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ВМІСТ ЛЕПТИНУ У СИРОВАТЦІ КРОВІ ВАГІТНИХ ЖІНОК З ОЖИРІННЯМ У ІІІ ТРИМЕСТРІ ВАГІТНОСТІ

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Реферат

Мета. *Визначити рівень лептину у сироватці крові вагітних жінок з ожирінням у ІІІ триместрі вагітності.*
Матеріал і методи. *Обстежено 32 жінки із ожирінням (І ст. - 13, ІІ ст. - 10, ІІІ ст. - 9) у ІІІ триместрі вагітності, яким визначали лептин (основна група) та 30 здорових вагітних жінок (контрольна група). Пацієнтки були рандомізовані за віком та патологією. Визначення лептину проводили методом імуноферментного аналізу. Ступінь ожиріння визначали за індексом маси тіла (ІМТ) - зріст-вага співвідношення, яке визначали за формулою: вага у кілограмах ділена на ріст у м^2. Нормальною вважали вагу тіла при ІТМ від >18,5 до <25 кг/м^2. Якщо ІМТ становив >30-35 кг/м^2 - це ожиріння І ст., при ІМТ >35-40 кг/м^2 - ожиріння ІІ ст., при ІМТ >40 кг/м^2 - ожиріння ІІІ ст.*
Результати й обговорення. *Серед ускладнень вагітності у жінок основної групи необхідно відмітити наступні: прееклампсія вагітних - 78,1%, ранній токсикоз - 59,4%, загроза передчасних пологів - 65,6%, ГРВІ - 40,6%, передчасне відходження навколоплідних вод - 34,4%, порушення плодово-плацентарного кровоплину - 34,4%, великий плід - 31,2%, рубець на матці - 34,4%, ЗВУР - 37,5%, передчасні пологи - 28,1%, шов на шийці матки - 21,9%, первинна слабість пологової діяльності, що не піддається медикаментозній корекції - 25%. При порівнянні рівня лептину у вагітних без ожиріння та вагітних контрольної та основної груп виявлено, що рівень лептину становив у здорових вагітних 27,11 нг/мл, у вагітних з ожирінням І ст. - 48,03 нг/мл , що у 1,77 разів більше, ніж у вагітних без ожиріння. При обстеженні вагітних з ожирінням ІІ ст., рівень лептину був у 2,13 разів вищий, ніж у вагітних контрольної групи, а у вагітних з ожирінням ІІІ ст. - у 2,45 разів, відповідно, (p<0,05). Звертає на себе увагу порівняння абсолютної величини рівня лептину у вагітних жінок із ожирінням різного ступеню (рис.). Спостерігали збільшення рівня лептину відповідно до зростання ступеню ожиріння. Так, при ожирінні ІІ ст. рівень лептину більший на 9,7 нг/мл (у 1,2 рази) у порівнянні з вагітними з ожирінням І ст. При ожирінні ІІІ ст. у порівнянні з ожирінням І ст. рівень лептину вищий на 18,48 нг/мл (у 1,38 разів), а при порівнянні з ожирінням ІІ ст. - вищий на 8,78 нг/мл (у 1,15 разів).*
Висновок. *У вагітних жінок із ожирінням є підвищеним вміст лептину в сироватці крові у ІІІ триместрі вагітності порівняно зі здоровими вагітними жінками. Вміст лептину у сироватці крові у жінок із ожирінням корелює зі ступенем тяжкості захворювання.(r=0,47; p<0,05). Наведені факти диктують необхідність проведення подальших досліджень у цьому напрямку, зокрема, з'ясувати залежність акушерських та перинатальних ускладнень від вмісту лептину у сироватці крові вагітних жінок із ожирінням.*
Ключові слова: *вагітність, ожиріння, лептин, пологи, метаболічний синдром*

Abstract

LEPTIN CONTENT IN BLOOD SERUM OF OBESE PREGNANT WOMEN DURING THE THIRD TRIMESTER OF PREGNANCY

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Aim. *To determine the leptin level in blood serum of obese pregnant women during the third trimester of pregnancy.*
Materials and Methods. *There were examined two groups of women. Group 1 consisted of 32 obese women (class 1 - 13, class 2 - 10, class 3 - 9) during their third trimester of pregnancy (main group). Group 2 consisted of 30 healthy pregnant women (control group). Patients from both groups had their leptin tested. Patients were randomized per their age and pathology. Leptin was determined via enzyme multiplied immunoassay method. Obesity class is defined based on the body mass index (BMI), i.e. mass and weight ratio calculated per the following formula: the mass in kilograms is divided by the height in m2. If BMI values range from >18.5 to <25 kg/m^2, the body mass falls within the norm. BMI values of > 30-35 kg/m^2 indicate class 1 obesity, of BMI > 35-40 kg/m^2 - class 2 obesity, of BMI >40 kg/m^2 - class 3 obesity.*
Results and Discussion. *Among the pregnancy complications in women from the main group the following should be mentioned: preeclampsia in pregnancy - 78,1%, early gestosis - 59,4%, threat of preterm birth - 65,6%, ARVI - 40,6%, premature leakage of amniotic fluid - 34,4%, foetal-placental perfusion disorders - 34,4%, big foetus - 31,2%, uterus scar - 34,4%, foetal growth retardation syndrome - 37,5%, preterm delivery - 28,1%, sutured uterine cervix - 21,9%, primary uterine inertia resistant to medical correction - 25%. When comparing the leptin level in pregnant women with no obesity and in pregnant women from the control and main groups it was detected that in healthy pregnant women leptin level was 27.11 ng/ml; in obesity class 1 pregnant women it was 48.03 ng/ml, i.e. 1.77 times greater than in women with no obesity. In obesity class 2 pregnant women the leptin level was 2.13 times higher than in pregnant women from the control group. In obesity class 3 pregnant women it was 2.45 times higher, respectively (p<0.05). The comparison of absolute value of leptin level in obese women with various*

obesity classes calls the specific attention. An increased leptin level in respect of the increased obesity class is observed. For instance, obesity class 2 shows the leptin level exceeding by 9.7 ng/ml (1.2 times) when compared to the obesity class 1 pregnant women. In the obesity class 3 pregnant women the leptin level is greater by 18.48 ng/ml (1.38 times) if compared with the obesity class 1 women. If compared to the obesity class 2 pregnant women, it is greater by 8.78 ng/ml (1.15 times).

Conclusions. *Obese pregnant women show the increase of leptin content in blood serum during the third trimester of pregnancy if compared with healthy patients. Leptin content in blood serum of obese women correlates with the disease severity (r=0,47; p<0,05). Presented facts necessitate the conduction of further studies on the given matter. In particular, it is required to clarify the dependency of obstetric and perinatal complications on the leptin content in blood serum of obese pregnant women.*

Keywords: *pregnancy, obesity, leptin, delivery, metabolic syndrome*

Introduction

The epidemic of obesity is a widely recognized phenomenon in the world that has significant implications for reproduction. Maternal obesity is associated with the numerous pregnancy complications including gestational diabetes mellitus (GDM) and preeclampsia (PE) [1, 2], macrosomia, foetal growth restriction (FGR), foetal death in utero and stillbirth [3,4]. In addition, the existing data also confirm the relationship between maternal obesity and the development of obesity in children when they reach adulthood [5, 9]. During pregnancy, these effects are considered to be due to a change in metabolic conditions and a low level of utero-placental metabolism. However, offspring postnatal health effects are caused by maternal obesity and are thought to be mediated by an abnormal intrauterine environment [6].

Obesity is associated with an increased concentration of free leptin in the blood circulation system [7]. Such an increase undoubtedly correlates with the BMI and the fat mass volume [8].

In the peripheral system, leptin acts as a paracrine/autocrine factor capable of altering sensitivity for insulin, tissue metabolism, stress response and reproductive functions. Various leptin reproductive functions foresee the stabilization of several processes such as placental nutrient transfer, placental angiogenesis, trophoblast mitogenesis and immunomodulation, all being the vital processes for foetal development and adequate function of placenta [8].

Notwithstanding the fact that there are several sources of leptin supply in the body, it is mostly produced by adipose tissue, and its level in plasma indicates the volume of this tissue. In particular, in humans (depending on the race), leptin is produced in placenta, and its amount can significantly affect the foetus during pregnancy. Mammary gland is also capable of producing leptin especially at the early stage of lactation. Besides, mammary gland is involved intransportation of leptin from mother to the milk that becomes an additional leptin source for new-borns. Leptin is also produced by stomach zymogen cells, which affect gastroprotective activity [1, 2].

Objective: to determine the leptin level in blood serum of obese pregnant women in the third trimester of pregnancy.

Material and Methods

There were examined 32 women with obesity (1st grade - 13, 2nd grade - 10, 3rd grade - 9), who were in their 3rd trimester of pregnancy. The leptin content was determined for the main group and the control group (30 healthy pregnant women). Patients were randomized per their age and pathology.

The leptin level was determined using enzyme multiplied immunoassay test (ELISA), analyser - TECAN spectrophotometer, test system - LDN Leptin ELISA (Germany).

The obesity grade was assigned per the body mass index (BMI) - the height-weight ratio, which is determined by the following formula: weight in kilograms divided by height in m^2. The body weight is considered to be normal if BMI ranges from >18.5 to <25 kg/m^2. If BMI is >30-35 kg/m^2 - it is the 1st stage obesity, if BMI is > 35-40 kg/m^2 - the 2nd stage obesity and if BMI is >40 kg/m^2 - 3rd stage obesity.

Results and Discussion

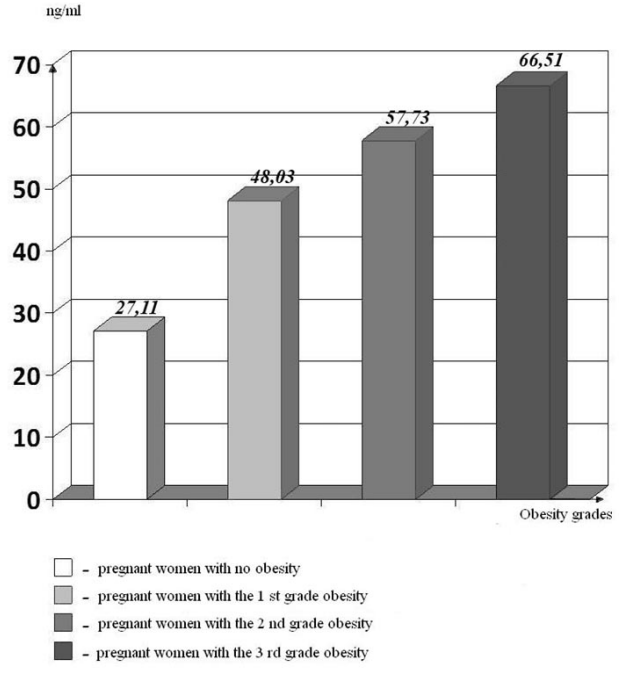
In women from the control group the somatic anamnesis was complicated by the following pathologies: diffuse goitre - 30%, anaemia in pregnancy - 10%, lower extremities varicose veins - 10%, chronic tonsillitis - 10%. Among the peculiarities of reproductive history and menstrual function there were distinguished primary infertility (10%), chronic salpingo-oophoritis (10%), polypectomy (10%), spontaneous miscarriage (10%), uterine adenomyosis (10%) and menstrual irregularity (10%).

In patients from the control group pregnancy was complicated by acute respiratory viral infection (ARVI) (30%), early toxicosis (20%), preterm delivery risk (20%), preterm outflow of amniotic fluid (20%), oedema in pregnancy (20%), anaemia in pregnancy (10%), big foetus (10%), and foetus-placental blood flow disturbances (10%).

In women from the main group the somatic anamnesis was complicated by the following pathologies: hypertension - 18.7%, average myopia of both eyes - 21.9%, localized dermatitis - 15.5%, appendectomy - 18.7%.

Also, the peculiarities of reproductive history and menstrual function should be noted: primary infertility - 37.5%, polycystic ovary syndrome (PCOS) - 28.1%, cervix erosion - 31.2%, spontaneous miscarriage - 21.9%, underdeveloped foetus - 21.9%, late menarche, menstrual disorder - 25%.

Among pregnancy complications in women from the main group it is necessary to mention the following ones: preeclampsia in pregnancy - 78.1%, early toxicosis - 59.4%, preterm delivery risk - 65.6%, ARVI - 40.6% , preterm outflow of amniotic fluid - 34.4%, foetus-placental blood flow disturbances - 34.4%, big foetus - 31.2%, uterine scar - 34.4%, FGR - 37.5%, preterm delivery - 28.1%, cervical stitch - 21.9%, primary uterine inertia that cannot be eliminated via medical correction - 25%.



Pic.

Blood serum leptin coutent in obese pregnant women and healthy women during the 3rd trymester of pregnancy, ng/ml

When serum leptin level in pregnant women without obesity and pregnant women with grade I obesity was compared, it was 27.11 ng/ml in healthy pregnancies and 48.03 ng/ml - in pregnant women with grade I obesity, which is 1,77 times more than in obese pregnant women ($p<0.05$). Upon examining pregnant women with grade II obesity it was found that the level of leptin was 2.13 times higher than that of the control group, and in pregnant women with grade III obesity it was 2.45 times, ($p <0.05$).

The results of comparison of absolute leptin levels in pregnant women with obesity of varying grades are shown in the picture below. As it can be seen, the interdependence of increased leptin levels and increased obesity is observed. For instance, in case of grade II obesity the leptin level is 9.7 ng/ml (1.2 times) higher when compared with the pregnant women with grade I obesity. Upon comparison of grade III obesity and grade I obesity, the leptin level is higher by 18.48 ng/ml (1.38 times), and on comparison with grade II obesity, it is higher by 8.78 ng/ml (1.15 times) ($p<0,05$).

According to literature, in rats hyperleptinemia in maternal blood during healthy pregnancy leads to central leptin-resistance due to the suppressing mechanism of regulation of the OB-Rb receptor in hypothalamus ventromedial nuclei and increased OB-Re isoforms in blood cycle. Both lead to weakening of leptin properties of transmitting a signal to the appetite regulation centre. Central leptin resistance can act as a compensatory mechanism to meet the needs of developing foetal nutrition; the same happens in the case of maternal insulin resistance at a later stage of pregnancy. It should be noted that in pregnant women with normal weight and obese non-pregnant women the level of leptin in blood system increases as compared with non-pregnant or healthy women from the control groups. They also demonstrated some changes in transmitting a signal to and from appetite regulation centre (both demonstrate some form of leptin resistance) [1, 2].

In addition to the above, the role of leptin in the regulation of the vascular and smooth muscle cells formation was determined. In endothelial cells of human umbilical vein, leptin, due to its binding to membrane-bound OB-Rb receptors present on endothelial cells, induces phosphorylation of receptor 2 of vascular endothelial growth factor

(VEGF-R2). Activated VEGF-R2 signals, via pathways p38 MAPK and Akt (alpha serine/ threonine protein kinase), cause proliferation, mobility, and formation of vessels. It was shown that leptin also inhibits the growth of smooth muscle cells of human arterial vessels, possibly due to the reduced regulation of the OB-Re isoform. In the same study, the authors reported a negative correlation between BMI and OB-Re isoform in atherosclerotic arterial wall in patients who underwent atherectomy. The potential interrelation of these processes becomes evident if we take into account the development and function of placenta, since angiogenesis in villi is essential for adequate embryonic vascularization of placenta and growth of smooth muscle vessels, and is also important for the vasomotor control of these vessels in stem villi. The deregulation of these processes can potentially alter the metabolism between the mother and foetus [3].

In the course of the study it was shown that leptin is characterized by mitogenic effect. The analysis of trophoblast cells (JEG-3 and BeWo - choriocarcinoma cell lines) in laboratory conditions has shown that leptin is capable of suppressing apoptosis and promoting proliferation. Perez-Peres et al. demonstrated that in JEG-3 cells leptin induced protein synthesis via the MAPK and PI3K pathways. This was achieved through activation and phosphorylation of key proteins in the translation apparatus, eukaryotic initiation factor of the translation of 4E (eIF4E) and eIF4E-binding protein 1 [4, 5].

The immune-immunomodulatory function of leptin starts in adipose tissue, where, as has been shown, leptin acts on monocytes and lymphocytes as a pro-inflammatory factor inducing the production of Th1 type cytokines. Pre-pregnancy systemic inflammatory response and high levels of leptin in blood circulation system in obese pregnant women are believed to be the basis for placental inflammation during pregnancy complicated by obesity. In this way, inflammation of placenta is expressed in production of pro-inflammatory cytokines such as IL-6 and TNFα activated by macrophages in the layer of placental stromal cells. Such pro-inflammatory state of placenta, which occurs due to obesity, can potentially simulate a non-infectious infarction of placenta villi, which results in its damage and change of function. Alongside, Roberts et al. did not observe such a reaction of the placenta villi in obese pregnant women. Although, no changes in immune cell populations or expression of IL-6 or TNF-α in placenta were observed, in specimens of obese pregnant women tissues an increase in the number of pro-inflammatory cytokines IL-1b, IL-8 and MCP-1 (monocytic chemotactic Protein 1) in placenta villi as well as an increase in the neutrophil population in interstitial space of maternal uterus was detected [7,8].

Conclusions

1. In obese pregnant women an increase of leptin content in blood serum is defined in their third trimester of pregnancy as compared to healthy pregnant women.
2. The leptin content in blood serum in obese pregnant women correlates with the severity of their disease ($r=0.47$; $p=0.05$).
3. The above presented facts encourage conducting further research in this area, in particular aimed at determining the leptin content in serum of newborns delivered by obese mothers.

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