ISSN 2518-1432 (Online); ISSN 2227-4782 (Print) https://doi.org/10.21856/j-PEP.2024.2.01

КЛІНІЧНА ЕНДОКРИНОЛОГІЯ

LEPTIN AND VISFATIN AS PREDICTORS OF GESTATIONAL HYPERTENSIVE COMPLICATIONS IN OVERWEIGHT WOMEN*

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Obesity is a comorbid pathology that is most common in developed countries in women of reproductive age [1]. Short- and long-term side effects of overweight on both the mother and the fetus are well known, which is reflected in the strong correlation of body weight with maternal infertility and the risk of gestosis, congenital fetal anomalies, and increased risk of spontaneous abortion [1]. Obese women have been shown to have an increased risk of spontaneous abortion and congenital fetal malformations [2]. A concomitant insulin resistance of the feto-placental barrier has a strong correlation with fetal birth weight and the risk of overweight at birth [3].

Over the past decades, fat tissue is not considered to be just energy depot but source of hormone-like peptides, adipokines [4]. Adipokines include both immunomediators (complement factors, prostaglandin E2, interleukins IL-1ß, IL-6, IL-8, IL-10, tumor necrosis factors, etc.) [5] and hormone-like substances such as leptin, visfatin (NAMPT), adiponectin, resistin, and others [6].

Leptin is one of the hormones secreted by visceral adipose tissue that regulates appetite, weight gain, and is also involved in fetal growth, angiogenesis, lipolysis, and has a proinflammatory effect [7]. Many recent studies show a strong correlation between body weight and serum leptin levels and the percentage of body fat and the development of leptin resistance [8–10].

Other adipokine, known as visfatin plays a significant role in the development of insulin resistance, metabolic syndrome, overweight/obesity, and is increased during pregnancy [11]. The available data about the possible use of visfatin as a potential predictor of pregnancy complications is still controversial [12, 13]. Further studies of the role of visfatin during pregnancy in both healthy and overweight women are needed to substantiate the feasibility of determining visfatin le-

* The study was carried out within the complex research project «Development of diagnostic tactics and pathogenetic substantiation of effective methods for preserving and restoring reproductive potential and improving the parameters of women's quality of life in obstetric and gynecological pathology» (state registration number 0121U109269).

The institution funding the study is the Ministry of Health of Ukraine.

The authors guarantee full responsibility for everything published in the article.

The authors declare no conflict of interest and any financial interest for writing the article.

The manuscript was received by the editorial staff 23.02.2024.

vels as a predictor of pregnancy complications [14–16].

Aim of the study. To determine the prognostic value of leptin and visfatin in predicting gestational hypertensive complications in overweight women.

MATERIALS AND METHODS

The study included 117 women who were divided into two groups according to BMI. The main group included 68 overweight women (BMI = 25.0–29.9), while the control group included 49 women with normal body weight (BMI = 18.5–24.9). The study was carried out in three stages:

1) before pregnancy;
2) in the first trimester;
3) in the third trimester.

At each stage, BMI and gestational weight gain (GWG), leptin and visfatin levels were determined. Quantitative determination of serum leptin (ELISA Kit No. CAN-L-4260, Canada) and visfatin (Visfatin-ELISA Kit (ab264623), Canada) was performed by enzyme-linked immunosorbent assay. Leptin reference values considered to be 3.7-11.1 ng/ml while 21.0–29.0 ng/ml was reference for visfatin.

Pregnancy complications — gestational hypertension (GH) and preeclampsia (PE) were diagnosed and treated according to current local guidelines [17].

The study was conducted according to the ethical requirements of the Ukrainian Association for Bioethics and the Standards of GCP (1992), GLP (2002), the principles of the Declaration of Helsinki on Human Rights, the Council of Europe Convention on Human Rights and Biomedicine and approved by the Ethics Committee of Ivano-Frankivsk National Medical University.

The statistical analysis of the results was performed using Microsoft Excel 365 and Statistica 12.0 (StatSoft Inc., USA). The normality of the distribution was determined using the Kolmogorov-Smirnov, Lilliefors, and Shapiro-Wilk tests [18]. Since the distribution of most groups was normal, the results were presented as the mean (M) and standard deviation (SD) as M ± SD or using 95% confidence interval (95% CI [LL, UL]). To assess the reliability of the data, the t-test was used, and the difference was considered significant if $p < 0.05$ [18].

RESULTS AND THEIR DISCUSSION

The baseline BMI for main group was 27.3 ± 1.1, and 22.7 ± 1.8 for control. GWG on the third trimester of pregnancy was 11.8 ± 2.5 for main group and 19.3 ± 3.4 for control group. The course of pregnancy in overweight women was complicated by gestational hypertension in 20 (29.4%) and preeclampsia in 25 (36.8%) patients. In women of control group, GH developed in 6 (12.2%) cases and PE in 6 (12.2%) cases.

A significant increased risk of gestational complications was found in patients with overweight (Table 1), namely, GH occurred 2.4 times more often, and the risk of PE was 3.0 times higher compared with the data of main group ($p < 0.05$).

In the group with uncomplicated pregnancy there was a significant increase in leptin concentration by 2.0 times in the first trimester of pregnancy compared with the pre-pregnancy

Table 1

Relationship between gestational weight gain, excessive BMI and pregnancy complications (multivariate logistic regression analysis), n = 117

	Increased BMI			Increased GWG		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Gestational hypertension	2.99	[1.10; 8.12]	0.04	6.71	[2.14; 21.03]	< 0.001
Preeclampsia	4.17	[1.55; 11.17]	0.005	6.71	[2.14; 21.03]	< 0.001

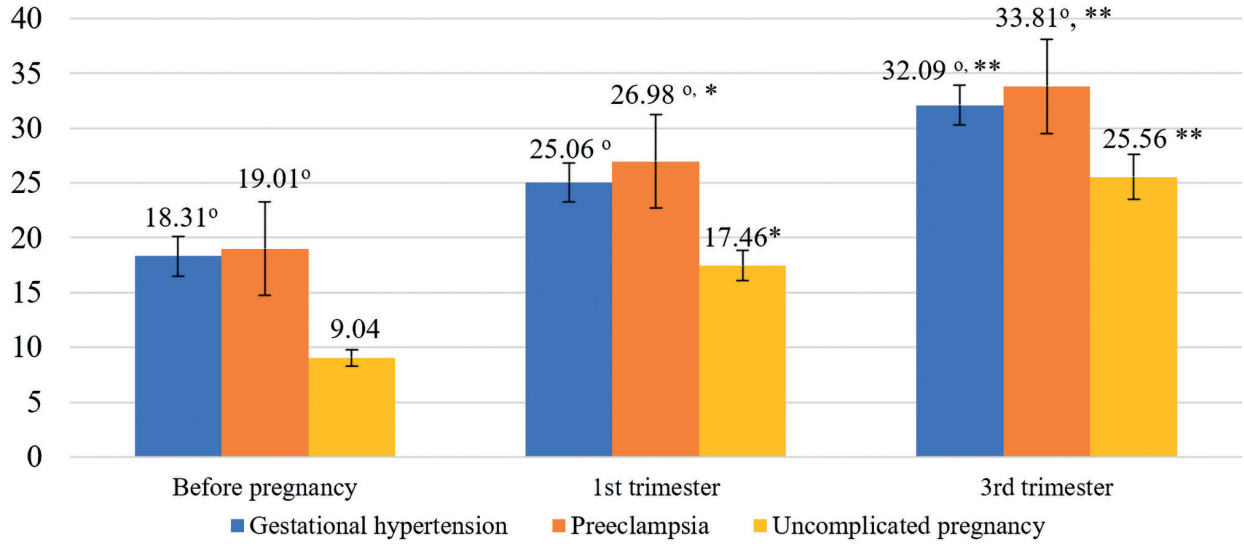

Fig. 1. Dynamics of serum leptin (ng/ml) in women of both groups at different gestational stages.
Notes: ° — compared with the index in uncomplicated pregnancy ($p < 0.05$);
* — compared with the index before pregnancy ($p < 0.05$),
** — compared with the index in the first trimester ($p < 0.05$).

level ($p < 0.05$), with an increase in the third trimester by 1.5 times ($p < 0.05$) (Fig. 1). The concentration of leptin in the third trimester in pregnant women with GH significantly increased by 21.9%, and PE by 20.2% compared with pre-pregnancy values ($p < 0.05$).

After dividing the data according to BMI (Table 2), it was found that women with high BMI and the development of hypertensive complications of pregnancy had a statistically significant ($p < 0.05$) higher serum leptin level before pregnancy.

As of the first trimester, leptin concentration significantly increased in both groups. However, whereas in overweight women a significant ($p < 0.05$) increase in leptin levels was noted compared with the group without complications by an average of 39.3% in cases of GH and 39.6% in cases of PE, in women with normal BMI there was no significant difference between the groups with and without GH or PE ($p > 0.05$).

In overweight women, the leptin level in case of GH or PE was on average 34.2% significantly higher than in women without hypertensive disorders ($p < 0.05$). In contrast, in women with normal BMI, there was no significant difference between the groups of women with and without GH or PE ($p > 0.05$).

In uncomplicated pregnancy, a significant increase in the concentration of visfatin by 1.3 times in the first trimester was found compared with the pre-pregnancy ($p < 0.05$) (Fig. 2).

Table 2

Dynamics of leptin (ng/ml) in women of both groups

	Gestational hypertension	Preeclampsia	Uncomplicated pregnancy
Main group (overweight)			
Before pregnancy	21.65 ± 1.79 *	21.90 ± 1.71 *	9.07 ± 1.12
1st trimester	28.43 ± 1.41 *, **, °	28.56 ± 1.59 *, **, °	17.25 ± 2.02 *, **
3rd trimester	33.69 ± 1.75 *, **, °	33.99 ± 1.64 *, **, °	22.21 ± 1.79 **
Control group (normal BMI)			
Before pregnancy	7.16 ± 0.97	7.33 ± 0.93	8.45 ± 1.14
1st trimester	14.26 ± 0.70 **	14.31 ± 0.89 **	13.35 ± 0.65 **
3rd trimester	21.83 ± 1.22 **, °	22.80 ± 2.40 **, °	19.75 ± 1.88 **

Notes:
* — significant difference compared to the group with normal BMI ($p < 0.05$);
** — significant difference compared to the previous stage of the examination ($p < 0.05$);
° — significant difference compared to the uncomplicated pregnancy ($p < 0.05$).

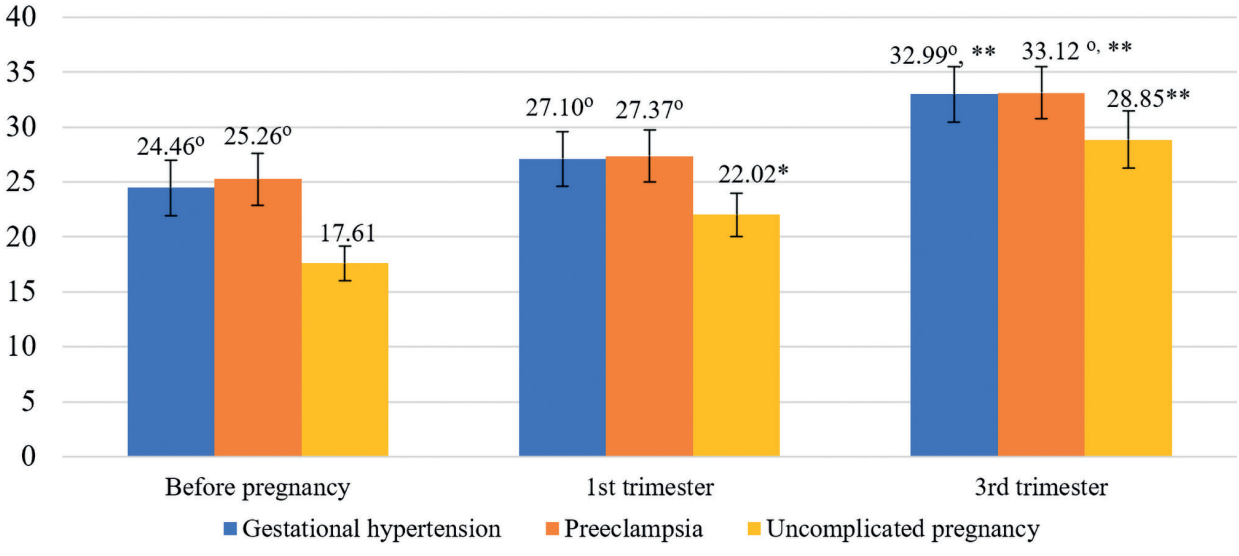

Fig. 2. Dynamics of visfatin levels (ng/ml) in women of both groups.
Notes: º — compared with the index in uncomplicated pregnancy ($p < 0.05$);
* — compared with the index before pregnancy ($p < 0.05$);
** — compared with the index in the first trimester ($p < 0.05$).

It's increase further by 1.3 times compared with the first trimester ($p < 0.05$). The level of visfatin in the third trimester in the group of patients with GH increased by 17.9%, PE by 17.4% compared to the beginning of pregnancy ($p < 0.05$ for all pathologies) and significantly exceeded the value in the group with uncomplicated pregnancy by 1.2 times ($p < 0.05$)

After standardization, on the onset of third trimester the mean visfatin level in overweight women with GH was 26.1% significantly higher compared to the value before pregnancy ($p < 0.05$) (Table 3). In main group within the third trimester in the presence of GH or PE, the concentration of visfatin was significantly higher than in women without hypertensive complications ($p < 0.05$). At the same time, in women with normal BMI who developed GH or PE, the value of visfatin did not differ compare to woman of same group without GH ($p > 0.05$).

In the study Peltokorpi concluded that pre-pregnancy elevated leptin levels are associated with the development of gestational complications — GH, PE, and gestational diabetes [19]. It should be borne in mind that leptin levels are strictly correlated with BMI both in the general population and in pregnant women [7, 10]. In our study, in women with normal BMI, the baseline leptin concentration was within the reference limits, whereas in overweight

Table 3

Dynamics of visfatin (ng/ml) in women of both study groups

	Gestational hypertension	Preeclampsia	Uncomplicated pregnancy
Main group (overweight)			
Before pregnancy	21.65 ± 1.79 *, º	21.90 ± 1.71 *, º	16.2 ± 1.42
1st trimester	28.43 ± 1.41 *, **, º	28.56 ± 1.59 *, **, º	20.45 ± 1.32 *, **
3rd trimester	33.69 ± 1.75 *, º	33.99 ± 1.64 *, º	29.21 ± 2.24 **
Control group (normal BMI)			
Before pregnancy	17.60 ± 1.17 º	17.90 ± 1.39 º	15.5 ± 1.24
1st trimester	22.96 ± 0.59 *, **, º	23.11 ± 1.75 *, **, º	16.33 ± 1.36
3rd trimester	29.16 ± 1.87 **	29.48 ± 1.77 **	28.45 ± 2.01 **

Notes:
* — significant difference compared to the group with normal BMI ($p < 0.05$);
** — significant difference compared to the previous stage of the examination ($p < 0.05$);
º — significant difference compared to the uncomplicated pregnancy ($p < 0.05$).

women, the leptin concentration significantly exceeded these limits. This may be due to lower leptin levels, since pharmacological reduction of leptin also reduces the risk of cardiovascular events, as well as body weight [20]. Meta-analysis also confirms that proinflammatory markers and adipokines are associated with the higher risk of PE [21].

We found that leptin level in women with normal BMI did not differ in the whatever GH or PE will develop or not, while it differs in overweight group. This is supported by the available data of the leptin predictions for hypertensive disorders of pregnancy in obese women [22] and data on the limitations of its use in women with normal BMI [23].

We founded that the concentration of visfatin increased dramatically in both women with normal BMI and overweight in early pregnancy. It is known that the concentration of visfatin in women changes during the menstrual cycle and especially increases with the onset of pregnancy [24]. Our data on the gradual increase in the concentration of visfatin during pregnancy coincide with the data obtained by Nunes [25]. The data obtained by Chandrasekaran indicate that visfatin correlates with the risk of preeclampsia in both normal weight and obese women [23]. However, in our study, a significant difference in visfatin levels between women with and without gestational hypertensive disorders was observed only in the group of overweight women, while in women with normal BMI the data were not statistically significant.

CONCLUSIONS

The analysis of the results showed that during pregnancy there was a significant increase in the levels of both leptin and visfatin in patients of both groups without a significant difference between them, although both the initial and final values during pregnancy were significantly higher in case of hypertensive complications. In particular, compared to normal BMI in overweight woman who developed hypertensive complications, leptin levels were found to be 3.0 and 2.0 times higher at first and third trimester. Visfatin levels were found to be 1.2 times higher at both stages.

Thus, leptin and visfatin can serve as qualitative predictors of hypertensive complications during pregnancy planning and early gestation in overweight women.

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ЛЕПТИН ТА ВІСФАТИН ЯК ПРЕДИКТОРИ ГЕСТАЦІЙНИХ ГІПЕРТЕНЗИВНИХ УСКЛАДНЕНЬ У ЖІНОК З НАДМІРНОЮ МАСОЮ ТІЛА

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Актуальність. За останні десятиліття жирова клітковина перестала бути просто енергетичним депо, а стала розглядатися як джерело гормоноподібних пептидів – адипокінів, наприклад лептину та вісфатину. Відома пряма кореляція маси тіла з ризиком розвитку гестаційних ускладнень.

Мета дослідження. Визначити прогностичну цінність лептину та вісфатину при прогнозуванні гестаційних гіпертензивних ускладнень у жінок з надмірною масою тіла.

Матеріали та методи. Обстежено 117 жінок, які були розподілені на дві групи: у основну групу ввійшли 68 жінок з надмірною масою тіла, до контрольної групи включили 49 жінок з нормальною масою тіла. Значення лептину та вісфатину визначали до вагітності, на I триместрі та на III триместрі.

Результати. У жінок із надлишковою масою тіла спостерігали гестаційну гіпертензію у 20 жінок (29,4%), прееклампсію у 25 жінок (36,8%). Концентрація лептину в третьому триместрі у вагітних з гестаційною гіпертензією зросла на 21,9%, прееклампсією на 20,2% порівняно з прегравідарними значеннями ($p < 0,05$) та перевищувала у 1,3 раза показник у жінок з неускладненим перебігом вагітності ($p < 0,05$). У жінок основної групи на III триместрі вагітності при наявності гестаційних гіпертензивних ускладнень концентрація вісфатину була вищою, ніж у жінок без гіпертензивних ускладнень гестації ($p < 0.05$). У групах жінок з розвитком гіпертензивних станів ми спостерігали достовірно вищі концентрації вісфатину впродовж усього гестаційного перебігу порівняно з групою пацієнток з неускладненою вагітністю. У жінок основної групи на III триместрі вагітності при наявності гестаційних гіпертензивних ускладнень концентрація вісфатину була вищою, ніж у жінок без ускладнень.

Висновки. У пацієнток з надмірною масою тіла з гіпертензивними ускладненнями лептин зріс у 3,0 рази на прегравідарному етапі та в 2,0 рази на I триместрі, а вісфатин у 1,2 раза на обох етапах. Лептин та вісфатин можуть служити якісними предикторами гіпертензивних ускладнень при плануванні вагітності та на ранніх термінах гестації у жінок з надмірною масою тіла.

Ключові слова: надмірна маса тіла, вагітність, гестаційна гіпертензія, прееклампсія, лептин, вісфатин.

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Background. Over the past decades, fatty tissue has ceased to be just an energy depot, but as a source of hormone-like peptides - adipokines, such as leptin and visfatin. There is a direct correlation between body weight and the risk of developing gestational complications. Aim of this study was to determine prognostic value of leptin and visfatin in predicting gestational hypertensive complications in overweight women.

Materials and methods. We examined 117 women divided into two groups: the main group included 68 overweight women, the control group included 49 women with normal body weight. Serum leptin and visfatin was established before pregnancy, in the first and third trimester.

Results. In overweight women, gestational hypertension was observed in 20 women (29.4%) and preeclampsia in 25 women (36.8%). The concentration of leptin in the third trimester during gestational hypertension increased by 21.9%, by 20.2% in preeclampsia compared before pregnancy ($p < 0.05$) and exceeded the value in uncomplicated pregnancy by 1.3 times ($p < 0.05$). In main group during third trimester in case of gestational hypertensive complications, the concentration of visfatin was higher than in women without complications ($p < 0.05$). In the groups of women with hypertensive conditions, we observed significantly higher concentrations of visfatin compared with the woman without complications. In main group in case of gestational hypertensive complications, the concentration of visfatin was higher than in women without complications on the third trimester.

Conclusions. In overweight patients who developed hypertensive complications, leptin found to be 3.0 times higher before pregnancy and 2.0 times higher in the first trimester. Visfatin were found to be 1.2 times higher at both stages compared with control group. Leptin and visfatin may serve as qualitative predictors of hypertensive complications before pregnancy and during early gestation in overweight women.

Keywords: overweight, pregnancy, gestational hypertension, preeclampsia, leptin, visfatin.