An analysis of factors determining serum leptin concentration in healthy and infected newborns

Beata Sadownik [1], Witold Lukas [2], Jakub Behrendt [1], Małgorzata Stojewska [1], Magdalena Kwiatkowska-Gruca [1], Katarzyna Rygiel [2], Krystian Adamik [2], Urszula Godula-Stuglik [1]

1 Neonatal Intensive Care Unit, Department of Pediatrics, Zabrze, Silesian Medical University, Poland
2 Department of Family Medicine, Zabrze, Silesian Medical University, Poland

Correspondence to: Jakub Behrendt, MD.
Neonatal Intensive Care Unit, Department of Pediatrics,
Silesian Medical University,
3 Maja 13/15, 41-800 Zabrze, Poland.
e-mail: jbeh@poczta.onet.pl, jbehrendt@sum.edu.pl

Submitted: 2009-05-28 Accepted: 2009-11-12 Published online: 2010-04-28

Key words: **leptin; anthropometric parameters; intrauterine infection; neonatal infections**

Neuroendocrinol Lett 2010; **31**(2):221–228 **PMID:** 20424594 NEL310210A02

Abstract

OBJECTIVE: The effect leptin on fetal growth in healthy and infected newborns is not well known. This study is aimed at: 1) evaluating serum leptin concentration in full term and preterm, healthy and infected newborns, according to their gender, birth asphyxia, intrauterine and neonatal infections, and 2) assessing the correlation between serum leptin levels and anthropometric parameters among healthy and infected newborns.

MATERIALS AND METHODS: The study involved 146 newborns: 73 full-term and 73 preterm, 86 male and 60 female, 56 healthy and 90 infected, aged from 2nd to 4th day of life. Anthropometric parameters, including: birth weight, length, head and chest circumference, and serum leptin concentration were measured in all the subjects. Intrauterine and neonatal infections were diagnosed by the standard criteria.

RESULTS: In this study, it was found that both healthy and infected, but full-term newborns had significantly higher mean leptin concentration than the premature ones ($p<0.05$). Statistically significant ($p<0.05$), positive correlations were found between serum leptin level and gestational age, birth weight, head and chest circumference, both in healthy, and in infected newborns.

CONCLUSIONS: Findings of this study suggest that the serum leptin concentration in full term newborns is higher than in the preterm ones, and in females it is higher than in males, 2) among both healthy and infected newborns, there is a positive, linear correlation between the serum leptin concentration and anthropometric parameters, 3) intrauterine and neonatal infections do not have a significant influence on serum leptin concentration. The role of leptin in fetal growth deserves further research.

ORIGINAL ARTICLE

INTRODUCTION

A very important group of factors regulating intrauterine fetal growth and development consist of fetal factors, among which the endocrine ones are synthesized in early stages of the development. These factors include insulin, growth hormone, insulin-like growth factors, adiponectin, epidermal growth factors, and leptin (Akcurin *et al.* 2005; Baby *et al.* 2004). The name leptin is derived from a Greek word "*leptos*" that means "lean". The leptin is a molecule composed of 146 amino-acids, circulating in bloodstream. Its half life is about 25 minutes (Bazela 2005). It is produced mostly by mature cells of the white adipose tissue, and to a lesser degree, by the brown adipose tissue. It is also synthesized, in smaller quantities, in muscle cells, epithelial mucosa of the stomach, as well as in the pituitary gland and placenta (Domali *et al.*2002; Esler *et al.* 1998).

Leptin exerts multidimensional actions in the entire body. It is transported from bloodstream to the central nervous system (CNS), where in hypothalamus, connects with its specific receptors, causing inhibition of the synthesis and secretion of the neuropeptid Y. Lowering the concentration of this neuropeptid leads to a decrease of an appetite, and in consequence, it may cause the decrease of body mass (bm) (Bazela 2005). In addition, leptin affects the secretion of other hypothalamic neuropeptides, including proopiomelanocortin, melanothropin, and corticoliberin. Corticoliberin is widely distributed in the CNS, particularly in the periventral area of hypothalamus, where it plays a potentially anorexigenic role, similarly to leptin. Furthermore, leptin may act independently or synergistically with insulin, causing an increase of glucose intake, inhibition of secretion of the neuropeptid Y, and appetite decrease. Hyperinsulinemia that lasts for a longer period of time leads to an increase of the leptin concentration (Kautzky-Willner *et al.* 2001). This effect is most probably caused by the trophic effect of insulin on adipocytes. Therefore, elevated leptin concentrations are found in newborns of diabetic mothers (Janeckova 2001).

According to some studies, the leptin deficit or resistance to it, leading to obesity, might also be a reason for obstructive respiratory disorders, such as sleep apnea-hypopnea syndrome. It is believed that leptin may play the role of growth factor in lungs, and serve as a neurohormonal modulator of the central regulation of respiration (Janeckova 2001). A high leptin value represents the degree of resistance to leptin at the hypothalamus level, and contributes to increased mobilization of the peripheral fatty acids (Kulik-Rechberger *et al.* 1998; Linnemann *et al.* 2000; Tamura *et al.* 1998). In contrast, in pregnancies complicated by pathology, like preeclampsia, the level of circulating leptin is much higher (Hytinanti *et al.* 2000; Laivuori *et al.* 2006; Laml *et al.* 2001). It is thought that the leptin level may be one of the factors of placental insufficiency, inhibiting intrauterine fetal growth. In recent studies, the role of leptin was analyzed under different nutritional conditions, both among children and adults, in processes of growth and sexual maturation, and also with relation to the body fat content (Barash *et al.* 1996; Domali *et al.* 2002; Esler *et al.* 1998; Iwagaki *et al.* 2004; Kotulska *et al.* 2002; Lepercq *et al.* 2003; Lin *et al.* 2005; Valle *et al.* 2003).

In the literature, there is only a limited number of papers that determine the serum leptin concentration in conditions of intrauterine infection and neonatal sepsis, in full term and preterm newborns (Akcurin *et al.* 2005; Chiesa *et al.* 2008; Matsuda *et al.* 1997; Ochoa *et al.* 2001; Orbak *et al.* 2003; Ozdemir *et al.* 2007; Petridou *et al.* 2005 Vatten *et al.* 2002; Yeung *et al.* 2003). For this reason, it is not possible to establish an association between the leptin values in sick (mostly infected) newborns, including their gender, general status after birth, and anthropometric parameters (Koc *et al.* 2003; Orbak *et al.* 2003; Shekhawat *et al.* 2000; Su *et al.* 2002). In addition, previous studies have suggested that in acute stages of infections, the leptin concentration may change (Orbak *et al.* 2003). In attempt to further explain this topic, we conducted the study that was aimed at: 1) evaluating serum leptin concentration in both full term and preterm, healthy and infected newborns, according to their gender, gestational maturity, birth asphyxia, intrauterine infection, and neonatal sepsis, and 2) assessing the correlation between serum leptin levels and anthropometric parameters in both healthy and sick newborns.

MATERIAL AND METHODS

Study subjects

The study population consisted of 146 newborns aged from 2nd to 4th day of life. It included 73 (50%) full term and 73 (50%) preterm newborns. There was 86 males and 60 females, among whom, 87 (59.6%) were delivered through natural birth passages, and 59 (40.4%) by cesarean section. The study was approved by the Ethics Committee of Silesian University of Medicine (SUM), in Katowice, Poland, on February 12, 2002 (NN-013-23/02). Parents or legal guardians of the newborns gave their informed consent to participate. The study was conducted in the years 2002–2005, at the SUM academic hospitals. Healthy newborns were delivered at the Obstetrics Department (OD) of the SUM in Zabrze, Poland, and the infected ones were treated at the Neonatal Intensive Care Unit (NICU) of the SUM in Zabrze, Poland. Newborns who were small for their gestational age, and the ones delivered from pregnancies complicated by maternal diabetes or other endocrine disorders were excluded from the study.

Clinical data of the study newborns were collected from their hospital OD and NICU case records. The degree of the study subjects' maturity was assessed based on the duration of pregnancy, according to Naegele formula, and subsequently verified by an ultra-

sound assessment. Normal birth weight (range 10–90 pc.) was evaluated, according to birth weight percentile charts for Silesian newborns population (these details are specifically described by Baumert *et al.* (1993)).

All the study newborns were divided into 4 groups, based on standard clinical criteria, considering the occurrence of intrauterine infection, and gestational age:

I group - included 41 healthy, full-term newborns,
II group - included 15 healthy, premature newborns,
III group - included 32 infected, full-term newborns,
IV group - included 58 infected, premature newborns.

Clinical characteristics of the study subjects are shown in Table 1.

Clinical and laboratory examination of the study subjects

Anthropometric measurements were performed in all the newborns immediately after birth, and included:

- birth weight – checked with a standard neonatal scale,
- birth length – measured with a medical centimeter scale, along physiological body curvatures, from vortex to the plantar plane of feet, positioned perpendicularly to shanks,
- head circumference (occipital-frontal) – measured with a medical centimeter scale, through the point on the forehead, between frontal tubers and the point located the furthest to the back of the occiput,
- chest circumference – measured with a medical centimeter scale, at the level of junction of the sternal body and xyphoid process.

With regard to the analyzed neonatal infections, in addition to their clinical evaluation, the following diagnostic criteria were applied as mandatory:

- for intrauterine sepsis – the presence of clinical inflammatory signs in at least two organs or systems, and a positive blood culture,
- for pneumonia (in an early stage; isolated, in the course of sepsis, or coexisting with the acute respiratory disease syndrome – ARDS) – the presence of concomitant respiratory failure within the first 48 hours of life, and changes on the chest X-ray,
- for purulent meningitis – abnormal results of the cerebro-spinal fluid (CSF) analysis, obtained by a lumbar punction, with pleocytosis (above 32/mm^3, predominance of PMNS), CSF protein concentration > 200 mg %, low CSF glucose level (<80% of serum level), and the presence of bacteria (conditional, due to finding of pathogens of the purulent meningitis only in 50% of cases),
- for urinary tract infection – bacteriuria (above 10^5 colonies/ml), with concomitant pyuria,
- for dermatitis – the presence of multiple purulent skin lesions, confirmed by bacterial cultures, obtained from the inflammatory skin changes (Staphylococcus aureus was found to be the most common pathogenic strain),
- for ARDS – clinical symptoms of respiratory insufficiency, and typical signs on the chest X-ray.

In addition, an intracranial hemorrhage was detected, by using a transfontaneal ultrasound scan of the brain, and the birth asphyxia was determined, according to low Apgar score at 1st minute of life, and the pH value below 7.16, from the venous cord blood.

Measurement of serum leptin concentration

Concentration of leptin in serum of the venous blood was determined by using a disposable commercial

Tab. 1. Clinical characteristic of examined four groups of newborns.

Group	Sex		Mean±SD (minimum–maximum)					
	M	F	Gestational age (weeks)	Body weight (g)	Lenght (cm)	Head (cm)	Chest (cm)	Apgar score (points) 1 min.
					circumferences			
Group I N=41	25	16	41.6±0.8 38.0–42.0	3 552±380.0 2 710–4 140	53.3±2.2 48–61	34.1±1.8 31–37	33.2±1.5 30–37	4–10
Group II N=15	7	8	35.7±0.7 32.0–37.0	2 492±210.0 1 710–2 850	47.4±1.8 40–53	32.2±1.2 29–35	29.2±1.6 25–33	5–10
Group III N=32	15	17	39.2±0.9 38.0–42.0	3 375±310.0 2 950–4 000	48.2±1.9 47–60	35.2±2.8 31–37	33.8±1.4 31–35	0–10
Group IV N=58	39	19	32.4±3.0 27.0–37.0	1 892±560.0 840–2 970	46.5±4.2 35–55	30.4±2.8 23–35	26.8±3.1 19–35	0–10

IRMA (immunoradiometric assay) test kits (manufactured by Diagnostic Systems Laboratories Inc., Webster, Texas, US). Samples of 1 ml of peripheral venous blood were collected at the exact time, from 8.00–9.00 AM, between 2nd and 4th day of life of a newborn. The specimens were immediately centrifuged, and the isolated serum was frozen and stored in the w temperature –28 °C, until measured. Testing procedures were performed by the same laboratory technician, in order to assure consistency of the results, and to minimize bias. All the analyses were performed at the Immunology Laboratory of the Silesian Pediatric Center, in Zabrze, Poland. The test results were reported in ng/ml. None of the study newborns received blood or any hematogenous preparation without a prior consent.

Statistical analysis

After establishing a normal distribution of the analyzed variables, by using the Kolmogorow-Smirnow test, comparisons between groups were performed using the Student t-test, when the distribution of data was normal, and the Mann-Whitney U test, when the distribution of data was different from normal. In addition, the Spearman correlation coefficient test was used for the evaluation of correlations between the leptin concentration, as a dependent variable and other study parameters. Multiple regression analysis was performed.

Statistical analyses were conducted using the *Statistica 7.1 program*. The data were presented as arithmetic mean ± standard deviation (SD), and the level of significance was accepted at $p<0.05$, for all the analyzed data.

RESULTS

Serum leptin concentrations in the four groups of newborns, including their gender, are shown in Table 2 and III. It has been demonstrated that both healthy and infected full term newborns had statistically significant, higher leptin concentration than the premature ones (Figure 1). No statistically significant differences between healthy and infected full term newborns and between healthy and infected premature ones were observed.

A significant positive linear correlations between the serum leptin concentration and gestational age in healthy (r=0.4196, $p<0.05$) and in infected newborns (r=0.3457, $p<0.05$), were found, as depicted in Figure 2.

Positive correlations between leptin concentrations and birth weight in healthy (r=0.4151, $p<0.05$), and in infected newborns (r= 0.4154, $p<0.05$) were also found. (Figure 3). In addition, the positive correlation between the leptin value and body length (r=0.415, $p<0.05$) was reported (Figure 4).

Furthermore, in both in healthy and infected newborns, a positive correlation between the leptin value and head circumference (r=0.3448, $p<0.05$ and r=0.3755, $p<0.05$) respectively, and the leptin value and chest circumference (r=0.4026, $p<0.05$ and r=0.389, $p<0.05$), respectively, were found.

Furthermore, based of multiple regression analysis, it was confirmed that there is an association between serum leptin concentration and low Apgar score (<6 points), female gender, gestational age, and birth weight of the newborns. These results are presented on Figure 5.

Tab. 2. Mean serum leptin concentration in examined four groups of newborns.

Group	n	Mean	CI. –95%	CI. 95%	Min	Max	Interval	Variation	St. dev.
Group Ia	41	3.73	3.26	4.20	1.27	7.90	6.63	2.22	1.49
Group Ib	15	2.44	2.25	2.63	1.82	2.93	1.11	0.12	0.35
Group IIa	32	3.94	3.29	4.59	1.66	9.08	7.42	3.23	1.80
Group IIb	58	2.44	2.12	2.75	0.92	6.92	6.00	1.44	1.20

Tab. 3. Mean serum leptin concentration in examined four groups of newborns regarding their sex.

Group of newborns		n	Mean	CI. –95%	CI. 95%	Min	Max	Interval	Variation	St. dev.
Group Ia	boys	25	3.96	3.23	4.69	1.27	7.90	6.63	3.14	1.77
	girls	16	3.36	2.93	3.79	2.32	5.08	2.76	0.66	0.81
Group Ib	boys	7	2.45	2.19	2.71	2.17	2.83	0.66	0.08	0.28
	girls	8	2.43	2.09	2.78	1.82	2.93	1.11	0.17	0.42
Gorup IIa	boys	15	3.22	2.53	3.91	1.66	6.27	4.61	1.55	1.25
	girls	17	4.58	3.55	5.60	2.53	9.08	6.55	3.99	2.00
Group IIb	boys	39	2.18	1.91	2.45	0.92	4.40	3.48	0.71	0.84
	girls	19	2.97	2.18	3.75	1.56	6.92	5.36	2.64	1.62

DISCUSSION

In our study, we examined the serum leptin concentration in healthy and infected newborns, with body mass appropriate for their gestational age. Our results have indicated a direct correlation between the serum leptin concentration and the birth weight. This observation is consistent with findings of other authors, who analyzed only the newborns born with body mass appropriate for gestational age (without an intrauterine dystrophy syndrome) (Matsuda *et al.* 1997; Vatten *et al.* 2002). A close correlation of the birth weight and serum leptin concentration was also found by Cetin *et al.* (2000), who studied newborns with different body mass, including normal, too small, or too big for the gestational age. In addition, these authors have shown, by calculating the serum leptin concentration per kilogram of the body mass, that there are no significant differences between the study groups. Also, research by Marchini *et al.* (1998) revealed that the newborns with excessive body mass, born from mothers, who had normal gestation, had their leptin concentration three times higher than the newborns with normal body mass. A correlation between the leptin concentration and birth weight was also confirmed by Polish authors (Garanty-Bogacka *et al.* 2003). According to their two-year analysis of the 54 newborns with the low body mass, including 31 premature, and 23 full term ones, there was no significant differences in the concentration of this hormone among full term newborns with low body mass, and the preterm ones, with a similar, low body mass.

Some authors have suggested that the leptin concentration in the cord blood is related to the body mass rather than to the gestational age and maturity. In our

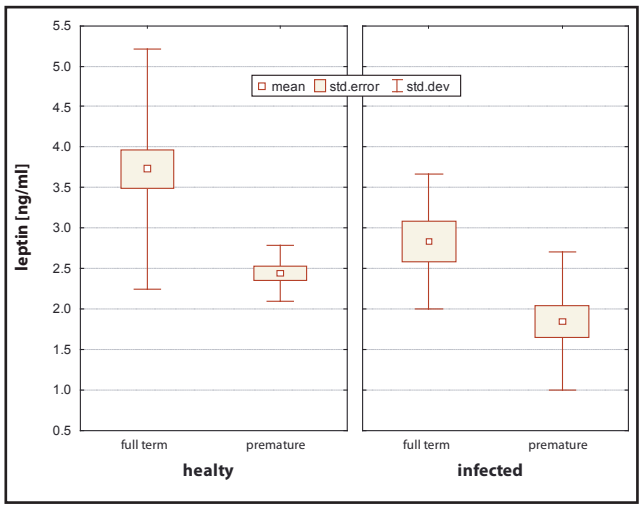

Fig. 1. Comparison of serum leptin concentration in groups of healthy and infected full-term and premature neonates.

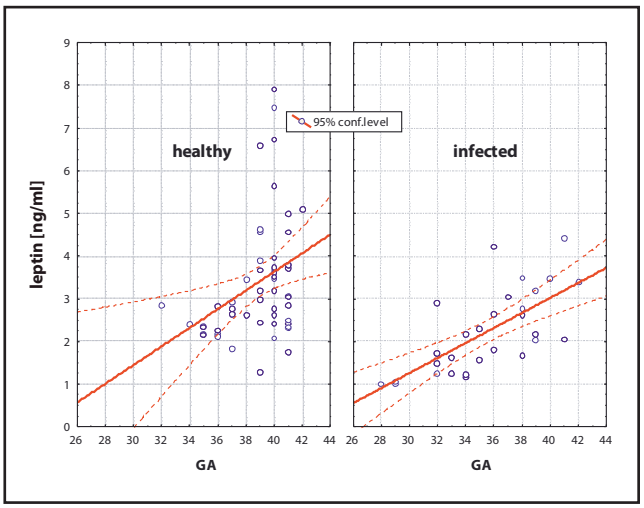

Fig. 2. Correlation between serum leptin concentration and gestational age in healthy and infected neonates.

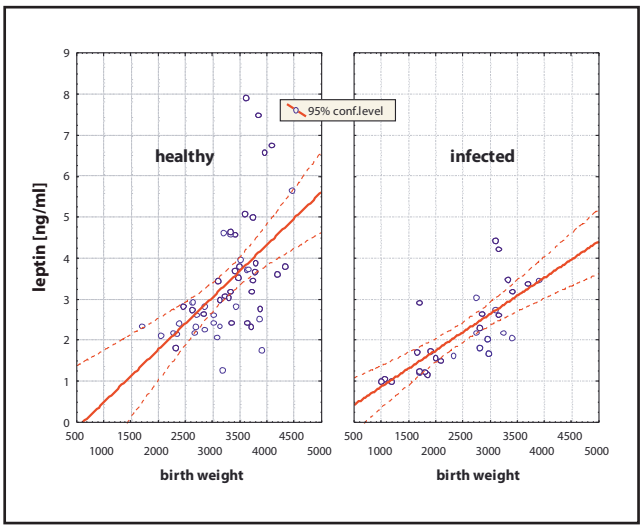

Fig. 3. Correlation between serum leptin concentration and birthweight in healthy and infected neonates.

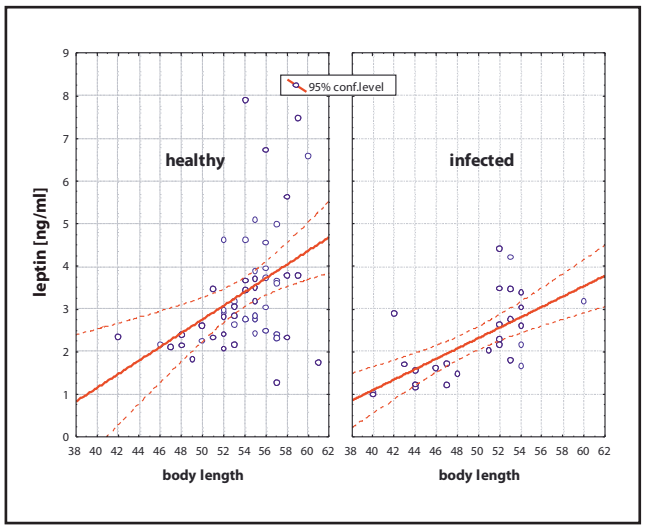

Fig. 4. Correlation between serum leptin concentration and body length in healthy and infected neonates.

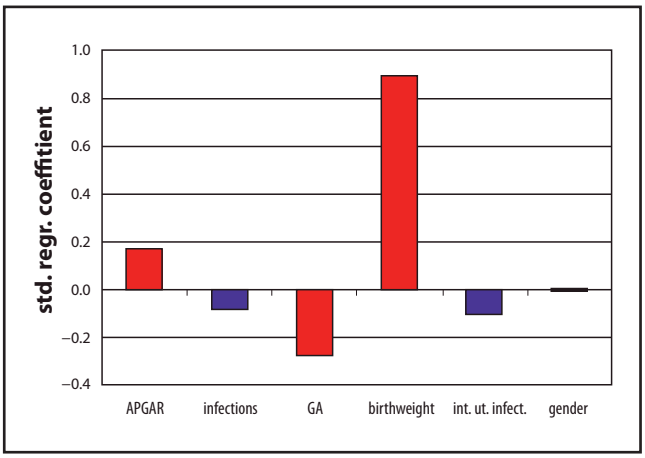

Fig. 5. Regression analysis of serum leptin concentration and Apgar score, incidence of infection, gestational age, birthweight, intrauterine infection and gender.

own material, in which we analyzed the relationship between the serum leptin concentration and gestational age of the newborns, born between 27 and 42 week of pregnancy, the positive correlation was found between these parameters, among both healthy and infected newborns. Similar to our results, Spear *et al.* (2001) fund a very low leptin concentration in preterm newborns, comparing to the full term ones. These findings may confirm some facts, related to the important role that leptin plays in the developmental processes, according not only to experimental studies (Barash *et al.* 1996), but also to the clinical ones, conducted by various research teams, among infants and older children (Frazer-Llado *et al.* 1996; Hassink *et al.* 1997; Savino *et al.* 2002; Spear *et al.* 2001). It has been suggested that the body mass, and closely related to it the appropriate amount of adipose tissue, are associated with the newborn's maturity more than the leptin concentration. This phenomenon may also be related to the pattern of newborn's feeding (Dundar *et al.* 2005). For instance, Savino *et al.* (2002) have found higher values of leptin levels in newborns fed naturally, comparing to the ones, who were fed with an artificial formula.

In addition, many authors consider that the gender of the newborn represents an important factor, which modulates the leptin concentration, apart from the body mass (Baby *et al.* 2004; Christou *et al.* 2001; Domali *et al.* 2002; Helland *et al.* 1998; Janeckova, 2001; Matsuda *et al.* 1997; Ng *et al.* 2001). In their studies, Laml *et al.* (2001), Petridou *et al.* (2005), and Helland *et al.* (1998) have shown statistically significant, higher leptin values in the cord blood among girls than among boys. Also, Okerere *et al.* (2002) have found a similar pattern of differences that can be partially attributed to the various content of adipose tissue, and to the lower body mass in male and female newborns, born to mothers with gestational diabetes.

According to Tome *et al.* (1997) some effect on the above phenomenon may also be attributed to a higher mass of placenta, found in pregnancies, from which female offspring were delivered. The placenta, as a short–living endocrine organ, manufactures and secretes different hormones, including leptin (Tome *et al.* 1997). In our study, we have indicated that the significantly higher leptin concentration in female newborns, comparing to the male ones, were present only among newborns with intrauterine infection, both full term and preterm. However, in these studies, only the newborns of the mothers with diabetes or other endocrine disorders were taken into consideration. These results, pertaining to the sick newborns, may indicate a considerable sexual dimorphism that is already emerging, during the initial period of life. In contrast, lack of this correlation among the healthy newborns in the study is probably related to a small study sample. Nevertheless, independent studies by some other authors did not confirm an association between the serum leptin concentrations and gender of healthy newborns (Akcurin *et al.* 2005; Kirel *et al.* 2000). Furthermore, many authors consider leptin to be an important factor, affecting anthropometric characteristics of a newborn that is evidenced by positive correlations between the leptin concentration and newborns' body length, head and chest circumference, measured at birth (Countant *et al.* 2001; Manderson *et al.* 2003; Matsuda *et al.* 1997; Petridou *et al.* 2005).

Our analysis of the leptin concentration in the two groups of newborns (the healthy ones, and the ones with intrauterine or neonatal infection), after adjusting for their gestational maturity, revealed no statistically significant differences between the healthy newborns and the ones with early stages of infections, including mainly sepsis and pneumonia, among full term and premature newborns. The results of our study support the ones of the other authors. In particular, Frazer *et al.* (1996) in their analysis of 100 children showed that among critically ill newborns, treated at the intensive care unit, the serum leptin concentration did not change significantly due to an infection. A similar observation was conducted by Koc *et al.* (2003), who analyzed the effect of sepsis on values of leptin, in a group of 20 newborns, and a correlation between the leptin concentration, and levels of TNF-alpha and IL-6, secreted in the course of sepsis.

Based on investigations by some other authors, the leptin, similarly to erythropoietin, appears to be a marker of the long-term fetal asphyxia that might represent a high predictive value with regard to further development of the child. The key role in stimulation of the leptin and erythropoietin gene expression, in response to hypoxia, is played by the transcriptive factor HIF-1 (hypoxia inducible factor), which is activated, depending on the cellular oxygen level. (Iwagaki *et al.* 2004; Tome *et al.* 1997). Based on the available literature, no information was found regarding any specific pattern of the leptin concentration in cases of acute hypoxia. In our study, we also analyzed

the leptin concentration in newborns, whose general clinical status during the first minute of life indicated current or past hypoxia around the delivery time. The number of points below 7 was established as a cut off value, according to the Apgar scale, as a standard criterion. By using the method of multiple regression analysis in healthy full term and preterm newborns, it was indicated that directly after birth, the worst was the status of the newborn, the higher was his/her serum leptin concentration. Therefore, hypoxia represents the second parameter, after the birth mass, which is closely correlated with leptinemia, in newborns without the intrauterine infection. On the other hand, lack of this correlation in sick newborns can be explained by the presence of serious infectious or inflammatory diseases, which can significantly attenuate the newborns' neuroendocrine reactivity. Furthermore, it is not possible to exclude the effect of time that elapsed from the initiation of hypoxia, since the examinations were performed during 3th and 4 th day of life, and because of that timing, there could have been a possibility of a decrease, or even cessation of hypoxemia, as well as its effects on the neuroendocrine and immune system, after the first 24 hours of life.

A strength of our analysis was its design that allowed us to examine and compare the serum leptin concentrations in full term and preterm, as well as in healthy and infected newborns, of both genders, taking into consideration their perinatal risk factors, such as intrauterine and neonatal infections, and birth asphyxia. Also, the laboratory methodology, assuring consistency of the results and in-patients settings of the academic medical center allowed us to perform a precise assessment of the correlation between the serum leptin levels and neonatal anthropometric parameters among the study subjects.

A limitation of this study was a small number of participants, one location, and its short duration. Also, only selected perinatal risk factors (related to infections and hypoxia) were analyzed. Nevertheless, the results of our study confirmed the prior notion that the early form of infection (around the delivery time), mostly generalized, does not play a significant role in the leptin secretion, during the first days of life. A detailed explanation of the importance of leptin in the process of fetal growth, especially in the earliest period of life of newborns with infections, still remains unresolved.

In conclusion, the findings of this study suggest that the:

- neonatal serum leptin concentration depends on the birth weight, gestational age, gender, and general status after birth. In full term newborns, it is higher than in the preterm ones, and in females it is higher than in males.
- among both healthy and sick newborns, there is a positive, direct, linear correlation between the serum leptin concentration and anthropometric parameters.
- intrauterine infection or others infectious complications of pregnancy do not have a significant influence on the serum leptin concentration in newborns.

Therefore, further experimental and clinical studies, providing more information about leptin's role in the process of fetal growth and development, as well as its regulation of the metabolism and energy utilization by growing organism of infant and small child are required on large population.

REFERENCES

1 Akcurin S, Velipasaoglu S, Akcurin G, Guntekin M. (2005). Leptin profile in neonatal gonadotropin surge and relationship between leptin and body mass index in early infancy. J Pediatr Endocrinol Metab. **18**: 189–195.
2 Baby ZA, Warsay AS, El-Hazmi MH, Addar MH. (2004). Leptin level in pregnant mothers at term and cord blood and effect of newborns gender. Saudi Med. **25**: 212–214.
3 Barash IA, Cheung CC, Weigle DS.(1996). Leptin is a metabolic signal to the reproductive system. **137**: 3144–3147.
4 Baumert M, Osuch-Jaczewska R, Paprotny M, Machalski T. (1993). Wskaźniki biologiczne rozwoju noworodków śląskich urodzonych między 30 a 42 tygodniem ciąży. **46**: 123–126.
5 Bazela K. (2001). Leptyna przekaz sygnału i współdziałanie z cytokinami. **28**: supl.16: 23–34.
6 Cetin J, Morpugo PS, Radaelli T. (2000). Fetal plasma leptin concentrations: relationship with different intrauterine growth paterns from 19 weeks to term. Pediatr Res.**48**: 645–651.
7 Chiesa C, Osborn JF, Haass C, Natale F, Spinelli M, Scapillati E, Spinelli A, Pacifico L. (2008). Ghrelin, leptin, IGF-1, IGFBP-3 and insulin concentrations at birth: is there a relationship with fetal growth and neonatal anthropometry? Clin Chem. **54**: 550–55
8 Christou H, Connors JM, Ziotopoulou M, Hatzidakis V, Papathanassoglou E, Ringer S.A., Mantzoros Ch. (2001). Cord blood leptin and insulin-like growth factor levels are independent predictors of fetal growth. J Clin Endocrinol Met. **86**: 935–938.
9 Countant R, Boux S, Douay O, Mathieu E, Rouleau S, Beringue F, Gillard Ph, Limal JM, Descamps P. (2001). Relationship between placental GH concentration and maternal smoking, newborn gender and maternal leptin: possible implications for birth weight. J Clin Endocrinol Metab. **86:** 4854–4859.
10 Domali E, Messinis IE. (2002). Leptin in pregnancy. J Matern Fetal Neonatal Med. **12**: 222–230.
11 Dundar NO, Anal O, Dundar B, Ozkan H, Caliskan S, Buyukgebiz A. (2005). Longitudinal investigation of the relationship between breast milk leptin levels and growth in breast-fed infants. J Pediatr Endocrinol Metab. **18**: 181–188.
12 Esler M, Vaz M, Collier G, Nestel P, Jennings G, Kaye D, Seals D, Lambert G. (1998). Leptin in human plasma is derived in part from the brain and cleared by the kidneys. Lancet. **351**: 879.
13 Frazer-Llado T, Reyes G, Garcia I, Jeanville P. (1996). Low expression of the obese gene product leptin in critically ill infants. Pediatr Res **39**: 309 A.
14 Garanty-Bogacka B, Czeszyńska MB, Syrenicz M, Gembala A, Kordek A, Janus D, Walczak M, Krupa B. (2003). Immaturity or hypotrophy? The cord blood leptin levels in preterm and small for gestational age neonates. Gin Pol. **74**: 356–361.
15 Hassink SG, De Lancey E, Sheslow DV, Smith-Kirwin SM, O'Connor DM, Considine RV, Opentanova I, Dostal K, Spear ML, Leef K, Ash M, Spitzer AR, Funanage VL. (1997). Placental leptin: An important new growth factor in intrauterine and neonatal development? Pediatrics. **100**: 1–6.
16 Helland IB, Reseland JE, Saugstad OD, Drevon ChA. (1998). Leptin levels in pregnant woman and newborn infants: gender differences and reduction during neonatal period. Pediatrics **101**: E12.

17 Hytinanti T, Koistinen HA, Koivisto VA, Karoten SL, Rutanen EM, Andersen S. (2000). Increased leptin concentration in preterm infants of preeclamptic mothers. Arch Dis Child Fetal and Neonatal Ed. **83**: 13–16.
18 Inoue M, Itabashi K, Nakano Y, Tobe T. (2008). High-molecular-weight adiponectin and leptin levels in cord blood are associated with anthropometric measurements at birth. Hormone Res. **70**: 268–272.
19 Iwagaki S, Yokoyoma Y, Tang L. (2004). Augmentation of leptin and hypoxia-inducible factor 1 alfa mRNA in the preeclamptic placenta. Gynacol Endocrinol. **18**: 263–268.
20 Janeckova R. (2001). The role of leptin in human physiology and pathophysiology. Physiol Res. **50**: 443–459.
21 Kautzky-Willner A, Pacini G, Tura A, Bieglmayer C, Schneider B, Ludvik B, Prager H, Waldhausl W. (2001). Increased plasma leptin in gestational diabetes. Diabetologia. **44**: 164–172.
22 Kirel B, Tekin N, Tekin B, Kilic FS, Dogruel N, Aydogdu SD. (2000). Cord blood leptin levels: relationship to body weight, body mass index, sex and insulin and cortisol levels of maternal-newborn pairs at delivery. J Pediatr Endocrinol Metab. **13**: 71–77.
23 Kyriakakou M, Malamitsi-Puchner A, Militsi H, Boutsikou T, Margeli A, Hassiakos D, Kanaka-Gantenbeich Ch, Papassotiriou I, Mastorakos G. (2008). Leptin and adiponectin concentrations in intrauterine growth restricted and appropriate for gestational age fetuses, neonates and their mothers. Eur J Endocrinol. **158**: 343–348.
24 Koc E, Ustundag G, Aliefendioglu D, Ergenekon E, Bideci A, Atalay Y. (2003). Serum leptin levels and their relationship to tumor necrosis factor-alpha and interleukin-6 in neonatal sepsis. J Pediatr Endocrinol Metab. **16:** 1283–1287.
25 Kotulska A, Kucharz EJ. (2002). Stężenie leptyny u chorych na nadczynność lub niedoczynność tarczycy w trakcie leczenia. Endokrynol Pol. **53**: supl.1: 408.
26 Kulik-Rechberger B, Kaminski K, Rechberger T. (1998). Stężenie leptyny w krwi matczynej i płodowej w ciąży donoszonej. Ginekol Pol. **69**: 725–729.
27 Laivuori H, Gallaher MJ, Collura L, Crombleholme WR, Markovic N, Rajakumar A, Hubel CA, Roberts JM, Powers RW. (2006). Relationship between maternal plasma leptin, placental leptin mRNA and protein in normal pregnancy, pre-eclampsia and intrauterine growth restriction without pre-eclampsia. Mol Hum Reprod **12**: 551–556.
28 Laml T, Preyer O, Hartman B, Rueckliner E, Soeregi G, Waganbichler P. (2001). Decreased maternal serum leptin in pregnancies complicated by pre-eclampsia. J Soc Gynecol Invest. **8**: 89–93.
29 Laml T, Hartman B, Ruecklinger E, Preyer O, Soeregi G, Wagenbichter P. (2001). Maternal serum leptin concentrations correlate with cord blood leptin concentrations in normal pregnancy. J Soc Gynecol Invest. **8**: 43–47.
30 Lepercq J, Guerro-Millo M, Andre J, Cauzac M, Hauguel-de Mouzon S. (2003). Leptin: a potential marker of placental insufficiency. Gynecol Obstet Invest **55**: 151–155.
31 Lin KC, Sagawa N, Yura S, Itoh H, Fujii S. (2005). Simultaneous increases of leptin and gonadotropin-releasing hormone following exogenous estrogen administration in women with normal menstrual cycle. Endocrin J **52**: 449–454.
32 Linnemann K, Mlek A, sager R, Blum W, Schneider H, Fusch C. (2000). Leptin production and relaese in the dually in vitro perfused human placenta. J Clin Endocrinol Metab **85**: 4298–4301.
33 Manderson JG, Patterson CC, Hadden DR, Traub AI, Lesliee H, McCance DR. (2003). Leptin concentration in maternal serum and cord blood in diabetic and non diabetic pregnancy. Am J Obstet Gynecol **188**: 1326–1332.
34 Marchini G, Fried G, Ostlund E, Hagenas L. (1998). Plasma leptin in infants: relations to birth weight and weight loss. Pediatrics **101**: 429–432.
35 Matsuda J, Yokota I, Iida M, Murakami T, Naito E, Ito M, Shima k, Kuroda Y. (1997). Serum leptin concentration in cord blood: relationship to birth weight and gender. J Clin Endocrinol Metab **82**: 1642–1644.
36 Ng PC, Lam CW, Lee CH, Wong GW, Fok TF, Chan IH, Ma KC. (2001). Changes of leptin and metabolic hormons in preterm infants: a longitudinal study in early postnatal life. Clin Endocrinol **54**: 673–680.
37 Ochoa R, Zarate A, Hernandez M, Galvan R, Basurto L. (2001). Serum leptin and somatotropin components correlate with neonatal birth weight. Gynecol Obstet Inves **52**: 243–247.
38 Okerere-Ndubueze C, Uvena-Celebrezze J, Hutson-Presley L, Amini Saeid B, Catalano P. (2002). The effect of gender and gestational diabetes mellitus on cord leptin concentration. Am J Obstet Gynecol **187**: 798–803.
39 Orbak Z, Ertekin V, Akcay F, Ozkan B, Ors R. (2003). Serum leptin levels in neonatal bacterial septicemia. J Pediatr Endocrinol Metab **16**: 727–731.
40 Ozdemir U, Gulturk s, Aker A, Guvenal T, Imir G, Erselcan T. (2007). Correlation between birth weight, leptin, zinc and copper levels in maternal and cord blood. J Physiol Biochem **63**: 121–128.
41 Petridou E, Mantzoros Ch, Belechri M, Skalkidou A, Dessypris n, Papathomas E, salvanos H, Lee JH, Kedkoglou S, Chrousous G, Trichopoulos D. (2005). Neonatal leptin levels are strongly associated with female gender, birth lenght, IGF-1 levels and formula feeding. Clin Endocrinol **62**: 366–371.
42 Savino F, Costamagna M, Prino A, Oggero R, Silvestro L. (2002). Leptin levels in breast-fed and formula-fed infants. Acta Pediatr **91**: 891–894.
43 Shekhawat PS, Garland JS, Alex C, Sasidharan P, Mick G, McCormic KL. (2000). Cord blood and postnatal serum leptin and its relationship to steroid use and growth in sick preterm infants. J Pediatr Endocrinol Metab **13**: 1571–1576.
44 Spear M, Hassink S, Leef K, O'Connor D, Kirwin S, Locke R, Gorman R, Funanage V. (2001). Immaturity or starvation? Longitudinal study of leptin levels in premature infants. Biol Neonate **80**: 35–40.
45 Su PH, Wang SL, Chen YJ, Lai CP, Jian SH. (2002). Serum leptin levels in preterm, healthy and sick-term newborns. Acta Pediatr **43**: 249–254.
46 Tamura T, Goldenberg RL, Johnston KE. (1998). Serum leptin concentrations during pregnancy and their relationship to fetal growth. Obstet Gynecol **91**: 389–395
47 Tome MA, Lage M, Camina JP, Garcia-Mayor RV, Diequez C, Cassanueva FF. (1997). Sex based differences in serum leptin concentrations from umbilical cord blood at delivery. Eur J Endocrinol **137**: 655–658.
48 Valle MY, Gascon F, Martos R, Bermudo F, Ceballos P, Suanes A. (2003). Relationship between high plasma leptin concentrations and metabolic syndrome in obese prepubertal children. Int J Obesity Rel Metabol Disorders **27**: 13–18.
49 Vatten L, Stein T, Odegard RA. (2002). Insulin like growth factor and leptin in umbilical cord plasma and infant birth size at term. Pediatrics **109**: 1131–1135.
50 Yeung LP, Wong AC, Wang X, Birmingham CL, Lewicka C, Chanoine JP. (2003). Different relationship between anthropometric markers and umbilical cord plasma leptin in Asian and Caucasian neonates. Pediatr Res **53**: 1019–1024.