496.60	1570 ± 589.90	0.349
At 6 m of CA	6714 ± 283.30	7155 ± 292.60	0.0003
Height* (cm)			
At birth	38.79 ± 1.06	39.38 ± 0.90	0.112
At 6 m of CA	65.20 ± 1.033	65.12 ± 0.78	0.811
Head circumference* (cm)			
At birth	27.93 ± 0.54	28.15 ± 0.58	0.305
At 6 m of CA	42.53 ± 0.42	42.60 ± 0.33	0.614

	PT of HD-Mothers (n=12)	PT of UTI-Mothers (n=21)	p value
Gestational age*(weeks)	30.58 ± 0.60	30.14 ± 0.60	0.059
Sex**	n (%)	n (%)	
Male	6 (50)	10 (47.62)	0.895
Female	6 (50)	11 (52.38)	

Note: \*t test \*\*Chi-squared test; p<0.05; PT = preterm; UTI = urinary tract infections; HD = hypertensive disorders.



Note: Data are mean ± SEM; PT of HD-Mother (n=12) and PT of UTI-Mother (n=21). Plasma metabolic biomarkers were evaluated at birth (Figure 3A; 3D; 3G and 3H) and at 6 m of CA (3B; 3E; 3H and 3K). The delta of each variable was obtained by the difference between the values at 6 m of CA and values at birth (3C; 3F; 3I and 3L). \*p<0.05; PT = preterm; UTI = urinary tract infections; HD = hypertensive disorders.

**Figure 3** - Metabolic plasma profile of preterm infants born of mothers with hypertensive disorders or urinary tract infections, Cascavel, Paraná, Brazil, 2016

## DISCUSSION

The etiology of PT birth is heterogeneous and frequently associated with different risk factors, such as maternal sociodemographic conditions (age, ethnicity, and schooling), behavioral habits (smoking and abuse of illicit drugs) in addition to prenatal care<sup>(5,20)</sup>. Among these factors, the presence of UTI and HD during pregnancy represent significant causes of PT birth<sup>(15,20)</sup>. Thus, the aim of the present study was to define the characteristics of



mothers with HD or with UTI during pregnancy and their respective PT infants at birth and at 6 m of CA. Interestingly, the presence of these pathologies during pregnancy can also be related to health complications in childhood and into adulthood<sup>(11-12,14)</sup>.

Maternal age ( $\leq 17$  and  $> 35$  years) represents a great risk factor for PT birth<sup>(21)</sup>. However, in the present study, mean maternal age in both groups was approximately 25 years, suggesting that this variable did not determine PT birth. Changes in body weight and BMI are also considered a risk factor for PT birth<sup>(13)</sup>. Although not statistically significant, the HD-mothers presented increased pre-pregnancy body weight, and according to BMI, greater percentages of overweight and obesity in comparison with UTI-mothers. A cohort study carried out by Nohr et al. 2007<sup>(22)</sup> with 62,000 women showed that pre-pregnancy obesity was associated with greater risk of PT birth, caused by ruptured membranes and also, greater frequency of induced PT births. A retrospective cohort study conducted by Girsén et al. 2016<sup>(23)</sup> also showed that low weight during pregnancy is a risk factor for PT birth. These findings reinforce the concept that maintaining adequate control over body weight during pregnancy is an important condition for preventing PT birth. The present study observed no differences among the mothers' ethnicity or economic status. However, a study conducted in Brazil demonstrated a relationship between socioeconomic condition and PT birth<sup>(1,4)</sup>.

As proposed by Barker et al. 1995, 2007<sup>(24-25)</sup> in the concept of metabolic programming, maternal conditions have a direct effect on fetal development, resulting in immediate effects at birth and leading to lifelong consequences. Hyperglycemia, dyslipidemia, and hypertension during pregnancy can be associated with PT birth, and, together, prematurity and maternal health status can program the fetal metabolism to favor a higher incidence of obesity and cardiovascular diseases in adulthood<sup>(25-26)</sup>.

Interestingly, knowing the exact metabolic and anthropometric profile of mothers and PT infants is essential, considering that these specific health conditions can be associated with diseases throughout life. For example, maternal and infant malnutrition is related to a higher incidence of cardiovascular diseases in adulthood, while maternal hyperglycemia and obesity are more intimately associated with insulin resistance and diabetes in adulthood<sup>(14,25)</sup>. In this context, the present findings show that HD-mothers had high levels of plasma triglycerides when compared with UTI-mothers.

The children of women with HD present a greater risk of blood pressure changes, dyslipidemia e increased BMI, both in adolescence and in adulthood<sup>(26-27)</sup>. The present study was the first to show that PT infants of HD-mothers presented higher triglyceride levels at 6m of CA when compared to PT infants of UTI-mothers; thus reproducing the metabolic changes observed in their mothers. However,

we cannot discard the possibility that the presence of maternal UTI during pregnancy is related to other PT pathologies. For example, PT infants born of mothers with UTI have delayed mental and motor development at 2 years of AG, as well as microcephaly<sup>(12)</sup>.

### Study Limitations

Although care was taken to avoid mistakes the present study has some limitations. First, the sample includes a small number of individuals, which probably interferes in the statistical analyses, and thus, changes in BMI, body weight of socioeconomic conditions were not confirmed. Furthermore, maternal diseases and some anthropometric data were self-reported on the questionnaire, which can lead to a possible error of information. However, as mentioned in the methods section, maternal self-reporting usually produces valid information.

### Contributions to the Nursing area

These findings corroborate the concept of evidence-based interventions as important elements to improve prenatal care of PT infants, preventing adverse and specific pathological effects over their lifetime, such as cardiovascular diseases.

### CONCLUSION

The results showed that increased plasma triglyceride values presented by mothers with HD can predispose to heightened plasma triglyceride concentrations in PT children, and may represent an important metabolic biomarker for this condition, and suggesting an early maternal programming effect in mothers with HD. These findings emphasize the need to separate PT in subcategories to adequately assess the association between the maternal health conditions in mothers with UTI or HD and their early repercussions on the metabolic profiles of PT infants.

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