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EFFECT OF OBESITY THERAPY IN WOMEN OF REPRODUCTIVE AGE ON LEPTIN LEVEL AND HORMONAL OVARIAN FUNCTION

© E.M. Ryazantseva[1], M.A. Tarasova[2], N.N. Tkachenko[2], A.M. Gzgzyan[2]

[1] Clinical Diagnostic Medical Center of the Office of the President of the Russian Federation, Saint Petersburg, Russia;
[2] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia

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▪ Hypothesis/aims of study. Ovarian insufficiency is present in more than 30% of reproductive-age obese women. The role of leptin in the pathogenesis of ovarian insufficiency is not yet established and has to be clarified. It is of interest to study the effect of obesity therapy on hyperleptinemia, hormonal and ovulatory function in reproductive-age women with alimentary obesity. The aim of this study was to assess the effect of obesity therapy on leptin level and hormonal ovarian function in women of reproductive age.

Study design, materials and methods. All studied women underwent a clinical and laboratory examination, including: medical history, anthropometry (height and weight measurement, waist and hip circumferences, body mass index calculation), blood pressure measurement, gynecological examination, ultrasound examination of the pelvic organs, osteodensitometry, determination of serum gonadotropins, sex hormones, insulin, leptin, and blood biochemical parameters, morning fasting blood glucose, and glucose after the glucose tolerance test. The survey and objective examination data were recorded in a specially developed application form, including the following parameters: the patient's age, menarche age, the type of the menstrual cycle, data on pregnancies, childbirth and reproductive plans, gynecological and somatic diseases.

Results. The relationship between the initial levels of leptin, estradiol, HOMA-IR, the number of follicles in the ovaries and the restoration of ovulatory function after the weight loss was revealed. The analysis produced a mathematical model to estimate the predictive value of these indicators in relation to the recovery of ovulation after the weight loss. An analysis was made of the effectiveness of drugs used to treat excess body weight (metformin and sibutramine).

Conclusion. The predictive value of the baseline levels of leptin and estradiol, the number of antral follicles and insulin resistance in relation to the achievement of ovulation after the reduction of body weight in patients with anovulation caused by excess body weight and obesity has been established. Ovulation recovery did not depend on the choice of a drug used to treat excess body weight. When comparing the groups of women who received medication for alimentary obesity using metformin and sibutramine, no significant differences in the frequency of ovulation recovery were found.

▪ **Keywords:** obesity therapy; metformin; sibutramine; ovarian failure; leptin; insulin resistance; estradiol; ovulation.

ВЛИЯНИЕ ТЕРАПИИ АЛИМЕНТАРНОГО ОЖИРЕНИЯ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА НА УРОВЕНЬ ЛЕПТИНА И ГОРМОНАЛЬНУЮ ФУНКЦИЮ ЯИЧНИКОВ

© Е.М. Рязанцева[1], М.А. Тарасова[2], Н.Н. Ткаченко[2], А.М. Гзгзян[2]

[1] Федеральное государственное бюджетное учреждение «Консультативно-диагностический центр с поликлиникой» Управления делами Президента Российской Федерации, Санкт-Петербург;
[2] Федеральное государственное бюджетное научное учреждение «Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта», Санкт-Петербург

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▪ ***Актуальность.*** Более чем у 30 % женщин репродуктивного возраста с избытком массы тела и ожирением наблюдается недостаточность яичников. Представлены данные о значимом влиянии лептина на репродуктивную систему, стероидогенез в яичниках и гормональную недостаточность яичников у женщин с алиментарным ожирением.

Представляет интерес влияние терапии ожирения на коррекцию гиперлептинемии и эффективность восстановления гормональной и овуляторной функций у женщин репродуктивного возраста с алиментарным ожирением.

Цель — изучить влияние терапии ожирения на уровень лептина и гормональную функцию яичников у женщин репродуктивного возраста.

Материалы и методы исследования. Всем женщинам проводили клинико-лабораторное обследование, включающее сбор анамнеза, антропометрию (измерение роста и веса, окружности талии и окружности бедер, вычисление индекса массы тела), измерение артериального давления, гинекологическое обследование, определение уровня гонадотропинов, половых гормонов, инсулина, лептина крови, биохимических показателей крови, уровня глюкозы натощак и пробу на толерантность к глюкозе, ультразвуковое исследование органов малого таза, остеоденситометрию по программе «все тело». Данные опроса и объективного обследования заносили в специально разработанную анкету, в которую вошли следующие показатели: возраст пациентки, возраст менархе, характер менструального цикла, данные о беременностях, родах и репродуктивных планах, гинекологических и соматических заболеваниях.

Результаты исследования. Выявлена взаимосвязь между исходным уровнем лептина, эстрадиола, количества фолликулов в яичниках и восстановлением овуляторной функции после снижения веса. Была составлена математическая модель для оценки вероятности восстановления овуляции после снижения веса. Проведен анализ эффективности лечения с применением препаратов метформин и сибутрамин в отношении восстановления овуляции после снижения массы тела.

Выводы. Полученные результаты позволяют установить прогностическое значение показателей содержания лептина и эстрадиола в крови, количества антральных фолликулов и инсулинорезистентности в отношении достижения овуляции после снижения массы тела у пациенток с ановуляцией, вызванной избытком массы тела и алиментарным ожирением. При сравнении групп женщин, получавших медикаментозное лечение алиментарного ожирения с применением препаратов метформин и сибутрамин, достоверных различий в частоте восстановления овуляции не отмечено.

Ключевые слова: терапия ожирения; метформин; сибутрамин; недостаточность яичников; лептин; инсулинорезистентность; эстрадиол; овуляция.

According to the World Health Organization (2016), more than 1.9 billion (39%) adults aged 18 years and older are overweight, and more than 600 million of them are obese (38% of men and 40% of women). Since 1980, the number of obese individuals worldwide has more than doubled. According to the Ministry of Health of the Russian Federation, the number of individuals diagnosed with obesity increased by 1.5 times in 5 years (from 856,500 in 2011 to 1,245,600 in 2016), wherein 30% to 40% are represented by women of working age [1]. In 2017, 2 million Russians were diagnosed with obesity, which accounted for 1.3% of the country population [2]. Excessive visceral adipose tissue is associated with metabolic and reproductive disorders, including anovulation and impaired fertility, and these disorders are observed in >30% of women with overweight or obesity [3–6]. Obesity significantly reduces the effectiveness of methods of treating infertility caused by impaired ovarian function, which makes it relevant to further study the mechanisms of the effect of obesity on reproductive function [7].

Currently, the treatment of obesity and ovarian failure is based on the pathogenetic role of insulin resistance in the development of ovarian failure in obese women. Evidence shows that leptin directly affects the ovaries, inhibiting the production of estradiol [8], and indirectly through the stimulation of impulse secretion of gonadotropin-releasing hormone by the hypothalamus and luteinizing hormone by the pituitary gland [9].

The therapeutic strategy is reduced to a decrease in body weight, androgen levels, and insulin resistance, which leads to a spontaneous restoration of ovulation and pregnancy in a significant number of patients [10]. Ovulatory function is restored in a significant number of patients with a decrease in body weight by 5%–10% [3–6, 11]. Regular exercise (30 min a day, at least 3 times a week) and diet (low-calorie, 1000–1200 kcal per day) constitute level I of therapy in such patients, and if this regimen is maintained for at least 6 months, then this is enough to decrease the level of insulin resistance and increase the level of the protein that binds sex steroids [10–13]. The difficulty is in selection of diet and physical activity, which patients are able to adhere to for a long time, because weight is restored, and endocrine disorders are noted again if the diet is not followed, and physical activity is stopped [14]. After approximately 6 months of diet and exercise, especially in women with a high body mass index (BMI) (≥27 kg/m^2), starting additional drug therapy that reduce appetite (sibutramine) is recommended

[11]. A special place in the pharmacotherapy of obesity and ovarian dysfunction is held by drugs that increase insulin sensitivity, biguanide derivatives (metformin). They cause a decrease in hepatic glucose production, increase peripheral insulin sensitivity, and are effective in reducing hyperinsulinemia, hyperandrogenism, and restoring ovulatory function [15–17]. Upadhyaya et al. [18] showed that the use of metformin in patients with polycystic ovarian syndrome (PCOS) significantly reduces leptin levels. Ovulation occurred more often in patients with significantly reduced leptin level. Metformin reduces leptin resistance in patients with PCOS.

The study aimed to investigate the effect of obesity therapy on leptin levels and ovarian hormonal function in women of reproductive age.

Materials and research methods

The main group included 38 women of reproductive age with a BMI of >25.6 kg/m^2. The control group consisted of 20 healthy women of reproductive age. Anthropometric examination and follicle-stimulating and luteinizing hormones, estradiol, and prolactin levels were assessed on days 2–5 of the menstrual cycle, and prolactin and progesterone levels were assessed on days 20–22 of the menstrual cycle. In the presence of amenorrhea, hormonal examination was performed once using a solid-phase competitive immunochemiluminescent method on an IMMULITE 2000 apparatus, DPC (USA). Leptin level was determined using an enzyme-linked immunosorbent assay using kits manufactured by DRG (USA). Fasting insulin and glucose levels were examined to assess carbohydrate metabolism, and glucose tolerance test was performed. Pelvic ultrasound was performed using a Siemens apparatus (Japan) using abdominal and vaginal probes with a frequency of 3.5 and 7.5 MHz, respectively. Within 6 months, women followed a low-calorie diet (1200 kcal per day) in combination with increased physical activity. In addition to diet, 19 women were administered metformin 500 mg twice daily, and 19 women were administered sibutramine at 10 mg/day. After 6 months, a repeat examination was performed, which included anthropometry, determination of leptin, gonadotropin, insulin, and sex steroid hormone levels in the blood, fasting glucose test, assessment of lipid metabolism, and pelvic echography.

Statistical test was performed using the R and Statistica 7.0 software packages. The arithmetic mean (M), mean error (m), and Pearson and Spearman correlation coefficients were calculated. Discriminant analysis was used. The independence of categorical features was tested using Fisher exact test. The Kruskal–Wallis test was used to assess the homogeneity of several independent samples. The confidence level of probability (p-values) was compared with a significance level of 0.05, and the null hypothesis was rejected at $p < 0.05$. The significant differences of the two groups was determined using the Wilcoxon test, and the Student t test was used if the distribution laws within the samples corresponded to the normal distribution law according to the Shapiro–Wilk test. To study the significance of the combined effect of different factors (belonging to a group with ovulation or anovulation or the time of follow-up before and after treatment), repeated measures model of analysis of variance for repeat monitoring, which checked the significance of fixed effects, namely group, time, and interaction of group factors and time.

The inclusion criteria in the main group:

- women aged 18–40 years;
- not pregnant during the study;
- BMI > 25 kg/m^2;
- alimentary obesity; and
- consent and desire of women to treat obesity and to follow the doctor's recommendations.

Criteria of withdrawal from the main group:

- diabetes mellitus type 1 or 2;
- prolactinoma of the pituitary gland;
- congenital hyperplasia of the adrenal cortex;
- hypothyroidism, diffuse toxic goiter;
- PCOS;
- gynecological pathology accompanied by hormonal ovarian failure;
- symptomatic obesity; and
- severe somatic pathology.

Research results and discussion

In the main group (n = 38), the BMI before the start of treatment of 15, 27, and 8 patients was <30, 30.1–35, and >35 kg/m^2. BMI significantly decreased from 31.2 ± 0.6 to 28.7 ± 0.7 kg/m^2

with anti-obesity therapy. The mean body weight significantly decreased from 87.2 ± 2.2 to 80.1 ± 2.45 kg ($p < 0.05$), and the ratio of waist/hip circumference (WC/HC) significantly decreased from 0.82 ± 0.009 to 0.80 ± 0.009 cm ($p < 0.05$). BMI decreased significantly ($p < 0.05$) from 30.8 ± 0.6 to 28.0 ± 0.9 kg/m^2 in the main group of women who achieved ovulation after treatment ($r = 0.86$, $p = 0.000013$), and it was significantly lower than that in the group with anovulatory cycle (30.5 ± 1.0 kg/m^2, $p < 0.05$).

The mean leptin level in the blood of the main group women decreased significantly after treatment from 35.9 ± 3.0 to 28.5 ± 3.0 ng/ml ($p < 0.05$) and correlated with the dynamics of BMI decrease ($r = 0.2$, $p < 0.05$).

Ovarian failure was detected in 72% of the women in the main group, and it was manifested as anovulation and luteal-phase defect in 54% and 18% of cases, respectively. After treatment, anovulation persisted in 24% of patients, and ovulation was confirmed in 76% of patients.

The data obtained by comparing two subgroups were analyzed. The patients in subgroups 1 and 2 were treated with sibutramine and metformin, respectively.

Based on their medical history, no significant differences were observed in the subgroups. The incidence of somatic pathology in women of both subgroups did not differ significantly. The mean age of patients in the sibutramine and metformin groups was 33.6 ± 1.2 and 31.7 ± 1.3 years, respectively. The gynecological history in both subgroups did not differ significantly; the mean age of menarche, the presence of menstrual irregularities, and infertility were assessed. The gonadotropin, prolactin, and sex steroid hormone levels in both groups were analyzed before and after treatment. In terms of hormonal parameters, no significant differences were obtained before and after treatment, except for the estradiol level, which decreased significantly ($p < 0.05$) from 593.7 ± 78.8 to 407.0 ± 55.5 pmol/l after treatment with metformin. After treatment with metformin, the estradiol level in the blood decreased by a mean of 186.6 ± 59.6 pmol/l and exceeded significantly ($p < 0.05$) in the subgroup of women treated with sibutramine (93.9 ± 58.9 pmol/l).

Changes in anthropometric parameters and body composition were studied before and after treatment. In both subgroups, the percentage of adipose tissue, mass of adipose tissue, and fat content in the abdominal region significantly decreased, whereas the lean mass and fat content in the thigh area did not change (Table 1).

After 6 months of treatment in the subgroup of patients treated with sibutramine, the decrease in body weight was 9.6 ± 0.2 kg (10.9% of the initial body weight). During treatment, BMI significantly decreased from 31.8 ± 0.6 to 29.5 ± 0.9 kg/m^2. During decrease in body weight, the WC and HC decreased. After 6 months of treatment, WC and HC decreased from 95.2 ± 2.5 to 90.1 ± 2.7 (mean, 5.1 ± 0.4 cm) and from 116.7 ± 1.7 to 110.6 ± 2.1 cm (mean, 6.1 ± 1.1 cm) (5.2%), respectively, and the WC/HC index decreased significantly from 0.815 ± 0.009 to 0.81 ± 0.009. The improvement in anthropometric indicators was accompanied by a change in body composition. In the subgroup of patients treated with metformin, the decrease in body weight was 7.0 ± 0.4 kg (8.2% of the initial body weight). During treatment, BMI decreased significantly from 30.7 ± 0.6 to 28.4 ± 0.9 kg/m^2. After 6 months of treatment, WC decreased from

Table 1 / Таблица 1

Changes in body composition 6 months after treatment

Изменения композиционного состава тела через 6 мес. после лечения

Measurement period	Adipose tissue content, %	Adipose tissue mass, kg	Lean mass, kg	Fat content in the abdomen, %	Fat content in the thigh, %
Before sibutramine treatment	40.1 ± 1.0	36.9 ± 1.1	52.4 ± 0.9	35.8 ± 1.1	42.6 ± 0.5
After sibutramine treatment	33.5 ± 0.6*	29.5 ± 1.1*	50.5 ± 0.9	31.8 ± 0.8*	41.6 ± 0.6
Before metformin treatment	38.3 ± 0.9	31.7 ± 1.7	50.5 ± 1.3	37.6 ± 0.9	41.8 ± 0.6
After metformin treatment	32.3 ± 0.5*	26.1 ± 1.0*	49.7 ± 0.8	27.8 ± 0.9*	40.5 ± 0.7

N o t e. *Difference from the indicator before the start of treatment $p < 0.05$.

Table 2 / Таблица 2

Changes in anthropometric indicators and body composition in patients after 6 months of treatment with sibutramine (1st subgroup) and metformin (2nd subgroup), as a percentage of the initial values

Изменения антропометрических показателей и композиционного состава тела у больных через 6 мес. терапии сибутрамином (первая подгруппа) и метформином (вторая подгруппа) в процентном соотношении от исходных значений

Indicators	Subgroup 1 (*n* = 19)	Subgroup 2 (*n* = 19)
BMI, kg/m^2	–7.2 %	–7.5 %
Body weight, kg	–10.9 %	–8.2 %
Waist circumference/hip circumference	–1 %	–3.4 %
Fat content in the abdomen, %	–4 %	–9.8 %
Adipose tissue mass, kg	–20 %	–18 %
Lean mass, kg	–3.6 %	–1.6 %

N o t e. *Difference of the compared indicators at $p < 0.05$.

93.7 ± 2.3 to 88.2 ± 2.0 cm (mean, 5.5 ± 0.3 cm), and HC decreased with a mean of 3.7 ± 1.1 cm (3.2%), and the WC/HC index decreased significantly from 0.818 ± 0.009 to 0.79 ± 0.009.

Thus, sibutramine and metformin were effective in reducing the body weight of all patients in the subgroups. The decrease in body weight was accompanied by an improvement in all anthropometric parameters. The body composition was analyzed using Fisher exact criterion, which showed a significant loss of adipose tissue in subgroups 1 and 2 by 20% and 18%, respectively (Table 2).

Metformin therapy resulted in a significantly more pronounced decrease in the proportion of abdominal adipose tissue and WC/HC ratio.

The leptin level in the blood of both subgroups was analyzed before and after treatment. The data obtained showed that the use of sibutramine led to a significant ($p < 0.05$) decrease in leptin level after treatment, whereas the use of metformin altered the leptin level less significantly before and after treatment (Fig. 1).

Before the start of treatment of 19 patients in subgroup 1 who were treated with sibutramine, 10 patients (53%) had a regular menstrual cycle, 8 patients (42%) had opsomenorrhea menstrual irregularities, and 1 patient had amenorrhea (5%). Ovulatory and anovulatory cycles were noted in 7 (37%) and 12 (63%) women, respectively. After 6 months of sibutramine therapy, ovulatory cycle was recorded in 13 (68%) women. Before the start of treatment of 19 patients in subgroup 2 who were treated with metformin, 11 patients (58%) had regular menstrual cycles, and opsomenorrhea or amenorrhea menstrual irregularities were noted in 8 patients (42.1%). After 6 months of metformin therapy, ovulatory cycle was recorded in 16 (84%) women.

Thus, the number of women with an ovulatory cycle increased from 37% to 68% and from 58% to 84% after 6 months of sibutramine and metformin treatment, respectively. The results in both subgroups did not differ significantly (Fig. 2).

In the subgroup of women treated with metformin, the fasting glucose and insulin levels and the HOMA-IR index decreased significantly compared with the subgroup of women treated

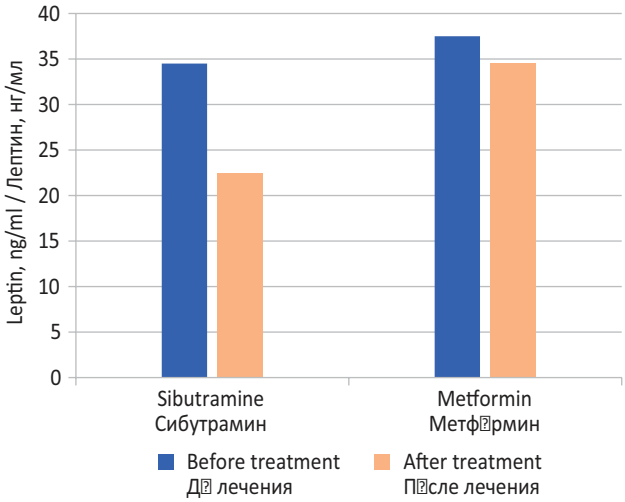

Fig. 1. Leptin levels in two subgroups before and after treatment

Рис. 1. Уровень лептина в двух подгруппах до и после лечения

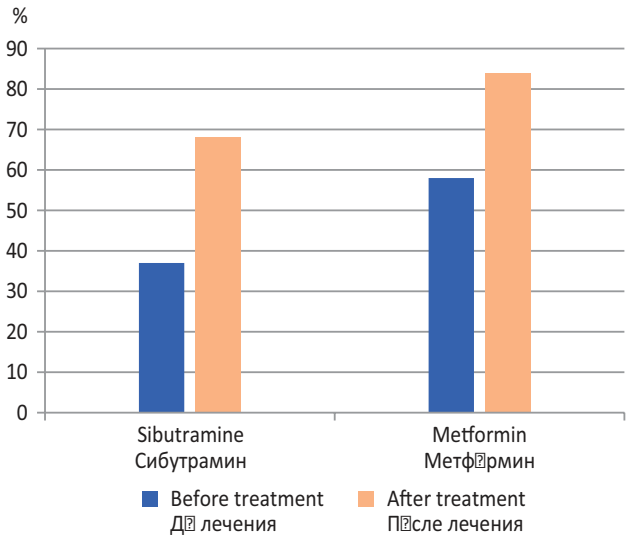

Fig. 2. Ratio of ovulatory cycles in two subgroups before and after treatment

Рис. 2. Соотношение овуляторных циклов в двух подгруппах до и после лечения

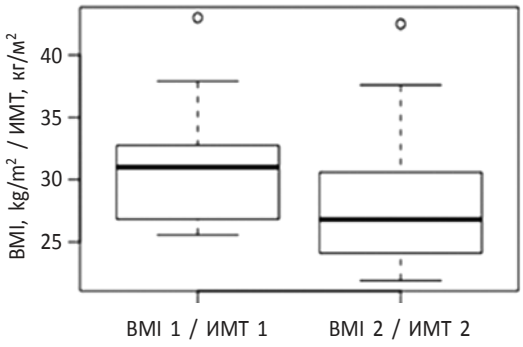

Fig. 3. Body mass index (BMI) decrease dynamics in patients with excess body weight and obesity depending on the achievement of ovulation as a result of treatment (n = 29)

Рис. 3. Динамика снижения индекса массы тела (ИМТ) у пациенток с избытком массы тела и ожирением в зависимости от достижения овуляции в результате лечения (n = 29)

with sibutramine, wherein the indicators before and after treatment did not differ significantly. Indicators before treatment in both subgroups also did not differ significantly (Table 3).

When comparing the effectiveness of the two drugs and their effect on the restoration of ovulatory function after weight loss in overweight women, using Fisher exact test, the probability of ovulation was 0.789 (79%) and 0.63 (63%) after using sibutramine and metformin, respectively, which was not significantly different (p = 0.476).

The indicators in the general group were analyzed to assess the prognosis of ovulation recovery after weight loss and to determine significant signs.

In the main group, in women with achieved ovulation after treatment, the BMI changed significantly (p < 0.05) from 30.8 ± 0.6 to 28.0 ± 0.9 kg/m^2. The Spearman r was 0.86 with p = 0.000013, and the Pearson r was 0.86 (Fig. 3).

The baseline leptin level (32.3 ± 3.7 ng/ml) in women who achieved ovulation as a result of therapy was significantly lower (p < 0.02) than that in female patients with anovulation after treatment (52.07 ± 6.8 ng/ml) (Fig. 4).

A correlation was found between the presence of ovulation in the group of women with excess body weight after treatment and the dynamics of changes in the blood level of leptin (Spearman r, 0.75; p < 0.02).

A correlation was found between the ovulation achieved during treatment and the dynamics of the decrease in the blood level of estradiol (Pearson r, 0.61; p < 0.02). A positive Spearman r correlation of 0.89 (p < 0.02) was obtained between the data on achieved ovulation and the number of antral follicles in the ovaries, whereas a negative correlation was obtained between the index of insulin resistance in obese women and prognosis

Table 3 / Таблица 3

Glucose and insulin levels and insulin resistance in women in the two study groups before and after treatment
Уровень глюкозы, инсулина и наличие инсулинорезистентности у пациенток обеих подгрупп до и после лечения

Measurement period	Fasting glucose, mmol/l	Glucose after 60 min, mmol/l	Insulin, mU/l	HOMA-IR
Before sibutramine treatment	5.3 ± 0.2	7.3 ± 0.4	9.5 ± 1.6	2.2 ± 0.2
After sibutramine treatment	5.2 ± 0.1	7.0 ± 0.2	9.01 ± 1.4	2.08 ± 0.2
Before metformin treatment	5.6 ± 0.2	7.4 ± 0.3	11.08 ± 0.9	2.7 ± 0.2
After metformin treatment	5.2 ± 0.1*	7.2 ± 0.2	8.7 ± 1.0*	1.9 ± 0.2*

N o t e. *Difference from the indicator before the start of treatment at p < 0.05.

of ovulation recovery after weight loss ($r = -0.59$, $p < 0.005$).

To determine the most significant prognostic signs for ovulatory cycle restoration in patients with overweight and obesity, a discriminant analysis (DF) was performed, which included four indicators that had the greatest effect on the achievement of ovulation in the correlation analysis.

As a result of the analysis, a mathematical model was compiled using the following equation:

$$Z = -0.02 \cdot X_1 - 0.535 \cdot X_2 - 0.64 \cdot X_3 + \\ + 0.001 \cdot X_4 - 5.684,$$

where Z is the discriminant function (DF), on the basis of which the treatment result can be predicted, namely ovulation restoration after weight loss; X_1 is the baseline leptin level; X_2 is the baseline indicator of insulin resistance (HOMA-IR); X_3 is the number of follicles in the ovaries; X_4 is the baseline estradiol level.

If Z is greater than −1.406, then a positive treatment result and ovulation restoration after weight loss are expected with a probability of 0.97, whereas if Z is lower than −1.406, the treatment result will be negative, which implies anovulation during weight loss (Fig. 5).

The predictive accuracy, sensitivity, and specificity of the model were 97%, 100%, and 91%, respectively.

It is generally accepted that a decrease or normalization of body weight in women of reproductive age with alimentary obesity and ovarian hormonal insufficiency often leads to the restoration of ovulatory function and normalization of the ovarian structure by eliminating secondary polycystic disease [1, 3–6, 10, 11]. Similar results were obtained in our work. The ovulatory cycle before treatment was noted in 46% of patients of the main group, and this indicator increased significantly after 6 months of treatment ($p < 0.05$) and increased to 76%. Currently, the mechanisms affecting the formation of hormonal insufficiency of the ovaries in patients of reproductive age with alimentary obesity have not been completely clarified. The pathogenetic factors that determine the development of hormonal insufficiency of the ovaries in case of obesity are insulin resistance and hyperandrogenemia. Hyperinsulinemia increases

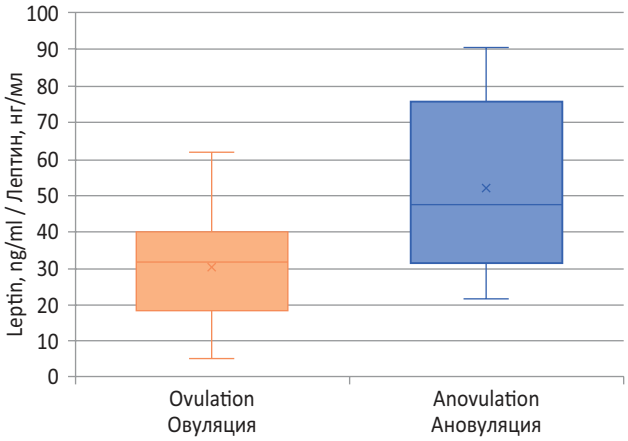

Fig. 4. Initial levels of leptin in the blood of patients with excess body weight and obesity, depending on the achievement of ovulation as a result of treatment

Рис. 4. Исходный уровень лептина в крови у пациенток с избытком массы тела и ожирением в зависимости от достижения овуляции в результате лечения

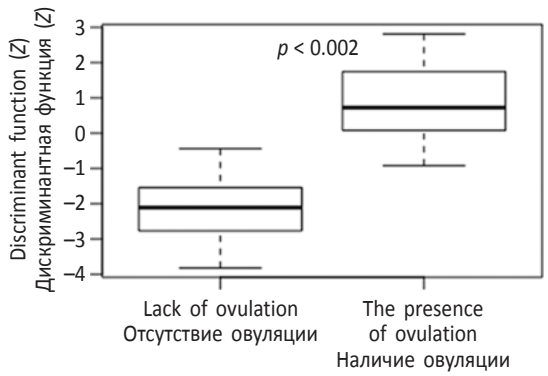

Fig. 5. Discriminant function coefficient values depending on the achievement of ovulation as a result of treatment

Рис. 5. Значения коэффициента дискриминантной функции Z в зависимости от достижения овуляции в результате лечения

ovarian sensitivity to the luteinizing hormone, causing luteinization of small follicles. This leads to the arrest of the growth of antral follicles and their atresia. Insulin can also suppress the production of sex steroid-binding globulin, which leads to an increase in the blood level of free androgens contributing to polycystic changes in the ovaries [4, 19, 20]. The examined women had a negative correlation between the baseline HOMA-IR level and ovulatory function of the ovaries ($r = -0.59$, $p < 0.005$).

In recent years, evidence showed that hyperleptinemia leads to the overproduction

of gonadotropin-releasing hormone by the hypothalamus and gonadotropins by the pituitary gland [9], which in turn is accompanied by changes in folliculogenesis and steroidogenesis. The results of the study showed that the baseline level of leptin in the group of women with an achieved ovulatory cycle after treatment was significantly lower than that in women with anovulation after treatment ($p < 0.005$). A negative correlation was established between the initial number of antral follicles in the ovaries and the presence of ovulation after treatment ($r = -0.89$, $p < 0.02$), as well as a positive correlation between the dynamics of estradiol decrease and the achievement of ovulation during weight loss ($r = 0.61$, $p < 0.02$). The primary stage in the treatment of obesity in combination with hormonal ovarian failure includes a low-calorie diet (1000–1200 kcal), regular physical activity, and the administration of centrally acting anorexic drugs (sibutramine) and drugs that increase insulin sensitivity, and biguanide derivatives (metformin). Data on the onset of ovulation after drug therapy in obese patients are contradictory. According to some authors, ovulation occurs more often in patients with a significant decrease in leptin levels after metformin administration in patients with PCOS [10]. Based on Russian and international clinical studies that assessed the efficacy and safety of the anorexigenic drug sibutramine for weight loss, body weight decreases, lipid metabolism significantly improves, and ovulatory function of the ovaries is restored after a 6-month course of the drug and subcaloric diet [11, 21].

There are insufficient data on the effect of anti-obesity therapy on leptinemia and on the effect of leptin on ovarian function in obese women. Our results indicate that ovulatory function restoration depends on the degree of BMI reduction. After treatment, BMI decreased significantly ($p < 0.05$) from 30.8 ± 0.6 to 28.0 ± 0.9 kg/m^2 in women who achieved ovulation ($r = 0.86$, $p = 0.000013$), and the dynamics of BMI decrease was more pronounced than in the group of patients with anovulation. A strong positive correlation was revealed between ovulation recovery after treatment and the dynamics of a decrease in the blood leptin level ($r = 0.75$, $p < 0.02$). A more pronounced and significant decrease in the leptin level was noted in the group of patients treated with sibutramine. In this group, ovulatory function after treatment was recorded in 68% of women. When using metformin, leptin level also tend to decrease, and ovulatory function was recorded in 84% of women.

Conclusions

1. In women with alimentary obesity, the mean leptin level after treatment decreased significantly from 35.9 ± 3.0 to 28.5 ± 3.0 ng/ml ($p < 0.05$) and correlated positively with the dynamics of BMI decrease ($r = 0.2$, $p < 0.05$).

2. The indicators, namely leptin level, blood estradiol level, number of antral follicles, and insulin resistance, have a prognostic value in achievement of ovulation after weight loss in women of reproductive age with alimentary obesity and ovarian hormonal insufficiency.

3. After a 6-month course of treatment, more significant dynamics of a decrease in the leptin level (34.9% of the baseline level) and the presence of ovulation (68% of women) were recorded in patients treated with sibutramine compared with patients treated with metformin (decrease in leptin levels was 6.5%, and ovulatory function was recorded in 84% of patients).

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Information about the authors *(Информация об авторах)*

Ekaterina M. Ryazantseva — MD, Head of the Department of Obstetrics and Gynecology. Clinical Diagnostic Medical Center of the Office of the President of the Russian Federation, Saint Petersburg, Russia. RSCI Author ID: 859980. SPIN-code: 3500-9510. **E-mail:** emr4@yandex.ru.

Екатерина Марковна Рязанцева — врач — акушер-гинеколог, заведующий акушерско-гинекологическим отделением. ФГБУ «Консультативно-диагностический центр с поликлиникой» Управления делами Президента Российской Федерации, Санкт-Петербург. РИНЦ Author ID: 859980. SPIN-код: 3500-9510. **E-mail:** emr4@yandex.ru.

Marina A. Tarasova — MD, PhD, DSci (Medicine), Professor. The Educational Department, the Department of Endocrinology of Reproduction, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. RSCI Author ID: 507261. SPIN-code: 8166-3356. **E-mail:** tarasova@ott.ru.

Марина Анатольевна Тарасова — д-р мед. наук, профессор, профессор учебного отдела. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. РИНЦ Author ID: 507261. SPIN-код: 8166-3356. **E-mail:** tarasova@ott.ru.

Natalia N. Tkachenko — PhD, Head of the Laboratory of Endocrinology. The Department of Endocrinology of Reproduction, the Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. https://orcid.org/0000-0001-6189-3488. ResearcherID: K-1734-2018. RSCI Author ID: 678294. SPIN-code: 9633-6701. **E-mail:** liberin@mail.ru.

Наталия Николаевна Ткаченко — канд. биол. наук, заведующая лабораторией эндокринологии отдела эндокринологии репродукции. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. https://orcid.org/0000-0001-6189-3488. ResearcherID: K-1734-2018. РИНЦ Author ID: 678294. SPIN-код: 9633-6701. **E-mail:** liberin@mail.ru.

Alexander M. Gzgzyan — MD, PhD, DSci (Medicine), Professor, Head of Reproduction Department. The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia. RSCI Author ID: 231438. SPIN-code: 6412-4801. **E-mail:** agzgzyan@gmail.com.

Александр Мкртичевич Гзгзян — д-р мед. наук, профессор, заведующий отделом репродуктологии. ФГБНУ «НИИ АГиР им. Д.О. Отта», Санкт-Петербург. РИНЦ Author ID: 231438. SPIN-код: 6412-4801. **E-mail:** agzgzyan@gmail.com.