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MATERNAL ADIPOKINES AND INSULIN AS BIOMARKERS OF OBSTETRIC AND PERINATAL PATHOLOGY IN OVERWEIGHT WOMEN

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Overweight women have an increased risk of decreased insulin sensitivity compared to normal weight women. In the study, it was shown that excessive gestational weight gain in prepregnancy overweight women is positively associated with increased production of leptin, resistin, and insulin, which are markers of insulin resistance and play an important role in the pathophysiology of gestational complications. It was proved that the chances of hyperleptinemia and hyperresistinemia increased in pregnant women with gestational hypertension and preeclampsia, especially in women with excessive gestational weight gain. In pregnant women with fetal growth retardation chances of insufficient leptin elevation in the second trimester increased in insufficient weight gain patients. A strong relationships between the concentration of leptin and resistin and the insulin resistance index in 22–24 weeks (r=0.83, p=0.000) and (r=0.83, p=0.000) and 37–39 weeks (r=0.86, p=0.000) and (r=0.84, p=0.000) were studied respectively. Due to insulin resistance, overweight women are at increased risk of metabolic dysregulation in pregnancy and associated negative results for the mother and fetus.

Key words: overweight women, adipokines, insulin resistance, reproductive health, obstetric and perinatal complications

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МАТЕРІНСЬКІ АДИПОКІНИ ТА ІНСУЛІН ЯК БІОМАРКЕРИ АКУШЕРСЬКОЇ ТА ПЕРИНАТАЛЬНОЇ ПАТОЛОГІЇ У ЖІНОК З НАДЛИШКОВОЮ МАСОЮ ТІЛА

Жінки з надмірною масою тіла мають підвищений ризик зниження чутливості до інсуліну порівняно нормальною масою тіла жінками. У роботі встановлено, що надлишкове ГЗМТ у жінок з надлишковою прегравідарною масою тіла позитивно асоціюється з підвищеною продукцією лептину, резистину і інсуліну, які є маркерами інсулінової резистентності і відіграють важливу роль в патофізіології гестаційних ускладнень. Показано, що у вагітних з гіпертензивними розладами зростають шанси гіперлептинемії, гіперрезистинемії саме у жінок з надлишковим гестаційним збільшенням маси тіла. У вагітних з затримкою росту плода у другому триместрі збільшуються шанси недостатнього збільшення рівня лептину серед вагітних з недостатнім приростом маси тіла. Виявлено сильний зв'язок між концентрацією лептину та резистину і індексом інсулінорезистентності в 22–24 тижні (r=0,83, p<0,001) і (r=0,83, p<0,001) та 37–39 тижнів (r=0,86, p<0,001) і (r=0,84, p<0,001) відповідно. Через резистентність до інсуліну жінки з надлишковою масою тіла мають підвищений ризик метаболічної дисрегуляції під час вагітності та асоційованих з цим негативних наслідків для матері та плоду.

Ключові слова: надлишкова маса тіла, адипокіни, інсулінорезистентність, репродуктивне здоров′я, акушерські та перинатальні ускладнення

The study is a fragment of the research project "Creation of diagnostic tactics and pathogenetic justification of effective methods of preservation and restoration of reproductive potential and improvement of parameters of quality of life of the woman with obstetric and gynecological pathology", state registration No. 0121U109269.

Prepregnancy overweight, excessive gestational weight gain (GWG) are one of the main risk factors for the insulin resistance development and lead to the development of gestational complications. Over the last decade, numerous studies indicate that adipose tissue is not just an energy depot, but a metabolically active tissue [5]. During overweight, the number and size of adipocytes are increased. Studies of adipocytes from pregnant women reveal alterations in lipolytic activity that promote maternal fat accumulation in early pregnancy and induce fat mobilization in late pregnancy. Hypertrophy of adipocytes is characterized by a dysregulation of the secretory function with an increase in the production of pro-inflammatory cytokines. This elevation of circulating pro-inflammatory cytokines, originated from adipose tissue, may stimulate increased inflammatory cytokine secretion by the placenta and cause placental dysfunction [15].

Adipokines, which are secreted from adipose tissue, are involved in a wide range of biological processes, including the regulation of energy homeostasis, adipocyte proliferation and differentiation, inflammation, angiogenesis and regulation of coagulation, and vascular function. Adipose tissue produces adipocytokines, such as leptin, adiponectin, tumor necrosis factor, interleukin-6, and the recently discovered resistin, visfatin, and apelin [14]. Leptin is suggested to be the strongest predictor of pregnancy-related insulin resistance. It is known that although leptin and resistin are produced mainly by adipocytes, there is convincing evidence that the placenta additionally produces these adipokines, which leads to an

increase in their serum concentration of a woman during pregnancy. On the other hand, pregnancy is considered as a leptin-resistant state, which also contributes to the state of hyperleptinemia [10].

Resistin impairs the consumption of glucose by adipocytes, increases the concentration of plasma glucose and, thus, reduces the sensitivity to insulin. In non-pregnant women, the level of resistin is higher in overweight and obesity. Costa MA et al have proved that during pregnancy, the placenta is an additional source of resistin, which is mainly synthesized in trophoblast cells. The authors emphasized the important role of this adipocytokine in the processes of the peri-implantation period – trophoblast invasion and proliferation, angiogenesis, with the aim of normal placentation and pregnancy progression [6].

From a practical point of view, gestational complications are one of the most important aspects of excessive body weight. According to modern literature [2, 4], pathological conditions during pregnancy, statistically dependent on body weight, include gestational hypertension (GH), preeclampsia, and intrauterine growth restriction (IUGR). To clarify this association, in our opinion, adipokines deserve deeper investigation given their potential role as biomarkers of excessive body weight and insulin resistance during pregnancy, and thus perinatal outcomes.

The purpose of the study was to determine the significance of determining the serum concentrations of leptin, resistin and insulin in overweight pregnant women for predicting obstetric and perinatal complications.

Material and methods. A total of 189 pregnant women, who visited the antenatal clinics and city clinical perinatal center in Ivano-Frankivsk, Ukraine, were enrolled from April 2016 until December 2021. The women were devided into two groups: the main group – 128 prepregnancy overweight patients (body mass index (BMI) 25.0–29.9 kg/m^2), the control group – 61 normal weight women (BMI 18.5–24.9 kg/ m^2). Inclusion criteria to the study were: age 18 years and older, singleton pregnancy, delivery at 37 weeks or more, the absence of severe extragenital diseases. Patients under 18 years old, diagnosed with multiple pregnancy, severe chronic diseases, BMI<18.5 and ≥30.0 kg/m^2 were excluded from the study. All women have signed "Informed consent to participate in the study". The research design was approved by the Ethics Committee of the Ivano-Frankivsk National Medical University (No. 93/16 from 01.12.2016).

112 of 189 (59.3 %) of the examined patients were nulliparous and 78 (40.7 %) were multiparous women (p>0.05). In all women, delivery took place in full-term pregnancy (39.3±1.4 weeks (95 % CI 38.1–39.5)). The average age of patients on the onset of examination was 25.8±5.6 years and 27.9±4.9 years, respectively, in the main and control groups (p>0.05). The average prepregnancy body weight in the main group was 75.5±4.5 kg, BMI – 27.7±1.6 kg/m^2 (95 % Cl 27.0–28.4), in the control group 55.3±4.8 kg, 20.3±1.5 kg/m^2 (95 % Cl 19.1–20.5), respectively.

All women were studied in each trimester of pregnancy (9–12, 22–24, 37–40 weeks). BMI was calculated according to the Quetelet formula (1865): the ratio of body weight (kg) to the square of height (m^2). Information about prepregnancy women's body weight was obtained by interviewing patients and from medical records. There were considered gestational hypertension (GH) (O13) (BP≥140/90 mm Hg) – the presence of arterial hypertension after 20 weeks of pregnancy without pathological proteinuria or other organ disorders, preeclampsia (O14) – the presence of arterial hypertension (BP≥140/90 mm Hg), which occurred after 20 weeks of pregnancy, in combination with proteinuria (≥0.3 g/day), according to the order of the Ministry of Health of Ukraine [1], intrauterine growth restriction (IUGR) (P05) – fetuses that have not reached a specific biometric or weight threshold for the appropriate gestational age ≤10th weight percentile [9]. The diagnosis of IUGR was established on the basis of standard ultrasound fetometry on the ALOKA SSD-1700 device during full-term pregnancy (37–41 weeks). GWG (kg) was evaluated by the difference between the weight before delivery and pre-pregnancy. The enzyme immunoassay method was used to determine the serum concentrations of leptin (ELISA Kit No. CAN-L-4260, Canada), resistin (Mediagnost, cat. No. E50 Resistin-ELISA US RUO E50 030113/6, Canada), insulin (Insulin Test System-2425-300, Monobind Inc., USA). Insulin resistance index was calculated by the formula for the homeostasis model assessment (HOMO-IR): fasting glucose (mmol/l) x fasting insulin (μU/ml)/22.5.

The results were statistically analyzed using Statistica 10.0 program pack (StatSoft Inc., USA) and the Microsoft Excel statistical analysis package, parametric methods of analysis were used. The parameters are presented as mean arithmetic value, mean standard deviation (x±SD). To represent the accuracy of the calculated arithmetic mean odds ratio (OR), 95 % confidence interval (CI), and p-value were obtained. Pearson's correlation-regression analysis method (r) was used to determine the presence, strength, and direction of the relationship between the parameters. The differences between the selections were considered statistically reliable at p<0.05 (Tukey's test).

Results of the study and their discussion. In the main group frequency of excessive GWG 2.4–fold, GH 3.77–fold, preeclampsia 2.8–fold, and IUGR 4.3–fold were significantly higher (in all cases p<0.05) compared to the control group (Fig. 1).

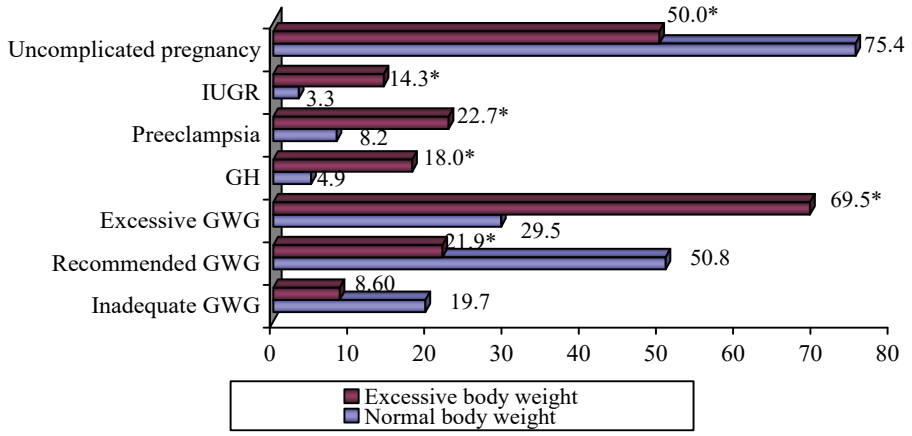

Fig. 1. The frequency of obstetric and perinatal complications in women with normal and excessive prepregnancy body weight, %: * – compared to the indicator in the normal body weight group (p<0.05). GWG – gestational weight gain, GH – gestational hypertension, IUGR – intrauterine growth restriction.

In the first trimester of pregnancy leptin concentrations 1.3–fold (27.87±1.33 ng/ml vs. 20.98±1.53 ng/ml) (p<0.05) in the main group and 2.0–fold times (13.96±1.00 ng/ml vs. 7.12±0.97 ng/ml) (p<0.05) in the control group were significantly higher compared to pre-pregnancy indicators. Leptin concentration was positively correlated with GWG at the end of pregnancy (r=0.63, p=0.000). In the group of women with uncomplicated pregnancy leptin level 1.4–fold was significantly higher in the third trimester compared to the early stages (p<0.02) (Table 1).

Table 1

Leptin, resistin, insulin levels in women with complicated pregnancy, (x±SD), n=189

Indices	Uncomplicated pregnancy (n=110)	Gestational hypertension (n=26)	Preeclampsia (n=34)	Intrauterine growth restriction (n=20)
Leptin, ng/ml				
– I trimester	19.10±2.47	20.23±3.18	27.57±1.40#	14.01±0.75
– II trimester	23.86±1.25	27.86±2.00*	31.48±1.33* #	20.60±0.96#
– III trimester	27.40±2.05*	31.97±1.03*#	32.90±1.55*#	22.13±1.16*
Resistin, ng/ml				
– I trimester	9.08±1.53	11.39±1.32	12.68±1.54#	9.00±1.20
– II trimester	11.15±1.32	14.98±1.19*#	15.97±1.13*#	10.41±1.36
– III trimester	13.55±1.01 *	16.35±0.95*#	16.45±1.02*#	12.31±1.08*
Insulin, μU/ml				
– I trimester	9.12±1.19	9.95±1.36	10.33±1.16	9.13±0.89
– II trimester	10.05±1.23	12.11±1.24	13.56±1.25	9.60±0.82
– III trimester	12.56±1.57	16.00±2.66*	17.91±2.11*#	8.59±1.16

Notes: * – compared to the index in the first trimester (p<0.05); # – compared to the group of women with uncomplicated pregnancy (p<0.05).

In the GG group of pregnant, leptin levels 1.4–fold in the second and 1.6–fold in the third trimesters were significantly higher than the values at the beginning of pregnancy (in both cases p<0.05). Also, in this group, the concentration of leptin at the end of pregnancy 1.2–fold was significantly higher, compared to the group of normotensive pregnant women (p<0.05). In the group of patients with preeclampsia, leptin concentrations 1.1–fold in the second and 2.2–fold were significantly higher in the third trimester than in the early stages (in both cases p<0.05). However, it was noted, that throughout pregnancy leptin levels significantly increased by 1.4–fold, 1.3–fold, and 1.2–fold (in all causes p<0.05), respectively in each trimester compared to the concentration in the uncomplicated pregnancy group. In the IUGR group, there was no significant elevation of leptin concentration in the middle of pregnancy and only before delivery it 1.6–fold was significantly higher compared to the first trimester, but it 1.2–fold was significantly lower in the middle of pregnancy (p<0.05) and without a statistical significance difference compared to the uncomplicated pregnancy group (p>0.05).

The study has revealed that in the first trimester the serum resistin concentration 1.4–fold was significantly higher compared prepregnancy level only in the main group (11.42±0.37 ng/ml vs. 8.24±0.51 ng/ml) (p<0.05), in the control group the difference was not statistically significant (8.45±0.40 ng/ml vs. 7.65±0.30 ng/ml) (p>0.05). Resistin levels were positively correlated with GWG in the second (r=0.27, p=0.0001) and third (r=0.52, p=0.000) trimesters. Resistin level at 22–24 weeks was positively correlated with GWG in late pregnancy (r=0.27, p=0.0001).

In the uncomplicated pregnancy group, resistin concentration in the third trimester 1.5–fold was significantly higher compared the ferst trimester ($p<0.05$). In GH pregnant group, resistin levels 1,3–fold in the second and 1.4–fold in the third trimesters were significantly higher the concentration of early pregnancy (in both cases, $p<0.05$). Also, it was found, that in this group, the resistin concentration in the middle of pregnancy and before delivery was significantly higher, compared to the uncomplicated pregnancy group (1.3–fold and 1.2–fold, respectively, $p<0.05$). In the preeclamptic group of patients, the resistin concentrations in the second and third trimesters significantly exceeded the early pregnancy (1.3–fold in both cases $p<0.05$). It was also diagnosed that during the pregnancy, resistin levels 1.4–fold, 1.4–fold, and 1.2–fold (in all cases $p<0.05$) were significantly higher respectively in each trimester compared to the uncomplicated pregnancy group. In the IUGR group resistin level significantly increased until the end of pregnancy ($p<0.05$), but its levels did not statistically significantly differ from the uncomplicated pregnancy ($p>0.05$).

The plasma insulin levels in the first trimester did not statistically significantly exceed the prepregnancy concentration in both the main group (10.95±0.33 μIU/ml vs. 10.89±0.46 μIU/ml) ($p>0.05$) and the control group (8.85±1.02 μIU/ml vs. 8.45±1.12 ng/ml) ($p>0.05$). Insulin levels were positively correlated with GWG in the second and third trimesters of pregnancy ($r=0.20$, $p=0.001$; $r=0.32$, $p=0.0001$, respectively).

The absence of significant changes in insulin concentrations during the gestational period was found in the uncomplicated pregnancy and in the IUGR groups ($p>0.05$). However, in the GH group, insulin levels at the end of pregnancy 1.6–fold were higher compared the first trimester ($p<0.05$) and 1.2–fold were significantly higher compared to the uncomplicated pregnancy group ($p<0.05$). In the preeclamptic group of women insulin levels before delivery 1.7–fold were higher compared to early terms and 1.4–fold significantly were higher compared to the uncomplicated pregnancy group (in both cases $p<0.05$).

The present study has proved that the chances of hyperleptinemia in GH pregnant 3.5–fold (OR=3.50; 95 % CI: 1.48–9.33; $p<0.05$), hyperresistinemia 3.2–fold (3.21; 1.22–8.82), in preeclamptic pregnant the chances of hyperleptinemia 6.0–fold (6.01; 2.43–15.02), hyperresistinemia 3.8–fold (3,82; 1.53–9.60) and hyperinsulinemia 5.0–fold (4.97; 1.63–15.01) significantly increase in excessive GWG women. The chances of an insufficient elevation of leptin level in the second trimester of pregnancy 5.3–fold (5.30; 1.92–14.31; $p<0.01$) is higher in insufficient GWG patients.

Leptin concentrations were positively correlated with body weight in pregnant women with uncomplicated pregnancy, GH, preeclampsia in the second and third trimesters, and in patients with IUGR in mid pregnancy. Resistin concentrations were positively correlated with body weight in pregnant women with uncomplicated pregnancy, GH, preeclampsia in the second and third trimesters, and the absence of a significant assosiation in the patients with IUGR (Table 2).

Table 2

Multiple regression analysis, p-value, for the relationship between serum leptin and resistin levels and maternal weight in complicated pregnancy variables

	Trimester II		Trimester III	
	Correlation coefficient (r)	p	Correlation coefficient (r)	p
Leptin and body weight				
– uncomplicated pregnancy	0.59	0.0001	0.67	0.0001
– gestational hypertension	0.58	0.006	0.69	0.0007
– preeclampsia	0.55	0.002	0.64	0.0002
– intrauterine growth restriction	0.83	0.0001	0.36	0.12
Resistin and body weight				
– uncomplicated pregnancy	0.64	<0.0001	0.67	<0.0001
– gestational hypertension	0.40	0.02	0.45	0.01
– preeclampsia	0.43	0.01	0.46	0.009
– intrauterine growth restriction	0.21	0.35	0.35	0.11

It is known that pregnancy is characterized by a state of insulin resistance for adequate energy supply of the fetus, mainly as a result of increased production of placental hormones. Ehe role of adipose tissue and adipokines in the induction and regulation of insulin resistance in non-pregnant overweight/obese womenis shown in the literature [3]. Due to the rapid elevation of the fat component, as the most labile component of GWG, we have been monitored the assosiation of hyperleptinemia and

hyperresistinemia with HOMA-IR. Leptin and resistin were positively correlated with the insulin resistance index in 22–24 weeks (r=0.83, p=0.000) and (r=0.83, p=0.000) and 37–39 weeks (r=0.86, p=0.000) and (r=0.84, p=0.000), respectively.

Insulin resistance in pregnancy is associated with a marked increase in fat depot, so it can be assumed that adipose tissue plays a role in the initiation and regulation of gestational insulin resistance. Our findings about the elevation of leptin and resistin concentrations in pregnancy, especially in excessive GWG, confirmed the correlation between adipokines and tissue resistance to insulin during pregnancy [13].

Excessive body weight leads to adipocyte dysfunction and correlates with an imbalance in the levels of adipocyte-specific factors. It can be assumed, that adipokine dysregulation in prepregnancy overweight women during pregnancy, as in an excessive energy load state, can strengthen the tissue resistance to insulin, and is considered the ground of gestational complications.

In the present study we have showed positive associations between adipokines and insulin levels with maternal and fetal outcomes. The leptin and resistin levels 2.0–fold and 1.4–fold were higher in overweight pregnant women compared to the normal weight group from the early stages of pregnancy, showing a positive correlation with GWG, GH, preeclampsia in the second and third trimesters. These results confirm the role of leptin in energy metabolism, inflammation and insulin resistance in overweight, which has already been found in other studies [15]. It is known, that during pregnancy adipokines are additionally synthesized by the placental trophoblastic cells and enter the mother's bloodstream. Gutaj P. et al. believe that the elevation of maternal leptin level of preeclamptic women is caused by placental hypoperfusion and hypoxia as a result of pathological invasion of the trophoblast and impaired angiogenesis of the placenta. Researchers emphasize, that the elevation of maternal serum leptin with the subsequent development of hypertensive disorders occurs even before the onset of clinical symptoms. On the other side, maternal hyperleptinemia induces hypertension due to the ability of leptin to activate the sympathetic nervous system and stimulate the secretion of catecholamines [7].

In scientific sources, we have found controversial conclusions regarding the level of resistin in hypertensive disorders of pregnant women. Thus, the elevation of serum resistin level has been shown, which thereby leaded to development of glucose tolerance in preeclamptic pregnant compared to normotensive women [12]. While other reserchers showed no association between this adipokine and hypertensive states or maternal BMI [8]. Scientists assume that the cause of low resistin concentration is placental dysfunction, which accompanies the development of preeclampsia, is manifested by a decrease placental size and leads to a decrease in placental adipokine production. In our study, we have found that the chances of hyperresistinemia in the GH and preeclampsia groups of pregnant women significantly increased in the group of excessive GWG women.

The role of leptin as one of the main inducers of placental angiogenesis is considered as a protective factor in relation to placental dysfunction and fetal hypoxic conditions. Experimental studies on human syncytiotrophoblast cells showed the role of leptin in the regulation of nutrient transport [6]. We did not establish a statistical difference in the concentration of this adipokine in patients with uncomplicated pregnancy and IUGR (p>0.05), and the absence of a reliable correlation between leptin concentration and body weight in the group of IUGR pregnant women was found (p>0.05). This can be associated with a compensatory mechanism – increased production of leptin by a small placenta under conditions of hypoxic stress, as suggested by other researchers [14] and even suggest the use of human recombinant leptin in the treatment of IUGR in the future. No association was found between the concentration of serum resistin levels of patients with IUGR and GWG (p>0.05).

Our findings support an association between markers of overweight/obesity and maternal-fetal outcomes. In the present research, it was established that excessive GWG in overweight women is positively associated with increased leptin, resistin, and insulin production, which are markers of insulin resistance and play an important role in the pathophysiology of gestational complications. Reserchers assume that preconception training for overweight women should be started 3–4 months before pregnancy, which allows for a full examination of future mothe and, if necessary, to carry out appropriate preventive treatment [11]. The results of present study indirectly support the importance of controlling the mother's weight before and during pregnancy to improve reproductive health and avoid negative consequences.

Conclusions

1. The study have shown the significance of determination the serum leptin, resistin, and insulin concentrations in prepregnancy overweight pregnant in the second trimester as predictors of obstetric and perinatal complications.

2. The research have found higher leptin, resistin, and insulin levels in groups of pregnant women with gestational hypertension, preeclampsia, and no significant difference between these indicators in groups with fetal intrauterine growth restriction and uncomplicated pregnancies. It was noted that hyperleptinemia and hyperresistinemia are characterised of pregnant women with gestational hypertension, preeclampsia, especially in women with excessive gestational weight gain, which in association with the insulin resistance state in the second and third trimesters can be considered a pathogenetic link in the formation of hypertensive disorders. It was established that in the group with fetal intrauterine growth restriction there was maternal high leptin level in the second and third trimesters compared to early periods, in the mid of pregnancy the leptin concentration was lower compared to individuals with a physiological course of gestation.

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