The Adiponectin/Leptin Ratio is a Useful Tool to Evaluate the Metabolic Status in an Obstetrical Intensive Care Unit

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Introduction. Critically ill patients, including obstetrical patients, face undernutrition but a reliable and cost effective study to assess their nutritional state is still missing. Our main objective was to analyze serum leptin and adiponectin concentrations in puerperal women attended in an Obstetrical Intensive Care Unit (OICU) in order to evaluate their potential role as nutritional metabolic parameter.

Methods. This was a descriptive, clinical, longitudinal and comparative study. We evaluated the anthropometric variables, clinical laboratories, daily calories and adiponectin and leptin serum levels of 16 puerperal women attended at the OICU of the Materno Perinatal Hospital "Mónica Pretelini" (HMPMP).

Results. For all women there was a negative correlation with Spearman test between leptin the day of discharge from the obstetrical intensive care unit and the days of stay –0.632 (p = 0.011). Considering an adiponectin/leptin ratio, the media in the first day was of 0.3 (0.07–13.6) and in the day of discharge it was of 2.4 (0.1–24.6) in overweight women. The same values for obese women were of 0.3 (0.2–0.4) and 0.5 (0.3–1.2).

Conclusion. After an average of six days of hospitalization, leptin showed a decrement in women attended at the OICU. As expected, adiponectin increased in both groups. The adiponectin/leptin ratio could be a useful metabolic parameter.

Key words: adiponectin, intensive care unit, leptin, puerperium.

Critically ill patients, especially those with sepsis or septic shock, even without pre-existing diabetes mellitus face three common metabolic features: hyperglycemia, glucose intolerance, and insulin resistance [1–3]. Several adipocytokines that mediate agonistic and antagonistic effects on insulin resistance have been identified in patients with obesity, metabolic syndrome, and type 2 diabetes [4, 5]. These hormones are a link among obesity, inflammation and systemic insulin resistance [5]. In this regard, pregnancy is a physiological state of overweight, obesity and insulin resistance.

Adiponectin, a product of the *apM1* gene, is highly expressed in adipose cells, and circulates in high concentrations in the blood with crucial importance in regulating insulin sensitivity. It has a globular domain and a collagen domain. Decreased serum levels of adiponectin are associated with insulin resistance.

The role of adiponectin in systemic inflammation and critical illness is not well defined. For example, low levels of adiponectin have been found in critically ill patients, although data is limited in human subjects at this stage. The variability in the serum adiponectin levels is partly attributed to various options for modulation of this hormone [6].

Pregnancy has an enhancing effect on the relationship between body fatness and insulin resistance [7]. According to the available information it is clear that plasma adiponectin levels are decreased in women who are in the last trimester of gestation.

Leptin, a 16-Kd protein encoded by the *Ob* gene, correlates directly with the mass of adipose tissue and its main function is to control the appetite. Leptin exerts its various actions on glucose metabolism and energy expenditure via binding to

the leptin-receptor in the brain and peripheral tissues as liver, pancreas, adipose tissue and in the immune system [8]. Several animal and human studies have shown that administration of endotoxin, tumour necrosis factor alpha (TNF-α) and other cytokines which act as inducers of severe systemic inflammation result in a significant elevation of serum leptin concentrations [9, 10].

Obese patients hospitalized in Intensive Care Units (ICUs) have increased mortality compared with non-obese. Both adiponectin and leptin have been found intertwined in studies examining the complex set of biochemical-metabolic reactions associated with the level of obesity, the degree of complications and prognosis in patients treated in ICUs. Thus, adiponectin and leptin levels may act as prognostic markers.

Christos *et al*., found in an observational study in adults a positive correlation between a diet rich in protein and serum leptin levels decrement. It has also been reported by Steiner *et al*., a direct relationship between the level of leptin, the protein intake in diet and the level of obesity in mouse models [5].

Taken in the context of the implication of adipocytokines and prognosis in critically ill patients, maintaining a normal glycaemia level has beneficial effects on outcome. Besides insulin, plasma glucose concentrations may be lowered by hypocaloric feeding, or by the type of formula used [11]. Whether such type of diets influences the results of serum levels of adiponectin or leptin is a matter of debate.

A reliable and cost-effective study to assess the nutritional state in obstetrical patients has yet to be designed. Our main objective was to analyze serum leptin and adiponectin concentrations in a cohort of puerperal women attended in an Obstetrical Intensive Care Unit (OICU) in order to evaluate their potential role as nutritional metabolic parameters.

MATERIAL AND METHODS

Study design and patient characteristics

This was a descriptive, clinical, longitudinal and comparative study. We enrolled consecutively 16 women in immediate puerperium upon admission to the medical OICU of the Materno Perinatal Hospital "Mónica Pretelini" (HMPMP) from February till March 2011.

Patients were not included in this study if they were expected to have a short-term (<24 h) intensive care hospitalization or if they suffered from gestational diabetes mellitus. Patient data, clinical information, and blood samples were collected prospectively.

The patients were classified in two groups by Body Mass Index (BMI): a) overweight (24.9 k/m^2 < BMI < 29.9 k/m^2) and b) obesity (BMI > 29.9 k/m^2) that did not differ in APACHE II score, vasopressor demand, or laboratory parameters. For reference of a normal value we processed samples of a normal weight puerperal woman.

Anthropometric measures

Height with a measuring tape and weight with an electric bed (Hill-Rom, Total Care) were uniformly recorded at the OICU. Corrected final weight (CFW) was calculated (if it was positive) as: final weight (kg)-accumulated hydric balance (L/1000). Blood pressure was measured with an electronic monitor (Infinity Delta XL, Dräger).

Laboratory

After delivery and during each day of hospitalization, with a fasting period of eight hours blood samples were collected into Vacutainer tubes and centrifuged to separate serum from plasma. We measured albumin (mg/dL), cholesterol (mg/dL), creatinine (mg/dL), glucose (mg/dL), triglycerides (mg/dL) and uric acid (mg/dL) (Dimension R × L Max, Dade Behring) and haemoglobin (g/dL) (Advia 120, Bayer Health). All these tests were measured in the HMPMP according to standardized procedures recommended by the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). Very low-density lipoproteins (VLDL) were calculated as triglycerides (mg/dL)/5.

Quantification of adiponectin and leptin

Adiponectin and leptin serum concentrations were measured at the Medical Research Center (CICMED), Autonomous University of the State of Mexico (UAEMex), using an enzyme-linked immunosorbent assay (ELISA) according to manufacturer's instructions (GenWay Biotech. Inc; High sensibility ELISA Sandwich Adiponectin reference 40-055-200002 and Human Leptin ELISA Sandwich reference 40-055-200004).

The present study was approved by the Ethical Committee of the HMPMP (Code: 2010-08-124) and was conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Written informed consent was obtained from the patient, her spouse, or the appointed legal guardian.

Statistical analysis

Statistical analysis was done using the Statistical Package for Social Science (SPSS) software, version 17 (SPSS Inc., Chicago, United States). Box plot graphics were used to illustrate comparisons between groups. Due to the skewed distribution of most of the parameters, data are given as median (range). Differences between two groups were assessed by Mann-Whitney-*U*-test.

RESULTS

The principal diagnoses of the attended patients were: preeclampsia, obstetric haemorrhage, HELLP syndrome, renal dysfunction and pneumonia.

Clinical data

Anthropometric measures are shown in Table I. Of eleven women with overweight, 54.5% [6] lost weight during their hospitalization, 36.3% (4) gained weight and one (9%) stayed without changes. Of the three women with obesity, all lost weight. Taking into account all women, 60% [9] lost weight, 33.3% [5] gained weight and one (6.6%) kept the same weight. One woman with overweight reached normal BMI at the end of the study. A statistical significant difference was found in initial and final weight and BMI and in initial systolic blood pressure. Adjusting BMI to CFW gives eight (72.7%) of the overweight women that showed a reduction in this value. There was no difference when analyzing the mean kcal/kg/day consumed.

Table I
Anthropometric and laboratorial characteristics

	Overweight	**Obesity**
Age (years)	28 (18-42)	34 (29-36)
Days of stay	6 (2-21)	5 (4-6)
kcal/kg/day	14.9 (7.3-31.7)	20.5 (12.3-21.1)
Weight (kg)[a] **	63 (54.5-72.6)	92.6 (73.3-97.2)
Weight (kg)[b] *	61 (51.8-77.6)	83.9 (66.6-94.3)
Height (m)	1.54 (1.47-1.66)	1.56 (1.52-1.6)
BMI (kg/m^2)[a] **	26.3 (25.2-28.5)	37.9 (31.7-38)
BMI (kg/m^2)[b] *	26.1 (22.8-30.9)	34.4 (33.3-36.8)
Adiponectin (µg/mL)[a]	8.6 (2.9-26)	7.9 (4.1-12.8)
Adiponectin (µg/mL)[b]	12.4 (5.1-22.9)	8 (3.6-9.5)
Leptin (ng/mL)[a]	8.6 (1-55.9)	23.3 (16.5-25.9)
Leptin (ng/mL)[b]	6.2 (0.7-33.3)	6.8 (6.4-27.3)
Glucose (mg/mL)[a]	127 (84-226)	165 (68-231)
Glucose (mg/mL)[b]	96 (75-194)	81 (73-157)

BMI: Body Mass Index; [a]: initial; [b]: final. Results in media (range). *: $p \leq 0.05$, **: $p \leq 0.01$

Laboratory

Overweight and obese women decreased their BMI (Fig. 1) and leptin (Fig. 2) while hospitalized, at the same time adiponectin showed an expected increase in both groups (Fig. 3). There were no differences in the studies realized, but glucose diminished in both groups. For all women there was a negative correlation with Spearman test between leptin the day of discharge from OICU and the days of stay –0.632 ($p = 0.011$).

Considering an adiponectin/leptin ratio, the media in the first day was of 0.3 (0.07–13.6) and in the day of discharge it was of 2.4 (0.1–24.6) in overweight women. The same values for obese women were of 0.3 (0.2–0.4) and 0.5 (0.3–1.2).

The mean in the adiponectin/leptin ratio in the first day of hospitalization was 7.9 fold higher in overweight than in obese women. In the last day of hospitalization this ratio was reduced to 6.1 fold. Intragroup modifications were also documented, as the previous ratio was 3.7 fold higher after ICU discharge in overweight women in comparison to the first day of hospitalization and 2.4 fold higher for obese women.

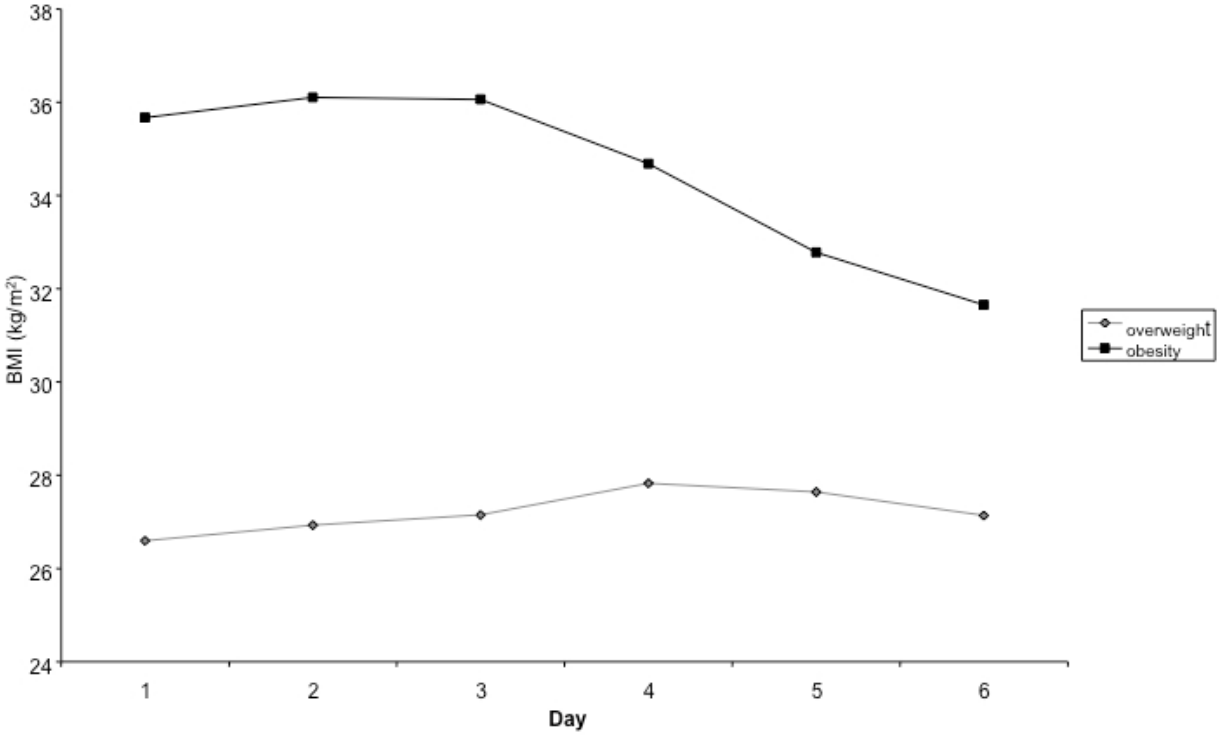

Fig. 1. Body mass index in obstetrical intensive care patients.

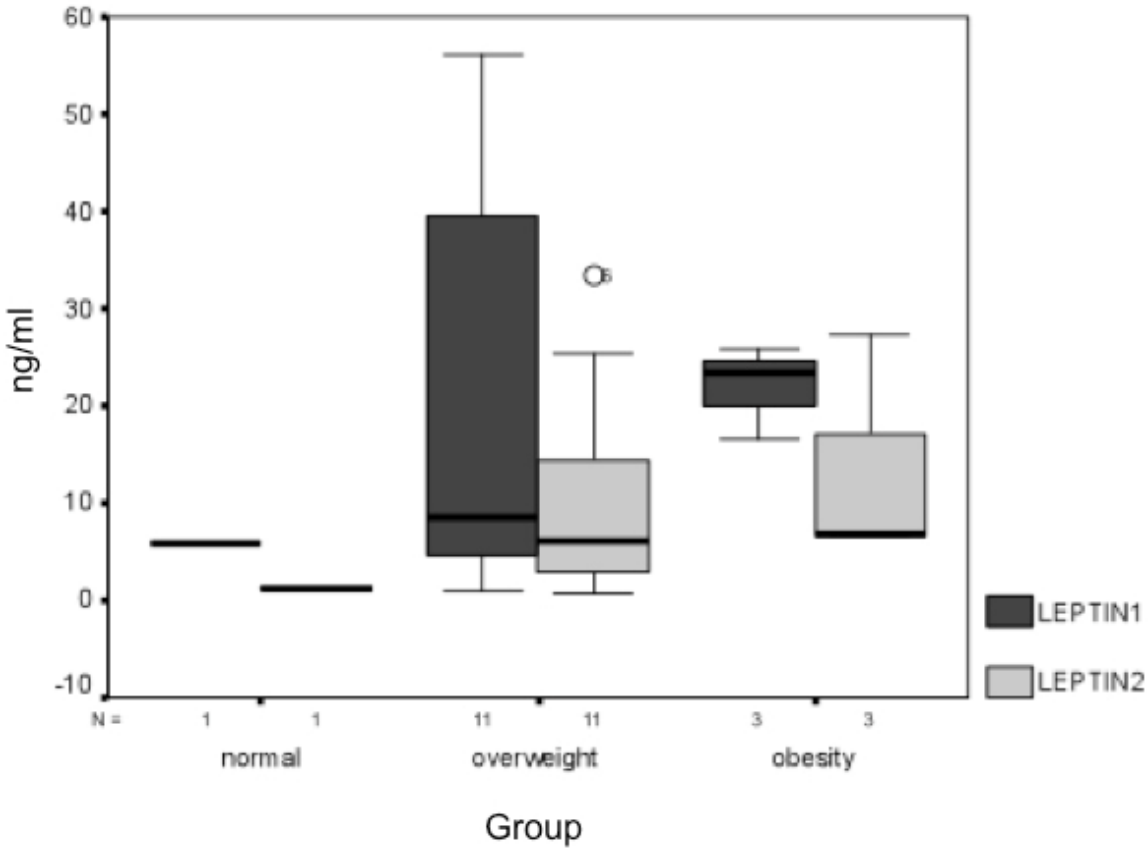

Fig. 2. Serum leptin concentrations in obstetrical intensive care patients.
LEPTIN1: serum leptin in the first day of hospitalization, LEPTIN2: serum leptin in the last day of hospitalization.

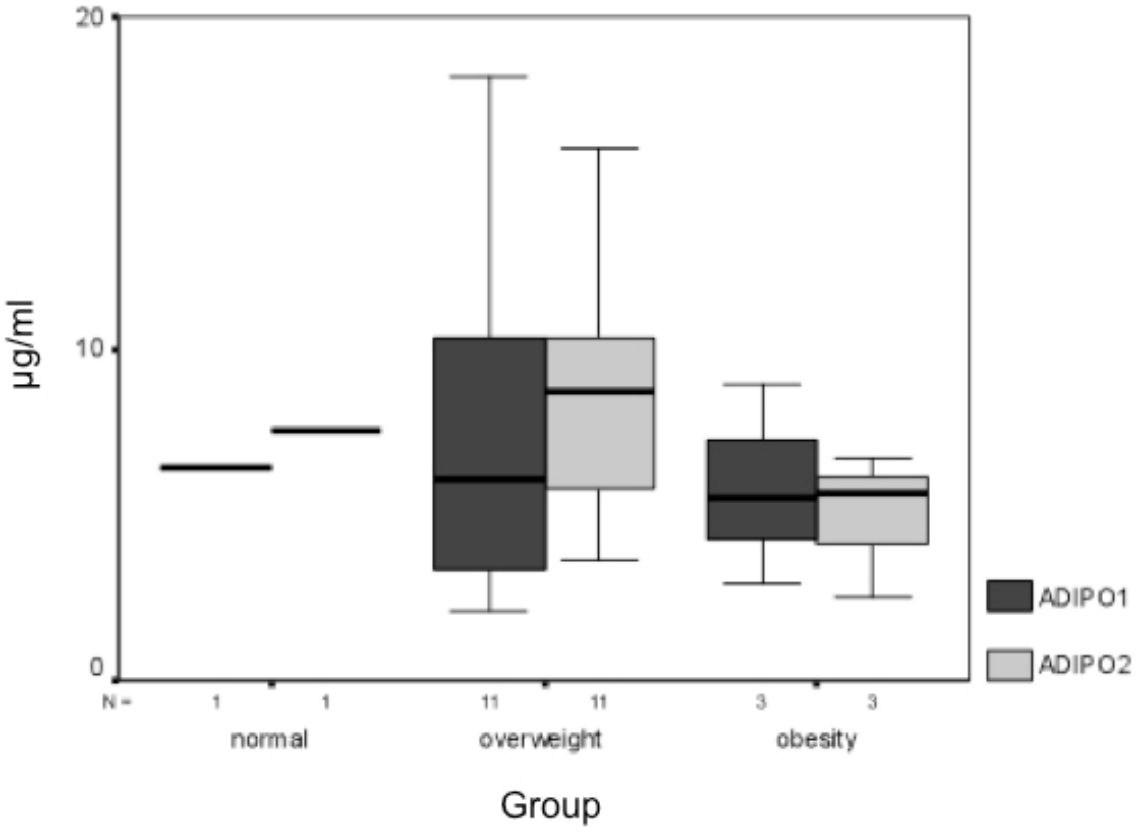

Fig. 3. Serum adiponectin concentrations in obstetrical intensive care patients.
ADIPO1: serum adiponectin in the first day of hospitalization, ADIPO2: serum adiponectin in the last day of hospitalization.

DISCUSSION

Overweight and obesity are frequent challenges in ICUs; previous research reported that about 50% of the patients admitted to an ICU have a BMI above 25 kg/m^2. In our unit, of 15 puerperal women incorporated in the study only one had BMI below 25. This is explained, in part, by the fact that gestation is a period of intense weight gain. Thus predisposing to metabolic problems not as common in other kind of ICUs.

A reliable assessment of nutritional state in obstetrical patients is of great importance to follow an evidence-based nutritional management protocol. Nevertheless, techniques used to assess body composition in this kind of patients may be affected by abnormalities in fluid status [12, 13] or are not practical as every day techniques for nutritional evaluation [14]. Research concerning the relationship between adiponectin and insulin action in humans is more complex than often suggested [15]. Adiponectin has significant anti-inflammatory and insulin-sensitizing effects and is diminished in morbidly obese and in critically ill patients. Reduced adiponectin could contribute to insulin resistance in these patients. Serum adiponectin upon admission to the intensive care unit may predict mortality in critically ill patients.

Although adiponectin serum concentration does not differ between healthy controls and critically ill patients, neither in patients with nor in patients without sepsis, low adiponectin levels at admission to ICU have been identified as an independent predictor of survival [16]. Leptin has been implicated to link inflammation and metabolic alterations by using the same clinical approach.

In women with normal cortisol levels, irrespectively of nutritional status, leptin levels reflect body fat content. In obese subjects, leptin levels may be influenced by cortisol levels, high levels of insulin, insulin growing factor-1 (IGF-1), and beta-endorphin as well as low levels of growth hormone [17]. Besides, leptin's concentrations directly reflect the current nutritional status in non-critically ill individuals. Moreover, it had been reported that circulating leptin levels are low in critically ill patients upon admission to the ICU, possibly due to an acute stress response, with the lowest levels in patients with sepsis [18].

Serum leptin is closely associated with obesity and diabetes, has a functional role in the pathogenesis of severe illness [19] and clearly

correlates with markers of metabolism and liver function. In fact, a prior study demonstrated decreased plasma leptin levels due to trauma which were explained to be partly related to the initial fasting conditions because of refeeding elevated serum leptin concentrations to normal levels [20]. We, therefore, tested leptin serum concentrations in critically ill obstetric patients, finding higher leptin levels in patients with a BMI greater than 30 kg/m^2.

Patients in ICUs are submitted to energy restriction that causes a fall of serum leptin apparently not mediated by gastrointestinal signals and it seems not to affect the long-term regulatory pathways of circulating leptin [21]. There are many critical conditions that put critical patients in parenteral or tube feeding for periods of hours to days. In this respect, there is a rise in circulating leptin concentrations, associated with tube feeding [22]. In rats fed with standard chow or infusion of total parenteral nutrition into the duodenum or intravenously, leptin mRNA and serum concentrations were similar, but intravenous glucose infusion was mostly responsible for stimulation of the leptin gene and hormone secretion [23]. In our work it is not excluded the possibility that the type of diet (enteral, parenteral, mix) could affect the adipocytokines' response in obstetrical patients but this topic was beyond the scope of this study due to the low number of patients.

Our results of adiponectin and leptin were consistent with those reported by other researchers. We also noted that leptin correlated negatively with the days of hospitalization. In this sense, caloric portion of the different diets could be affecting the adipocytokines' levels [2, 5]. However, in this study, there was no difference in the average kcal/kg/day provided in obese *versus* overweight women.

The influence of fluid status on the body composition and nutritional evaluation has been tested by various techniques such as its relation to left ventricular end-diastolic diameter, assessed by echocardiography, and by estimating the ratio between extracellular water and total body water, assessed by bromide and deuterium dilution [12]. An important point of view derived from our work is that the total body weight is not a reliable data on hospitalized patients to calculate BMI because the water balance affects it, consequently, we used a CFW formula trying to avoid under-recording of weight loss.

It is clear from this study that an adiponectin/ leptin ratio could be useful to evaluate the metabolic state in critical obstetric patients, due to the exclusive secretion of leptin by adipose tissue. Although we did not find a statistically significant difference in this ratio between obese and overweight women, the p value decreased 3.2 times (from 0.55 to 0.17), which suggests that a longer period of hospitalization may lead to a difference in this ratio. It is likely that this difference could be more notorious when comparing to normal weight women.

A limiting factor of this descriptive study is the small number of patients, but the trend in the response of the adipocytokines analyzed seems to reinforce the statement that the type of diet is not as critical as the BMI (corrected for water balance) to determine their serum levels.

Introducere. *Pentru pacienții în stare critică, inclusiv pacienții cu probleme obstetricale, subnutriți, lipseşte un studiu de eficiență fiabilă de a evalua starea lor nutrițională. Principalul nostru obiectiv a fost de a analiza concentrațiile serice de leptină şi adiponectină la femei cu endometrită, ce au participat într-o Unitate de Terapie Intensivă de Obstetrică (OICU), în scopul de a evalua rolul lor potențial ca parametru metabolic nutrițional.*

Metode. *Acesta a fost un studiu clinic descriptiv, longitudinal şi comparativ. Am evaluat variabilele antropometrice, clinice, de calorii pe zile şi nivelurile serice de adiponectină şi leptină la 16 femei cu endometrită ce au participat la OICU a Spitalului Materno Perinatal „Monica Pretelini" (HMPMP).*

Rezultate. *Pentru toate femeile a existat o corelație negativă cu Spearman test între leptina în ziua externării din Unitatea de Terapie Intensivă de Obstretică şi de zilele de şedere –0,632 (p = 0,011). Având în vedere raportul adiponectină / leptinămedia în prima zi a fost 0,3 (0,07–13,6) şi în ziua de încheiere a fost de 2,4 (0,1–24,6) la femeile supraponderale. Aceleaşi valori pentru persoane supraponderale au fost 0,3 (0,2–0,4) şi 0,5 (0,3–1,2).*

***Concluzie**. După o medie de şase zile de spitalizare, concentraţia de leptină a arătat o scădere la femeile ce au participat la OICU. Cum era de aşteptat, concentraţia de adiponectină a crescut în ambele grupuri. Raportul adiponectină/ leptină ar putea fi un parametru metabolic util.*

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