Maternal Serum and Cord Blood Leptin Concentrations at Delivery in Normal Pregnancies and in Pregnancies Complicated by Intrauterine Growth Restriction

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Keywords

Leptin · Intrauterine growth restriction · Birth weight · Pregnancy · Cord leptin

Abstract

Introduction: Leptin is a polypeptide hormone, and in pregnancy, it is secreted by the placenta and maternal and fetal adipose tissues. Normal leptin production is a factor responsible for uncomplicated gestation, embryo development, and fetal growth. The study compared maternal serum and cord blood leptin concentrations at delivery in normal pregnancies and in pregnancies complicated by intrauterine growth restriction (IUGR). **Methods:** The study was performed in 25 pregnant women with isolated IUGR and in 194 pregnant women without any complications. Leptin concentrations in maternal serum and in cord blood samples collected at delivery were measured by ELISA and subsequently analyzed by maternal body mass index (BMI), mode of delivery, and infant gender and birth weight. For comparative analyses of normally distributed variables, parametric tests were used, that is, the Student *t* test and a one-way ANOVA. The nonparametric Mann-Whitney test was used when the distribution was not normal. The Pearson correlation coefficient was calculated to assess the correlation between normally distributed variables ($p < 0.05$). **Results:** In

pregnancies complicated by IUGR, the mean maternal serum leptin concentration at delivery was significantly higher (52.73 ± 30.49 ng/mL) than in normal pregnancies (37.17 ± 28.07 ng/mL) ($p = 0.01$). The mean cord blood leptin concentration in pregnancies complicated by IUGR was 7.97 ± 4.46 ng/mL and significantly lower than in normal pregnancies (14.78 ± 15.97 ng/mL) ($p = 0.04$). In normal pregnancies, but not in pregnancies complicated by IUGR, a statistically significant correlation was established between maternal serum leptin concentrations and maternal BMI at delivery ($r = 0.22$; $p = 0.00$). No statistically significant correlation was found between cord blood leptin concentrations and maternal BMI in either study subjects or controls. In normal pregnancies, but not in pregnancies complicated by IUGR, a strong correlation was observed between cord blood leptin concentrations and birth weight ($r = 0.23$; $p = 0.00$). **Conclusions:** Elevated maternal blood leptin concentrations in pregnancies complicated by IUGR may indicate a significant adverse effect of elevated leptin on fetal growth. The differences in leptin concentrations, measured in maternal serum and in cord blood, between the study subjects and controls suggest that deregulated leptin levels may increase the risk of obstetric complications associated with placental insufficiency.

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Introduction

Extensive research into leptin conducted since its discovery over 2 decades ago has revealed its involvement in normal and pathological pregnancies [1]. It has been demonstrated that normal leptin production is a factor responsible for normal gestation, embryonic/fetal development, and fetal growth. The presence of leptin in cord blood is another sign of its significant role in fetal development. Because of the pleiotropic mechanisms of its action and changes in concentrations throughout pregnancy, leptin levels may be considered a potential predictor for some complications of pregnancy, but this application requires further studies [1]. Leptin plays a key role in the earliest stages of pregnancy as it modulates the processes of proliferation, protein synthesis, or placental apoptosis, while the control of cellular proliferation is of significant importance for normal development of the placenta. In intrauterine growth restriction (IUGR), the structure of the blood vessel wall in the uterus and placenta is altered. The inner wall layers thicken, and the lumen narrows which leads to changes in uteroplacental blood flow. Decreases in circulating blood volume lead to increases in blood viscosity and vascular resistance which result in placental flow disorders [2]. With an insufficient placenta, the exchange of nutrients between mother and developing fetus and adequate blood oxygenation are impaired. A reduced blood flow in the uteroplacental and feto-placental circulation adversely affects the maternal-fetal exchange and ultimately leads to chronic hypoxia and fetal growth arrest [3, 4]. Intrauterine fetal growth is a multifactorial process determined by numerous genetic, metabolic, and hormonal causes in mother, developing fetus, and placental tissue. IUGR is a complex obstetric problem which results from these etiologic factors acting together [3]. Disturbance of fetal growth dynamics which do not correspond to gestational age can be hazardous to gestation and is in fact the second leading cause of perinatal mortality after prematurity. Studies of the role of leptin in reproduction stress that its normal concentration is associated with normal embryonic/fetal development, while deregulated levels may be responsible for abnormal birth weight [1]. Many authors consider leptin to be a regulator of fetal growth [1, 5]. Blood concentrations of leptin reflect maternal nutritional status and additionally when deregulated are a risk factor for IUGR [1]. Low leptin levels have been associated with disorders of fetal growth. A correlation between the maternal leptin concentration at delivery and the neonate's birth weight has been reported [6]. Research has confirmed that maternal

serum leptin concentrations at delivery were significantly elevated and cord blood concentrations were lower in pregnancies complicated by IUGR than in non-IUGR pregnancies [7–11]. This may suggest a compensatory mechanism by which small placentas produce more leptin [10]. It has been also suggested that leptin may be a marker of placental insufficiency, which is associated with increased placental leptin production. On the other hand, some authors did not find any significant differences in cord blood leptin concentrations between IUGR and normal pregnancies [12]. These inconsistent findings show that the association between IUGR and leptin concentrations remains to be clarified and further prospective studies are needed. To date, studies have been conducted in small groups of subjects and they did not involve concurrent leptin measurements in maternal serum at delivery and in cord blood in mother-infant pairs. Our study aims at filling this gap in knowledge.

Considering a significant role of leptin in fetal development, we decided to investigate whether there was any association between maternal and fetal leptin levels and IUGR. We measured leptin concentrations in the maternal serum and in the cord blood of the infants in normal pregnancies and in pregnancies complicated by IUGR, and the collected data were analyzed.

Objective

The objective of the study was to compare at delivery maternal serum and cord blood leptin concentrations in normal pregnancies and in pregnancies complicated by IUGR.

Material and Methods

The study included 25 pregnant patients with isolated IUGR and 194 normal pregnant women who served as controls and was conducted in the period between January 2015 and June 2017 in 2 first- and second-level hospitals in Warsaw. All women gave written informed consent to participate in the study. The study was approved by the Bioethics Committee at the Medical University of Warsaw (approval code: KB/204/214).

In all study subjects, IUGR was diagnosed by ultrasonography (abdominal circumference below the 5th percentile abdominal circumference of corresponding gestational age) and by postnatal assessment of the neonate (birth weight below the 10th percentile weight of corresponding gestational age) [13, 14]. In all cases, the asymmetrical type of IUGR was diagnosed, mostly the result of placental insufficiency. Maternal serum leptin concentrations were measured at delivery, in women with IUGR between gestation weeks 33 and 39 and in controls between gestation weeks 33

Table 1. Subject characteristics

	Controls (N = 194)						IUGR (N = 25)					
	mean	min	max	25th quartile	75th quartile	SD	mean	min	max	25th quartile	75th quartile	SD
Maternal age, years	30.0	18.0	44.0	26.0	34.0	5.2	31.0	25.0	37.0	30.0	34.0	3.3
Third-trimester BMI, kg/m ²	28.1	17.5	40.2	25.2	30.7	4.1	25.7	21.0	33.9	24.0	27.8	3.3
Gestational age at delivery, weeks	38.9	37.0	40.0	38.0	40.0	1.1	37.0	33.0	39.0	36.0	37.0	1.3
Birth weight, g	3,454.3	1,480.0	5,030.0	3,190.0	3,780.0	503.9	2,440.0	1,750.0	3,770.0	2,030.0	2,650.0	497.6
Birth length, cm	54.9	44.0	62.0	54.0	57.0	2.7	49.0	42.0	57.0	47.0	50.0	3.1

kg/m², kilograms/meters squared; IUGR, intrauterine growth restriction; BMI, body mass index.

and 41. Multiple gestations, complications of pregnancy other than IUGR, maternal chronic disease, and intrauterine fetal death were the exclusion criteria.

The study material consisted of leptin samples derived from 2 sources, placental leptin measured in maternal blood, and fetal leptin measured in cord blood. Maternal blood samples (9 mL) were collected from an antecubital vein at delivery, and fetal blood samples (9 mL) were collected from the umbilical vein immediately after delivery. After centrifugation of full blood, sera were stored at -80°C until leptin measurement. Measurements were performed by the immunoenzymatic test ELISA using commercial kits (R&D Systems, Bio-Techne). The assay employed a monoclonal antibody specific for human leptin coated on a 96-well microplate. Immediately before the assay, each serum sample was diluted 1:100 with 1× Calibrator Diluent RDSP (10 μL of serum sample and 999 μL of 1× Calibrator Diluent). 100 μL of Assay Diluent RD1-19 was added to each well. 100 μL of serum sample and 100 μL of standard provided by the manufacturer were added to each well, and the plate was incubated for 2 h at room temperature. After incubation, the supernatant was aspirated from wells which were washed 4 times with 400 μL of wash buffer. After the last wash, 200 μL of leptin conjugate (antileptin antibodies conjugated with horseradish peroxidase) was added to each well and the plate was incubated for 1 h at room temperature. After incubation, the supernatant was aspirated from wells which were then washed 4 times. Next, 200 μL of substrate solution (substrate for horseradish peroxidase) was added to each well and the plate was incubated for 30 min at room temperature, in the dark. After incubation, 50 μL of stop solution (sulfuric acid) was added to each well. The absorbance of the enzyme reaction color product of each well was read at 450 nm using the ASYS UN340 microplate reader. Based on the absorbance of each well with standard solutions, the standard curve was generated and subsequently used to calculate leptin concentrations in serum samples. For a sample size of 25 μL , the detection limit was 0.17 ± 2 SD. All samples were run in duplicate, and the coefficient of variation cutoff point for each duplicate was 15%.

The following were recorded for each mother-infant pair: maternal body mass index (BMI) at the time of leptin measurement, gestation weeks at delivery, birth weight, mode of delivery, and infant gender. BMI was calculated as weight in kilograms divided by height in meters squared. Standard anthropometric measurements of the infants were performed. The measurements of the body length and weight were precise to 0.1 cm and 0.1 kg, respectively.

Statistical analysis was performed with STATISTICA PL package (StatSoft, Krakow, Poland). Descriptive statistics were used to present descriptions of quantitative variables. For comparative analyses of normally distributed variables, parametric tests were used, that is, the Student *t* to test the assumption of homogeneity or nonhomogeneity of variance and a one-way ANOVA when >2 groups were compared. The nonparametric Mann-Whitney test was used when the distribution was not normal. The Pearson correlation coefficient was calculated to assess the correlation between normally distributed variables ($p < 0.05$).

Results

The mean age of women was 30.0 ± 5.2 years in the control (non-IUGR) group and 31.0 ± 3.3 years in the study (IUGR) group. The mean BMI at delivery was 28.1 ± 4.1 kg/m² in the control group and 25.7 ± 3.3 kg/m² in the study group. The mean length of gestation was 38.9 ± 1.1 weeks in the control group and 37 ± 1.3 weeks in the study group. The mean birth weight and length of neonates were $3,354 \pm 503.9$ g and 54.9 ± 2.7 cm, respectively, in the control group and $2,440 \pm 497.6$ g and 49 ± 3.1 cm, respectively, in the study group (Table 1).

The mean maternal serum leptin concentration in pregnancies with IUGR was 52.73 ± 30.49 ng/mL, and it was significantly higher, by 42%, than in normal pregnancies ($p = 0.01$). The mean cord blood leptin concentration in IUGR was 7.97 ± 4.46 ng/mL, and it was significantly lower, by 46%, than in infants without IUGR ($p = 0.04$) (Table 2; Fig. 1, 2).

In women with normal pregnancies, a statistically significant positive correlation was established between maternal serum leptin concentrations and third-trimester BMI ($r = 0.22$; $p = 0.00$) (Fig. 3), but not between cord blood leptin and third-trimester BMI. In women with pregnancies complicated by IUGR, no statistically significant correlations were established between third-trimes-

Fig. 1. The differences in maternal serum leptin concentrations between normal pregnancies (controls) and pregnancies complicated by IUGR (the median, quartiles, and outliers). IUGR, intrauterine growth restriction.

Fig. 2. The differences in cord blood leptin concentrations between normal pregnancies (controls) and pregnancies complicated by IUGR (the median, quartiles, and outliers). IUGR, intrauterine growth restriction.

Table 2. Statistical analysis of the differences in leptin concentrations between normal pregnancies (controls) and pregnancies complicated by IUGR

Leptin concentration	Controls mean	IUGR mean	<i>t</i>	df	<i>p</i>	Controls <i>N</i>	IUGR <i>N</i>	Controls SD	SD IUGR
Maternal serum	37.17	52.73	-2.58	217	0.01	194	25	28.07	30.49
Cord blood	14.78	7.97	2.12	217	0.04	194	25	15.97	4.46

t, Student's *t* test; df, degree of freedom; *p*, *p* value; SD, standard deviation; IUGR, intrauterine growth restriction.

ter BMI and either maternal serum leptin or cord blood leptin.

In women with normal pregnancies, no statistically significant correlation was found between leptin concentrations in maternal serum and infant birth weight. However, a statistically significant positive correlation was established between leptin concentrations in cord blood and infant birth weight ($r = 0.23$, $p = 0.00$) (Fig. 4). In pregnancies complicated by IUGR, no correlation was found between maternal serum and cord blood concentrations of leptin and infant birth weight. In both IUGR and non-IUGR pregnancies, there was no correlation between maternal serum and cord blood concentrations of leptin and infant gender or mode of delivery.

Discussion

Studies have demonstrated a significant role of normal leptin levels for fetal and neonatal growth and development, and many authors believe that leptin actually acts as a regulator of fetal growth [5, 10, 15, 16]. This claim and opinion that leptin is also a marker of energy stores and a modulator of many biochemical processes during pregnancy are confirmed by the identification of leptin receptors in the placenta and in fetal tissues, including bone and cartilage [1]. Studies in pregnancies complicated by IUGR prove that placental abnormalities strongly correlate with low birth weight. Biswas et al. [4] observed increased focal degeneration of the syncytio-

Fig. 3. Correlation between maternal serum leptin concentrations and third-trimester BMI. BMI, body mass index.

Fig. 4. Correlation between cord blood leptin concentrations and infant birth weight ($r = 0.23$, $p = 0.00$).

trophoblast basal membrane in placentas from pregnancies complicated by IUGR compared to placentas from normal pregnancies. Further observations demonstrated that chronic inflammation within the placental villi could be responsible for a significant reduction of the fetal-maternal exchange. Reduced transport of leptin gene transcriptions in the placentas of IUGR fetuses and low cord blood leptin concentrations have been reported. Catov et al. [8] found lower leptin levels in neonates with IUGR diagnosed prenatally. Studies in twin pregnancies found significantly lower cord blood concentrations of leptin in the twins with IUGR than in the co-twins with normal growth. In the study by Sooranna et al. [9], the cord blood leptin concentrations in the twin with normal growth were at least 2-fold higher than those in the co-twin with IUGR. All these findings suggest a significant role of leptin as a regulator of fetal growth. In an earlier study, we established in normal pregnancies the reference intervals for leptin concentrations in the maternal serum and in cord blood. This study demonstrates significant differences in leptin concentrations, both in maternal serum and in cord blood, when measurements in normal pregnancies and in pregnancies complicated by IUGR are compared. In this study, we found that the mean maternal serum leptin concentration was significantly higher in pregnancies complicated by IUGR than in normal pregnancies. Comparison of the median leptin concentrations in maternal serum measured at delivery in the third trimester showed that in pregnancy weeks 36–39, the median maternal serum leptin levels in IUGR pregnancies were consistently higher than in normal pregnancies. The differences in leptin concentrations between normal and IUGR pregnancies suggest that leptin may have a role in the pathomechanism of some complications of pregnancy. Comparing leptin concentrations in IUGR pregnancies against the reference intervals established in normal pregnancies shows that leptin concentrations may be a useful prediction tool for complications of pregnancy. Semczuk-Sikora et al. [6] reported similar findings of higher mean serum leptin levels in pregnant women with IUGR than in women with healthy pregnancies. Elevated leptin levels may be maintained by an intrinsic compensatory mechanism as small placentas may produce more leptin in response to poor oxygen delivery. Our findings of significantly lower cord blood leptin concentrations in the infants with IUGR than in the infants with normal growth are in agreement with the results reported by Yildiz et al. [16] and Pighetti et al. [10]. Decreased cord blood concentrations of leptin in IUGR are thought to be related to reduced adipose tissue

deposition in fetuses with IUGR and may signal long-lasting alterations in adipocyte function, possibly resulting in metabolic disorders in later life [15]. Some authors believe that IUGR is strongly associated with maternal nutrition at specific stages of gestation [17–19]. Maternal obesity carries an increased risk of complications in pregnancy including IUGR [18–20]. On the other hand, studies in hypotrophic neonates found that low-birth-weight infants were more frequently born to mothers who had protein- and calorie-restricted (600–900 kcal/day) diets in the second and third trimesters. Pre-pregnancy maternal body weight and its gain during pregnancy are the most important factors correlated with the infant's birth weight. However, maternal body weight is not a sole or most important risk factor for IUGR as the etiologies are diverse. Restricted maternal diets, for example, glucose restriction, may result in fetal hypotrophy as glucose is the main nutrient necessary for fetal growth [2]. Accordingly, research was conducted to investigate any possible relationship between maternal leptin levels, BMI, and glucose levels and to find out whether disturbances in carbohydrate metabolism could be another risk factor for IUGR. Like Pighetti et al. [10], we did not find any significant correlations between BMI and leptin concentrations in either maternal serum or cord blood in pregnancies complicated by IUGR, but in non-IUGR pregnancies a significant correlation was established between maternal BMI and serum leptin levels. Marino-Ortega et al. [21] reported similar findings and demonstrated a strong association between blood leptin concentrations and weight gain in pregnancy. Shroff et al. [15] described a moderate correlation between maternal blood leptin concentrations and BMI. Yildiz et al. [16] found a positive correlation between maternal serum leptin concentrations and BMI in pregnancies with IUGR. These discrepancies in the results reported from studies in IUGR and non-IUGR pregnancies show that the relationship between BMI and maternal blood leptin concentrations has not been fully elucidated and maternal leptin levels could be influenced by other factors or complications of pregnancy. Studies in premature and small for gestational age infants with low birth weight found lower cord blood concentrations of leptin than in infants with high birth weight [22–26]. The authors argue that in utero leptin acts as a regulator of neuronal circuits controlling nutrient intake and appetite. Leptin not only regulates body weight but also has an important role in newborn adaptation to extrauterine life. The level of neonatal stress depends on factors such as gestational age, birth weight, or mode of delivery. Leptin reduces

neonatal responsivity to stress by an increased expression of glucocorticoid receptors in the central nervous system and an increased sensitivity to glucocorticoid negative feedback [21]. In this study, no correlation was established between birth weight and maternal serum leptin levels in pregnancies complicated by IUGR, which was in agreement with the results reported by Pighetti et al. [10]. These findings may confirm the hypothesis that placental and fetal leptins act individually. Lower leptin concentrations in cord blood may suggest that it is secreted mainly by fetal adipose tissue rather than the placenta [10]. Also, Yildiz et al. [16] did not find any correlation between maternal serum leptin concentrations and infant birth weight, although a correlation between cord blood leptin and infant birth weight, but not infant BMI, was established by Pighetti et al. [10] and Tamura et al. [27]. These observations suggest that leptin is not a sole regulator of intrauterine growth disorders. Most published studies in IUGR pregnancies do not describe any correlation between maternal blood leptin concentrations and fetal weight [27–29]. Since no significant correlations have been established and the results reported from different centers are inconsistent, the relationship between leptin levels and fetal growth/development obviously needs further studies. In this study, we also assessed maternal serum leptin concentrations and infant birth weight in normal pregnancies and found no statistically significant correlation. However, there was a statistically significant correlation between cord blood leptin concentrations and birth weight. The findings are confirmed in the literature and attributed to the role played by leptin in the regulation of appetite and metabolism. Leptin may be responsible for body weight changes in neonates in the first days after birth, and its levels may serve as an indicator of nutritional status [8, 23–26, 30, 31]. Further studies should examine maternal leptin levels in IUGR by gestational week to see at what pregnancy week(s) leptin levels significantly differ from the reference range in normal pregnancy. This would allow assessment of the utility of leptin as a predictor of the severity and progression of IUGR.

Strengths and Limitation

The presented results have certain limitations which should be taken into account in their analysis and interpretation. This was a cross-sectional study, and the study group was relatively small. However, considering that in pregnancies complicated by IUGR we found significantly higher maternal serum leptin concentrations than in normal pregnancies, it may be assumed that maternal blood

leptin could be a valuable additional marker (diagnostic tool) to use for predicting some complications of pregnancy. Before its clinical use could be reliably recommended, further studies and clinical observations are needed. It would be advisable to check the reproducibility and generalizability of the present results in cohort studies and in prospective studies in definitely larger populations of women recruited in earlier stages of pregnancy, to assess leptin levels for changes over time, by gestational age. Another important question deserving research is the relationship, if any, of low blood cord leptin concentrations in infants with IUGR and their further weight gain as they get older.

Conclusions

1. Maternal serum leptin concentrations were elevated in pregnancies complicated by IUGR.
2. In pregnancies complicated by IUGR, significant differences in leptin concentrations between maternal serum and cord blood may suggest the effect of an intrinsic compensatory mechanism, whereby small placentas release larger amounts of leptin.
3. Prospectively, leptin can be assessed as a marker of placental insufficiency in complications of pregnancy other than IUGR.
4. Impaired leptin production was found in infants with IUGR compared to infants in normal pregnancies.
5. Low leptin concentrations in the cord blood of infants with IUGR indicate lower adipose tissue deposition and point to leptin involvement in the pathomechanism of IUGR.

Acknowledgments

The investigators wish to express their thanks to the patients for their participation in the study.

Statement of Ethics

Participants gave their consent in writing to the use of their samples for research. All women gave informed written consent to participate in the study. The study was approved by the Bioethics Committee at the Medical University of Warsaw (approval code: KB/204/214).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The research was financed from the fund for scientific research and development projects selected on a highly competitive basis at the Faculty of Health Sciences, Medical University of Warsaw (decision code: NZG/PM4/16). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Author Contributions

Małgorzata Stefaniak contributed to conceptualization, data curation, formal analysis, methodology, and writing – original draft, review, and editing. Ewa Dmoch-Gajzlerska contributed to conceptualization, review, and editing.

Data Availability Statement

The data that support the findings of this study are openly available in <https://figshare.com/s/4acec1d7f0f3814a09cb> reference number 10.6084/m9.figshare.10058114.