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The influence of gestational hypertension on cord blood adiponectin levels: a case-controlled study

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Abstract

Introduction: Gestational hypertension is one of the most common complications of pregnancy and childbirth worldwide and may be associated with metabolic disorders. Adiponectin is an adipocyte-specific plasma protein with insulin-sensitizing, vascular-protective, anti-inflammatory properties, and its role in metabolic disorders in prenatal and postnatal development in neonates remains unclear. The primary purpose of this study was to determine whether gestational hypertension is a condition lowering cord blood adiponectin level. Next, we have evaluated whether cord blood adiponectin level correlates with selected anthropometric parameters in neonates.

Material and methods: The case–control study included 89 newborns divided into two groups: 30 neonates in the study group whose mothers were diagnosed with gestational hypertension and 59 healthy neonates born from normotensive pregnancies. Adiponectin determinations were performed in both groups, and neonatal anthropometric measurements and perinatal data were collected.

Results: There was no statistically significant difference ($p = 0.27$) between adiponectin concentration in cord blood of newborns from the study group [median (Q1–Q3) 9.86 μg/ml (8.16–13.26 μg/ml)] compared with the control group [median (Q1–Q3) 10.65 μg/ml (8.69–14.29 μg/ml)]. No statistically significant correlations were observed between adiponectin level and gestational age, body weight, body length, and chest circumference. A significant correlation was observed between adiponectin level and head circumference among newborns in the control group and among the entire population of newborns included in the study.

Conclusion: No significant influence of gestational hypertension on cord blood adiponectin levels or their correlation with neonatal anthropometric measurements was observed.

Keywords: adiponectin, gestational hypertension, cord blood, newborn

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Introduction

According to the current knowledge, hypertensive disorders of pregnancy (HDP) affect approximately 5–10% of pregnancies worldwide and, noteworthy, are considered the leading cause of maternal and neonatal mortality. These disorders adversely affect fetal development, often resulting in intrauterine fetal growth restriction, increased risk of preterm delivery, placental abruption, and increased probability of emergency cesarean section, which threatens the lives of both the newborn and the mother.[1,2]

Gestational hypertension is diagnosed after 20 weeks of gestation when, in two separate measurements, blood pressure values remain ⩾140 mmHg for systolic blood pressure (SBP) and/or ⩾90 mm Hg for diastolic blood pressure

(DBP) without significant proteinuria or any hematological or biochemical abnormality. More severe forms of HDP such as preeclampsia and eclampsia are characterized by additional symptoms, including proteinuria and/or maternal kidney injury, maternal liver injury, neurological symptoms, hemolysis, or thrombocytopenia.[3,4]

Adiponectin is one of the most widely described adipokines with insulin-sensitizing, vascular-protective, anti-inflammatory properties. Numerous research studies indicate that adiponectin influences macrophages by inhibiting the maturation of their precursor cells and silencing the function of adult forms. Furthermore, it also stimulates the production of anti-inflammatory interleukin-1 (IL-10), inhibits monocyte adhesion, suppresses the production of reactive oxygen species in human neutrophils, enhances nitric oxide in endothelial cells, and suppresses the inflammatory signaling cascades via AMP-activated protein kinases and the cyclic AMP–protein kinase A-linked pathway.[5–7]

Despite extensive knowledge of the multiple functions of adiponectin, its role and involvement in either physiological or pathogenic metabolism processes are ambiguous. The decreased levels of adiponectin in human plasma (hypoadiponectinemia) have been observed in the course of obesity, type 2 diabetes, insulin resistance, atherosclerosis, hypertension, and coronary heart disease, even in endometriosis and endometrial cancer.[7,8] On the contrary, elevated adiponectin levels (hyperadiponectinemia) have been described in patients with systemic lupus erythematosus, cystic fibrosis, inflammatory bowel disease, rheumatoid arthritis, and anorexia nervosa.[5,9] A whole group of proinflammatory factors such as hormones and adipokines secreted by adipose tissue cells have been associated with the occurrence of cascade of metabolic disturbances. Certain metabolic disorders (especially dyslipidemia and hyperinsulinemia) have been reported to be more common in adults who were prenatally exposed to intrauterine fetal growth restriction or low birth weight conditions which are common in newborns of mothers suffering from HDP.[10]

Furthermore, recent studies indicate that women who are affected by HDP are more exposed to lipid disorders, insulin resistance, glucose intolerance, and obesity than women with normotensive pregnancies.[11,12] Some of the trials suggest that some of these women are at risk of insulin resistance syndrome as early as the perinatal period, but this risk continues even several years after delivery.[13]

In this study, we aimed at comparison of adiponectin level in cord blood of newborns from pregnancies complicated by gestational hypertension and from normotensive pregnancies. Furthermore, we extended our investigation by analyzing the associations between cord blood adiponectin level and neonatal anthropometric measurements.

Patients and methods

This case–control study included 89 newborns divided into a study group (30 newborns whose mothers were diagnosed with gestational hypertension) and a control group (59 healthy newborns from normotensive pregnancies). All newborns were born in the Multi-Specialist Hospital in Gliwice between 2018 and 2020. Mothers of newborns in the study group were diagnosed with gestational hypertension according to the guidelines of the Polish Society of Gynaecologists and Obstetricians as hypertension occurring after 20 weeks of pregnancy, without accompanying proteinuria or other biochemical and hematological disorders. These mothers did not have any other medical conditions during pregnancy. Moreover, the neonates classified in the study group were eutrophic, born on time, and the delivery was physiological.

The criteria for inclusion in the control group were eutrophic neonates, born from physiological pregnancy and delivery, from normotensive mothers.

All participating women were acquainted with a method and purpose of research and signed a consent form to participate. The research plan was approved by the Bioethics Committee of the Silesian Medical University in Katowice (Resolution No KNW/022/KB1/109/18).

Medical data concerning the mother of the child (age, history of pregnancies and deliveries, accompanying diseases), delivery (course of delivery, gestational age, prenatal group B Strep screening result, color of waters), and the newborn (APGAR score, gender, birth weight, body length, head circumference, chest circumference) were recorded.

Table 1. Demographic and anthropometric characteristics among the two studied groups, *p-values for Mann–Whitney U test.

Parameter	Control group ($n = 59$)			Study group ($n = 30$)			p*
	Median	Q1	Q3	Median	Q1	Q3	
Age of mother (years)	30.00	27.00	32.00	30.00	27.00	32.00	0.21
Gestational age (weeks)	40.00	39.00	40.00	39.00	38.50	40.00	0.03
Birth weight (g)	3300.0	3090.0	3650.0	3265.0	3290.0	3745.0	0.28
Body length (cm)	55.00	54.00	56.00	53.75	53.50	56.00	0.006
Head circumference (cm)	34.00	32.00	35.00	33.00	33.00	34.50	0.1
Chest circumference (cm)	33.00	32.00	34.00	32.00	32.00	35.00	0.048

Cord blood was collected from the umbilical vein in the third stage of labor, just after the umbilical cord was tightened. Blood was collected into the EDTA (Ethylene Diamine Tetra Acetic acid) tubes, samples were centrifuged, and then the serum samples were frozen and stored at −80°C. Adiponectin determination was performed at the Department of Medical and Molecular Biology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia in Katowice. Plasma adiponectin concentration was determined by an immunoenzymatic method using Bio-Vendor LLC (BioVendor – Laboratorní medicinal a.s. Czech Republic)-Human Adiponectin ELISA, High Sensitivity, cat. no. RD 191023100, according to the manufacturer's instructions. A calibration curve was prepared to determine the concentrations of the test samples using the standards included in the kit. Absorbance readings were performed using a Universal Microplate Spectrophotometer-μQUANT instrument from BIO-TEK INC (Bio-Tek World Headquarters, Santa Clara, CA, USA), at 450 nm, and processing of the results was performed using the KCJunior software (Bio-Tek). The sensitivity of the kit was 0.5 pg/ml, and the imprecision (repeatability in simultaneous series) of the method was 4.4%.

Because the study variables did not meet the assumptions of normal distribution in each group, the data were presented as median with quartile range. The Mann–Whitney U test was used to compare variables between groups. Spearman's rank correlation coefficient was used to analyze the relationship between variables. Rstudio package and Seaborn library for Python language in Jupyter notebook environment were used to perform the analysis. Values of $p < 0.05$ were considered significant.

Results

All infants involved in this study were born at term (between 37 and 42 weeks of gestation) as eutrophic neonates, rated on APGAR scale for good condition (above 8 points), born from clear waters by natural forces (89.6%) or by Cesarean section (10.4%) for pre-planned reasons. In a comparison of anthropometric and demographic factors (Table 1), it was found that neonates from pregnancies exposed to gestational hypertension had statistically significantly lower gestational age, body length, and head circumference compared with neonates from normal pregnancies.

No statistically significant correlations were observed between adiponectin level and gestational age, body weight, body length, and chest circumference. A significant correlation was noticed between adiponectin level and head circumference among newborns in the control group and among the entire population of newborns included in the study (Table 2).

The comparison of adiponectin values in the study and control groups is presented graphically (Figure 1) and as median with quartile range (Table 3). There was no statistically significant difference ($p = 0.78$) between adiponectin

Table 2. Correlation coefficients between anthropometric parameters and adiponectin levels (*$p<0.05$).

	Adiponectin		
	Control group ($n=59$)	**Study group ($n=30$)**	**All neonates ($n=89$)**
Gestational age	0.04	0.27	0.10
Birth weight	0.23	0.02	0.17
Birth length	0.18	0.08	0.07
Head circumference	0.27*	–0.02	0.19*
Chest circumference	0.20	–0.02	0.16

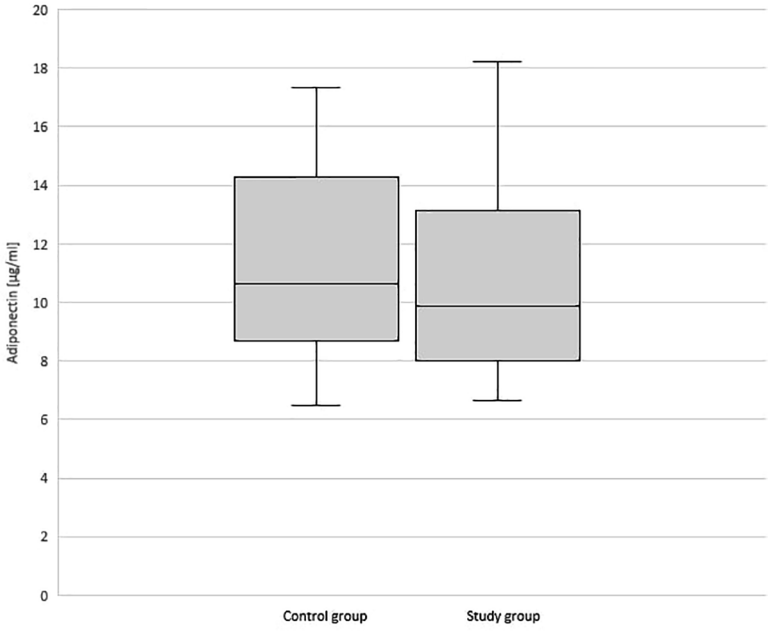

Figure 1. Adiponectin levels in all studied groups.

concentration in cord blood of newborns from the study group [median (Q1–Q3) 9.86 µg/ml (8.16–13.26 µg/ml)] compared with the control group [median (Q1–Q3) 10.65 µg/ml (8.69–14.29 µg/ml)].

Discussion

Adiponectin and gestational hypertension

In the following study, we found no difference in cord blood adiponectin level between infants born after 37 weeks of gestation exposed to gestational hypertension and those from normotensive pregnancies. The association between abnormal adiponectin levels and gestational hypertension has been repeatedly investigated, but in a slightly different way than in our study; the research material selected and the criteria for the selection of the study groups differed.

In studies where the study material was maternal peripheral blood collected during pregnancy, higher level of adiponectin was observed in women affected by preeclampsia than in women with normotensive pregnancies.[14,15] Peripheral blood of newborns was studied by Kotani *et al.* who found significantly higher level of adiponectin in the peripheral blood of healthy newborns compared with healthy adults. In their discussion, the authors suggest it may be related to a difference in the distribution of body fat compared with adults, meaning much more subcutaneous and less visceral fat.[16]

Studies involving older children as well were concluded by Jeffrey *et al.* who observed significant associations between adiponectin and the incidence of metabolic syndrome among obese adolescents. Studies in normal-weight children have not indicated such connections. It has also been suggested that high adiponectin level in the youngest children is associated with rapid weight gain occurring during this period of development.[17]

The effect of the presence of HDP on both maternal and neonatal adipocytokine levels, including adiponectin, has been investigated several times; however. the results are inconclusive. Ogland *et al.* conducted a study comparing adiponectin level in the cord blood of newborns from pregnancies exposed to preeclampsia and normotensive

Table 3. Adiponectin concentrations in all studied groups (*p*-value for Mann–Whitney *U* test).

Parameter	Control group (*n* = 59)			Study group (*n* = 30)			*p*-value
	Median	Q1	Q3	Median	Q1	Q3	
Adiponectin (μg/ml)	10.65	8.69	14.29	9.86	8.16	13.23	0.27

pregnancies, but they did not include mothers with gestational hypertension. Adiponectin level raised with increasing gestational age, but when comparing levels in the study group and the control group, there was no statistically significant difference. However, it was observed that in the group of newborns born prematurely and those whose delivery started with spontaneous contractions, the level of adiponectin in the cord blood of the group exposed to preeclampsia was significantly higher than in the control group.[18] Similar conclusions are presented by Magalhães *et al.*[10] who investigated cord blood in a population of preterm infants and found significantly higher adiponectin level among pregnancy-induced hypertension–exposed infants compared with a healthy control group. Observations comparable to the above were made by Kajantie *et al.*[19] who observed an increase in cord blood adiponectin level with increasing gestational age. Linking the data from the above studies to our findings, we hypothesized that abnormal adiponectin level in cord blood mainly affects neonates born prematurely.

The important role of adiponectin during pregnancy is also evidenced by the study by Chen *et al.*,[20] which documented that this hormone is produced and secreted by the human placenta. An interesting conclusion was also reached by Takemura *et al.* who documented the expression of genes for adiponectin in the endometrium, mainly in epithelial and stromal cells. In their study, they concluded that the expression of AdipoR1 and AdipoR2 receptor genes for adiponectin increased during the midluteal phase, which is the period of embryo implantation.[21] The most likely pathogenesis of hypertensive disorders of pregnancy is abnormal perfusion in the placenta resulting from abnormal invasion of cytotrophoblasts into spiral arterioles, but the involvement of adipocytokines including adiponectin in this process remains unknown so far. In our opinion, increasing knowledge about the fluctuations of adiponectin levels in cord blood is extremely important, as the factors leading to these abnormalities may ultimately result in metabolic complications in the newborn and mother.

Adiponectin and anthropometric measurements

Although only eutrophic neonates born after 37 weeks of gestation were included in our study, differences in anthropometric measurements and perinatal data were observed between the two groups. Newborns in the study group presented statistically significantly lower gestational age, body length, and chest circumference. Literature data suggest that gestational hypertension predisposes to an increased risk of hypotrophy, and neonates born from pregnancies complicated by HDP have statistically lower body weights, which was not reflected in the neonates in our study groups.[22]

Based on the knowledge that gestational hypertension can have an impact on neonatal anthropometric measurements, it seemed appropriate to correlate them with adiponectin determinations; however, no significant association of adiponectin level with anthropometric measurements was found. It would be reasonable to extend further studies also to neonates born prematurely and to compare adiponectin level among neonates born from pregnancies complicated by more advanced hypertensive conditions such as preeclampsia or eclampsia. In addition, it seems advisable to expand the study by determining adiponectin level in the peripheral blood of newborns as further checkpoints of the study and to follow the development of children, their anthropometric measurements, and adiponectin level in later childhood.

Conclusion

This study demonstrated that among eutrophic neonates born at term, cord blood adiponectin level was the same after exposure to gestational hypertension as in normal pregnancies. Furthermore, adiponectin level does not appear to be significantly associated with neonatal

anthropometric measurements. Further investigations in children should be conducted, as they may identify potential individuals at risk of future metabolic and cardiovascular complications.

Author contributions

Justyna Czubilińska-Łada was involved in conceptualization, writing (original draft), and visualization; Aleksandra Gliwińska was involved in software and formal analysis; Elżbieta Świętochowska was involved with resources; Lucyna Nowak-Borzęcka was involved in data curation; Beata Sadownik was involved in investigation and supervision; Jakub Behrendt was involved in validation and supervision; Maria Szczepańska was involved in methodology and writing (review and editing).

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Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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