Cord blood lipid profile in healthy newborns: A prospective single-center study

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Abstract

Background. Atherosclerosis may originate during the fetal period, therefore it is reasonable to identify early risk markers of lifestyle diseases.

Objectives. The aim of the study was to determine the relationship between fetal and maternal factors, and the neonatal cord blood lipid profile in term newborns.

Material and methods. In the study group, there were 206 healthy Polish newborns. Newborn characteristics included sex, gestational age at birth, Apgar score, and anthropometric data (weight and length at birth, neonatal ponderal index, head, chest and abdominal circumferences, placenta weight, and placental-fetal weight ratio). Cord blood samples were collected for total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TG). Information regarding selected maternal factors was collected.

Results. The cord blood concentration of TC (p = 0.0007), HDL (p = 0.001) and LDL (p = 0.003) was higher in girls than in boys. A significant positive correlation was found between TG and gestational age (p < 0.0001; r = 0.29). Significant negative correlations between maternal preconception BMI and TC (p = 0.03; r = -0.14), HDL (p = 0.04; r = -0.13) and LDL (p = 0.02; r = -0.15) were observed.

Conclusions. In our study group, the influence of the newborns' gender, gestational age and mothers' preconception BMI on lipid concentration was observed. Further investigations are needed to determine markers in cord blood that may predict future metabolic disorders.

Key words: cord blood, lipids, placenta, atherosclerosis, newborns

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Introduction

Cardiovascular diseases, mainly ischemic heart disease and stroke, are the leading causes of death in the world.¹ The genetic and lifestyle risk factors of these diseases are well known, and include hypercholesterolemia, hypertension, smoking, obesity, and inadequate physical activity. As the prevalence of these factors (particularly hyperlipidemia and obesity) has been increasing in the pediatric population, research on the earliest determinants of these disorders has been proposed.² There are studies suggesting that cardiovascular diseases originate in childhood, and it has even been determined that atherosclerosis may originate during the fetal period.³

In the 1980s, English physician and epidemiologist David Barker of the University of Southampton formulated a hypothesis stating that the intrauterine environment influences patterns of physiological processes in the fetus that, in certain conditions, may influence the presence of medical disorders in future life. The assumption seems to be in line with the fetal programming theory, according to which an unfavorable setting in the womb causes lifelong alterations in the structure and function of the fetal tissues. Furthermore, these programmed changes may result in an earlier manifestation of metabolic disorders. Barker described the connection between birth weight and death rates from lifestyle diseases. He noticed a strict correlation between low birth weights and high morbidity and mortality rates from cardiovascular diseases in certain regions of England and Wales.⁴ When analyzing data from Hertfordshire, concerning the birth weight of all newborns from 1911 and their development through the infancy period, Barker noted that, over a period of 60 years, the people whose birth weight was higher had lower mortality rates from cardiovascular disease and stroke.⁵

Many studies have confirmed the importance of proper intrauterine development, and all the factors that affect it, for future life. Therefore, it is reasonable to search for the first risk markers of lifestyle diseases as early as the neonatal or even fetal period. The aim of the present study was to examine possible relationships among several fetal and maternal factors, and the neonatal cord blood lipid profile in term newborns in order to detect any possible characteristics that may predispose neonates to a higher risk of developing cardiovascular diseases in the future.

Material and methods

This prospective study was conducted in the Department of Neonatology at Independent Public Voivodeship Specialist Hospital in Chełm. The study group consisted of healthy newborns from singleton pregnancies that were free of complications, born at term (between 38 and 42 weeks), with 5-minute Apgar scores ≥8 points. Recorded newborn characteristics included sex, gestational age at birth, Apgar score at the 1st, 5th and 10th minute after birth, as well as anthropometric data – birth weight, birth length, and head, chest and abdominal circumferences. Newborn length was measured on a length board to the nearest centimeter, and the circumferences were assessed with a non-stretchable tape measure to the nearest half centimeter. The neonatal ponderal index (NPI) was computed according to the following formula:

NPI $[g/m^3] = (weight [g]/length^3 [cm^3]) \times 100.$

After the delivery, placenta weight was measured and placental [g] to fetal [g] weight ratio was calculated. The birth weight and placental weight were measured with an electronic scale to the nearest 5 grams.

In all the newborns, umbilical cord blood samples were collected for total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides (TG). Serum lipid concentrations were assessed using the enzymatic spectrophotometric method (Advia Hematology System, Siemens AG, Munich, Germany). Data regarding the mother's age, parity, weight and height before pregnancy, antenatal events or complications, as well as maternal health problems, education and family history were collected from medical records. The mothers' preconception body mass index (BMI) was calculated according to the following formula:

BMI $[kg/m^2] = body weight [kg]/height^2 [m^2].$

Maternal weight gain during pregnancy was computed by subtracting from the mother's weight at delivery her weight before the pregnancy.

The statistical analysis was carried out using STATIS-TICA v. 10 software (StatSoft, Tulsa, USA). The results are presented as means \pm SD. Comparisons between 2 groups were performed using the Mann-Whitney U test. The Kruskal-Wallis H test was used to check differences among more than 2 means. Spearman's rank correlation coefficient was used for the analysis of correlations between parameters. The results were considered statistically significant at p < 0.05.

Written informed consent was obtained from the mothers before enrollment in the study. The study was approved by the Bioethics Committee at the Medical University of Lublin (KE-0254/74/2009).

Results

A total of 206 newborns, including 115 boys (56%) and 91 girls (44%), were recruited for the study. Out of them, 91 newborns (44%) were born to primipara mothers, 69 (33%) were from second parities, and 46 (23%) came from \geq 3 parities. The majority of the children (128; 62%) were born by spontaneous vaginal delivery, while 78 (38%) were born by elective cesarean section. The characteristics of the newborns and mothers are presented in Table 1.

Table 1. Characteristics of the newborns and mothers (means \pm SD)

Parameter	All n = 206	Females n = 91	Males n = 115	p-value between females and males			
newborns							
Gestational age [week]	39.5 ±1	39.6 ±1.0	39.6 ±0.9	0.99			
1 min Apgar	8.9 ±1.0	8.9 ±0.7	8.9 ±1.3	0.68			
5 min Apgar	9.2 ±0.9	9.2 ±0.6	9.2 ±0.7	0.65			
10 min Apgar	9.2 ±0.6	9.2 ±0.5	9.2 ±0.6	0.69			
Birth weight [g]	3406.7 ±438.8	3317.2 ±406	3477.6 ±452.5	0.02			
Length [cm]	55.9 ±2.9	55.5 ±2.6	56.2 ±3.0	0.03			
Head circumference [cm]	34.4 ±1.4	34.0 ±1.3	34.6 ±1.4	0.003			
Chest circumference [cm]	33.4 ±1.7	33.0 ±1.6	33.6 ±1.6	0.04			
Abdominal circumference [cm]	32.7 ±2.0	32.6 ±1.8	32.8 ±2.1	0.6			
Neonatal ponderal index [g/m³]	19.4 ±2.5	19.5 ±2.3	19.6 ±2.1	0.81			
Placental weight [g]	676.1 ±133.7	682.1 ±128.6	671.4 ±137.9	0.59			
Placental-fetal weight ratio	0.2 ±0.03	0.203 ±0.04	0.193 ±0.03	0.007			
Total cholesterol [mg/dL]	78 ±33.1	84.2 ±36.9	73.1 ±28.9	0.0007			
High density lipoprotein [mg/dL]	24.1 ±9.1	25.9 ±8.4	22.7 ±9.6	0.001			
Low density lipoprotein [mg/dL]	25.6 ±17.9	28.0 ±18.6	23.8 ±17.3	0.003			
Triglycerides [mg/dL]	57.1 ±50.4	60.7 ±67.8	54.3 ±30.2	0.69			
mothers							
Age [years]	27.2 ±5.1	27.0 ±5.4	27.5 ±4.9	0.4			
Preconception weight [kg]	59.7 ±11.6	58.7 ±12.7	60.4 ±10.6	0.45			
Height [cm]	164.9 ±5.6	165.0 ±6.1	164.8 ±5.1	0.76			
Preconception BMI [kg/m ²]	21.9 ±4.0	21.5 ±4.6	22.2 ±3.6	0.21			
Weight gain in pregnancy [kg]	16.2 ±5.8	16.0 ±5.5	16.4 ±6.0	0.74			

TC - total cholesterol; TG - triglycerides; LDL - low-density lipoprotein; HDL - high-density lipoprotein.

 Table 2. Spearman's rank correlation coefficient among cord blood lipids (by gender)

Parameter	Females			Males				
	TC	TG	LDL	HDL	TC	TG	LDL	HDL
TC	-	0.49*	0.80*	0.58*	-	0.30*	0.83*	0.63*
TG	0.49*	-	0.36*	-0.04*	0.30*	-	0.23*	-0.18*
LDL	0.80*	0.36*	-	0.34	0.83*	0.23*	-	0.50*
HDL	0.58*	-0.04	0.34*	-	0.63*	-0.18*	0.50*	-

* p-values <0.05 are statistically significant; TC – total cholesterol; TG – triglycerides; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

There were significant differences between females and males in birth weight and length, as well as in head and chest circumferences and placental-fetal ratio. Maternal factors did not differ significantly between boys and girls.

The cord blood concentration of TC (p = 0.0007), HDL (p = 0.001) and LDL (p = 0.003) was found to be higher in girls than in boys. The concentration of TG was also higher in girls; however, this difference did not reach statistical significance. Table 2 presents the concentration of lipids according to the newborns' gender. As shown in Table 3, there were no differences in cord blood lipid profile between newborns delivered naturally and those delivered by cesarean section. The analysis of variance showed significant differences between the TC concentrations of newborns from 1st and 2nd pregnancies (F = 3.30;

Table 3 Cord	blood lipid	nrofile according	to the type	of delivery
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Parameter	Vaginal Cesarean delivery section n = 128 n = 78		p-value	
TC [mg/dL]	76.6 ±29.8	80.23 ±38.3	0.22	
HDL [mg/dL]	24.2 ±9.3	23.9 ±9.1	0.79	
LDL [mg/dL]	25.0 ±17.6	26.7 ±18.7	0.21	
TG [mg/dL]	54.2 ±36.3	61.6 ±67.9	0.20	

TC – total cholesterol; TG – triglycerides; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

p = 0.04) and between the TG concentrations of newborns from 1st and 2nd pregnancies (H = 10.17; p = 0.006).

Relationships between selected clinical parameters of the newborns and their cord blood lipid profiles are

Parameter	TC	HDL	LDL	TG
Gestational age p-value correlation coefficient	0.58 (–)	0.34 (–)	0.76 (–)	<0.0001 0.29
1 min Apgar p-value correlation coefficient	0.89 (–)	0.39 (–)	0.99 (–)	0.03 0.15
5 min Apgar p-value correlation coefficient	0.59 (–)	0.94 (–)	0.54 (–)	0.04 -0.14
10 min Apgar p-value correlation coefficient	0.86 (–)	0.72 (–)	0.91 (–)	0.10 (–)
Birth weight p-value correlation coefficient	0.64 (–)	0.99 (–)	0.54 (–)	0.60 (–)
Length p-value correlation coefficient	0.71 (–)	0.61 (–)	0.72 (–)	0.70 (–)
Head circumference p-value correlation coefficient	0.33 (–)	0.45 (–)	0.29 (–)	0.50 (–)
Chest circumference p-value correlation coefficient	0.97 (—)	0.50 (–)	0.74 (–)	0.90 (–)
Abdominal circumference p-value correlation coefficient	0.17 (—)	0.52 (–)	0.18 (–)	0.99 (–)
Neonatal Ponderal Index p-value correlation coefficient	0.12 (–)	0.42 (–)	0.14 (–)	0.09 (–)
Placental weight p-value correlation coefficient	0.67 (–)	0.13 (–)	0.88 (–)	0.49 (–)
Placental-fetal ratio p-value correlation coefficient	0.38 (–)	0.07 (–)	0.44 (-)	0.64 ()

 Table 4. Relationships among clinical characteristics and cord blood lipid profiles

TC – total cholesterol; TG – triglycerides; LDL – low-density lipoprotein; HDL – high-density lipoprotein.

presented in Table 4. A significant positive correlation was found between the concentration of TG and gestational age (p < 0.0001; r = 0.29) and weak negative correlations were noted between the TG concentration and Apgar scores at the 1st and 5th minute after birth (p = 0.03, r = -0.15; p = 0.04; r = -0.14, respectively). There were no correlations between the lipid profiles and the anthropometric parameters of the newborns, their NPIs, placental weights or placental-fetal weight ratios.

Significant negative correlations were observed between the maternal preconception BMIs and TC (p = 0.03; r = -0.14), HDL (p = 0.04; r = -0.13) and LDL (p = 0.02; r = -0.15) concentrations. However, there was no correlation between the TG concentration and the maternal BMI. There were also no correlations between cord blood lipid profile and maternal age, preconception weight or weight gain during pregnancy.

Discussion

In the present study, the mean TC concentration was higher than in the study of 137 Polish newborns (78 mg/dL vs 65.05 mg/dL); however, the mean TG concentration corresponds with the results of that study (57.1 mg/dL vs 58.75 mg/dL).⁶ The mean HDL in this study was higher (24.1 mg/dL vs 19.63 mg/dL) and the mean LDL was lower (25.6 mg/dL vs 34.12 mg/dL) than in that study group.⁶ Taking into consideration some inter-population variances, the TG concentration was higher in Iranian term newborns than in Polish ones, which may suggest the presence of some differences among various ethnic groups and put some societies at an increased risk of cardiovascular diseases developing from early childhood.⁷

The present study noted that the cord blood concentration of TC, HDL and LDL was significantly higher in girls than in boys; these findings correspond with some previous studies. Gender related differences in cord serum lipids were also studied in 548 term singletons from Spain. Cord TC and LDL were significantly higher in females than in males, which suggests that gender related factors might influence lipid levels as early as the delivery period.⁸ In a group of 100 healthy term infants born in India, cord blood levels of TC, HDL and LDL were significantly higher in females than in males.⁹ Cord blood lipid profiles were also analyzed in 378 full-term Iranian newborns; according to the study, female neonates had significantly higher concentrations of TC and HDL than males. Other factors were not significantly different between genders.⁷ A similar trend was found in studies that included both full-term and pre-term newborns. TC and HDL were significantly higher in girls than in boys.¹⁰ The differences found in the present study correspond with another Polish study, which showed that gender does influence the concentration of lipids in the cord blood serum of newborns from gestational weeks 36–42; in the study population, TC, LDL and HDL were higher in girls.⁶ However, in a study involving also very preterm babies (born between 28th and 42th week), umbilical blood lipid concentration (TC, HDL, LDL, very low density lipoprotein, TG) did not differ significantly between genders.¹¹

In the present study, a significant positive correlation was found between the TG concentration and gestational age, which is consistent with observations made by other researchers.^{7,12} However, it should be noted that in a study by Kharb et al., the opposite trend was reported.⁹ Nevertheless, we found no relationship between the cholesterol concentrations and gestational age in the term newborns in our study group. In this context, in the Iranian birth cohort study, the cholesterol concentrations did not differ between pre-term and full-term neonates, while in the Canadian cohort, newborn concentrations of LDL and HDL were lower at more advanced gestational ages.^{12,13}

Newborns who are small for their gestational age, as well as those who are large for their gestational age, are thought

to be at a higher risk of cardiovascular diseases later in life, so the importance of birth weight as a component in the analysis is clear.4,14 Some observational studies should be mentioned, although they considered both pre-term and full-term infants. A follow-up study involving 3447 Finnish women revealed that coronary heart disease in women is associated with low birth weight and even more strongly with short body length at birth.¹⁵ Similarly, a study of a cohort of Finnish men confirmed that men with low birth weights, particularly those who are thin at birth (with lower NPIs), have high death rates from coronary heart disease; the rates increase further if the mother's BMI increased during pregnancy.¹⁶ NPIs were strongly related to placental weight.¹⁶ In both sexes, the effect of impaired fetal growth on the risk of coronary heart disease was augmented by catch-up growth.^{15,16} This influence was more accentuated in girls whose growth was accelerated, and in boys whose catch-up growth resulted in gaining body mass. The authors suggested that different body proportions are associated with an increased risk for the sexes: short birth length in woman and thinness in men.¹⁵ A U-shaped relationship between the birth weight of full-term newborns and several components of metabolic syndrome at the age of 8 was confirmed in a different study. The highrisk cluster consisted of children with increased triceps skin folds and lower placental to fetal weight ratios. At the age of 8, they tended to have higher BMIs, blood pressure, serum TC and TG concentrations, and lower HDL concentration.¹⁷

In the present study of term newborns, no correlations were found between the lipid profile and anthropometric parameters of the newborns, but in other studies, some trends were noticed. The mean serum lipid levels (TG, TC, LDL, and very low density lipoprotein) were higher in groups with low birth weight (<2500 g) and high birth weight (>4000 g) than in the group with normal weight.¹¹ In the previously mentioned Iranian study, the TG concentrations in babies who were small for their gestational age were significantly higher than in the babies with the appropriate weight for their gestational age.¹⁰ Moreover, in the children who were small for their gestational age, the highest TG concentrations and the lowest LDL concentrations were noticed in comparison to the group with the ageappropriate weight.¹⁰ Other Iranian researchers reported that the birth weight correlated with the cord TG level.¹³

In the present study, no correlations were observed between the lipid profiles and anthropometric parameters of the newborns, such as their birth weight and length, head, chest and abdominal circumferences or NPIs, which corresponds to previous findings.⁷ Similarly, Badiee and Kelishadi found no significant correlations between an infant's NPI, birth weight, length, head circumference and any lipid concentrations in a population of Iranian term newborns; only chest circumference significantly correlated with TG.⁷ In a different study, TG levels were significantly higher in babies with higher NPIs (>10th percentile).¹⁰ Significant differences between females and males were found in birth weight, length, head and chest circumferences, as well as the placental-fetal index. In a similar Finnish study, which involved 3447 women and 3302 men, general variances in birth parameters were described, such as head circumference, birth weight and length, while the mean placental weights were similar.^{15,16}

It is vital to observe how the anthropometric parameters of newborns influence the potential risk of developing cardiovascular diseases in the future. The authors of a follow-up study of 219 people whose size at birth had been recorded noticed that reduced rates of fetal growth are related to an impaired lipid profile in adult life.¹⁸ Abdominal circumference proved to be especially noticeable, because it reflects the size of the liver in the newborn - the liver plays an essential role in cholesterol metabolism. Those who had a small abdominal circumference as infants tended to have raised serum concentrations of TC and LDL as adults. The relationship observed was independent of gestational age, which suggests that reduced fetal growth is more important than premature birth. The human fetus responds to nutrient deprivation by maintaining brain growth at the expense of the torso. Also, fetal adaptations to hypoxemia reduce umbilical venous flow through the hepatic tissue, which leads to liver growth impairment. This may suggest that impaired liver growth during pregnancy may permanently alter lipid metabolism.¹⁸ Another result corresponds to the concept of "brain sparing": LDL levels in Indian neonates with higher abdominal circumferences (>32 cm) were significantly lower than in those with lower abdominal circumferences.¹⁰

In recent years, there has been an increasing interest in placenta, as deeper understanding of early human development might throw a new light on the problem of the epidemic of metabolic diseases.¹⁹ Studies concern not only the association between placental size and pregnancy complications, but also the development of diseases in adult life.²⁰ In Norway, placenta weight percentile curves for singleton deliveries and birth weight to placental weight ratios in male and female infants were produced on the basis of data from nearly 200,000 deliveries.²¹ Subsequently, percentile curves for the ratio of placental weight to birth weight were created for singleton and twin deliveries in Canada.²²

The ratio of placental weight to birth weight can be used as a marker of intrauterine growth restriction, as it correlates better than birth weight itself with an increased risk for cardiovascular diseases, such as high systolic blood pressure in childhood.²³ Placental weight tended to be an independent predictor of coronary heart disease among men in Finland.¹⁶ In women, this trend was not noteworthy, but a significant correlation between hazard ratios for coronary heart disease and an increased placental weight to birth weight ratio was noticed.¹⁵ It has often been repeated that Martyn et al. demonstrated a U-shaped association between the placenta to birth weight ratio and subsequent deaths from coronary heart disease. Death rates were lowest if the placenta weighed just below 20% of birth weight.²⁴ Barker et al. also observed that blood pressure and the risk of hypertension among men and women around 50 years of age can be predicted by studying the placenta to birth weight ratio. The highest blood pressure was among people who had been small babies with large placentas.²⁰ A prospective analysis based on a population of 31,307 Norwegian men and women showed that the placenta to birth weight ratio was positively associated with cardiovascular disease mortality, particularly with stroke.²⁵ As a large size of placenta relative to birth weight could be a sign of an inefficient placenta, this could express an adaptation to a difficult intrauterine environment. In our study, no correlations between the lipid profile and placental weight or placental-fetal weight ratio were found. In the Canadian study mentioned above, the placental-fetal weight ratio was also unrelated to other components analyzed, such as the TG concentration or HDL/apolipoprotein A concentration.¹²

It has been suggested that there is a link between the body composition of a pregnant woman and increased levels of cardiovascular risk factors in her offspring. Generally, lipids do not cross the placenta easily, but the placenta possesses receptors for lipoproteins and has various lipases, making fatty acids available to the growing organism.²⁶ This may link accumulations of maternal fat (expressed as BMI, for example) with certain cord blood lipid profiles. However, in late gestation, the main source of cholesterol seems to be fetal synthesis de novo.²⁶ Nevertheless, extremes of maternal body composition in pregnancy - both undernourishment and obesity - are associated with adverse effect in the offspring. An association has been described between low weight and BMI in mother and dyslipidemia in adult offspring.²⁷ In another study, TC and LDL levels were significantly higher in subjects whose mothers' BMI was $\leq 25 \text{ kg/m}^2$ compared to $> 25 \text{ kg/m}^{2.11}$

Some researchers have concluded that in developed countries pre-pregnancy BMI is a significant predictor of fetal growth.²⁸ A relationship between low maternal preconceptional BMI (<20 kg/m²) and fetal growth restriction and pre-term delivery has been documented.²⁹ However, high obesity rates bring new threats. An American study revealed that, with the high frequency of obesity, abnormal body habitus has a stronger influence than diabetes mellitus during pregnancy on the prevalence of deliveries that are large for their gestational age.³⁰ Obese women have increased rates of both fetal macroand microsomia, because the fetoplacental unit develops under conditions of both excess nutrients and chronic inflammation.^{14,30} In an Asian population with an ethnic predisposition to metabolic syndrome, underweight and overweight mothers were associated with an atherogenic lipid profile in the cord blood. A preconception maternal BMI of ≥ 25 kg/m² correlated significantly with cord TG, whereas a preconception BMI <18 kg/m² correlated with low HDL.13

Surprisingly, some gender differences have been found to affect the offspring's future health. Maternal BMI during pregnancy was not related to developing coronary heart disease in daughters, but in sons such a trend was observed.^{15,16} The results of the present study are to some extent in line with this finding. Significant negative correlations between maternal preconception BMI and concentrations of TC, HDL and LDL were observed. However, there was no correlation between the TG concentrations and maternal BMI. According to other authors, maternal preconceptional BMI or post-delivery BMI had no influence on the neonates' lipid profiles.^{7,10} Also, maternal lipid profile characterized by hyperlipidemia compared to the same woman's non-pregnancy lipid profile had only a weak influence on the newborn's cardio-metabolic components.^{12,26} In well-nourished populations, nutritional factors are probably of much less importance to fetal growth; they may be more vital in developing countries.³¹ In the current study, population preconception weight and weight gain during pregnancy did not affect any components of the analysis.

As in a previous study, the present research found no correlation between the cord blood lipid profile and maternal age.⁷ In different studies, TC and LDL were significantly lower in neonates whose mothers were younger than 30 years of age than in the case of older mothers.¹¹ Maternal age was also inversely associated with the newborns' TG and HDL concentrations.¹²

Conclusions

To conclude, fetal cardiovascular adaptations appear to have a long-term influence on health in postnatal life. The placenta may be of importance in determining these changes. Our study described differences between the genders in cord blood lipid profiles. The influence of gestational age and the mothers' preconception BMI on lipid concentrations was also observed. Further investigations are needed, focusing not only on short-term outcomes, such as the influence of various harmful factors on the anthropometry of the offspring, but also on some biochemical markers in umbilical cord blood that may be used in the diagnosis of metabolic disorders. It is possible that in the future, by detecting such factors and markers, the identification of newborns with a higher risk for developing cardiovascular diseases will be possible.

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