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Forecasting Disorders Of Reproductive Function In Women Of Fertile Age On The Obesity Background.

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ABSTRACT

The risk factors for the occurrence of reproductive disorders in women with overweight and obesity at the stage of pregravid preparation (before pregnancy) were estimated. A comprehensive clinical examination of 160 women aged 21-35 years was carried out. The analysis of clinical and anamnestic data, laboratory and instrumental methods of investigation is presented. The results of the study of the metabolic status of the subjects are analyzed and the data on clinically significant associations of lipid metabolism indices are presented. On the basis of the data obtained, the logistic regression equation was constructed to predict the probability of belonging of the subjects to a group with an increased risk of menstrual function disorders that can be used for preclinical prognosis of the development of fertility dysfunction. Practical application of the model will prevent reproductive losses, accelerate the implementation of generative function and reduce the material costs of therapy aimed at maintaining pregnancy and treating complications. In addition, the decision support system for predicting reproductive disorders in women with overweight and obesity in terms of risk factors makes it possible to optimize a set of preventive medical, social and organizational measures to protect the reproductive health of the population and ensure a reduction in the level of reproductive losses.

Keywords: obesity, reproductive function, prognosis of reproductive disorders

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INTRODUCTION

In recent years, the problem of overweight and obesity has become one of the most important problems for residents of most countries in the world. This is largely due to the high prevalence of this disease and the severity of its consequences. It is established that the number of people suffering from obesity progressively increases every 10 years by 10%. It is expected that by 2025 obesity will have 40% of men and 50% of women living on the planet.

Of particular importance is obesity for the health of women of childbearing age, being a serious risk factor for not only cardiovascular diseases, diabetes mellitus, cholelithiasis, but also infertility, perinatal pathology, breast cancer, endometrium and ovaries. The degree and frequency of these risks increase depending on the severity of obesity[2,4].

There is an opinion that obesity plays a significant role in impaired fertility, as the disorders of metabolic processes lead to the emergence of various forms of menstrual function disorders. However, the data on this issue are contradictory and do not allow one to unequivocally interpret the pathogenesis of menstrual cycle disorders in obese patients. To the end, the role of hormonal and metabolic changes in the formation of reproductive disorders in women suffering from obesity is not defined. Despite the available scientific works on this issue, a number of issues remain insufficiently consecrated, reasoned, and in some cases inconclusive. In this regard, the work is relevant and timely [1, 3, 7].

Factor's that determine obesity have a wide range and can act both together and separately. The most common of these are genetic predisposition, behavioral features (overeating, hypodynamia), and endocrine disruption. Obesity contributes to the development of other diseases, which essentially makes it impossible to differentiate the pathogenesis of a number of diseases from each other[5]. The pathogenesis of obesity is not fully understood, which makes it difficult to develop optimal methods of treatment and prevention. It is believed that the basis of obesity is the energy imbalance, which is the inconsistency between the amount of calories coming from food and the energy expenditure of the body. In turn, imbalance is a consequence of inadequate interaction of genetic (the genes responsible for the accumulation and distribution of fat in the body) and external (social, food, psychological, physical load) factors [8]. The development of menstrual function has a significant effect on the reproductive system, although the data on the features of the reproductive function in obesity are quite contradictory. Thus, with obesity, a longer reproductive life is associated with the earlier menarche and pleiotropic effects of the mutation of the beta-3-AP gene on a number of physiological systems, including the body mass index, reproductive status, which may be the evolutionary reason for support in the population. Others consider the early age of menarche to be not only a reproductive factor, but also an independent predictor of the increase in the body mass index and other complications of obesity [6].

MATERIALS AND METHODS

A survey of 160 women of reproductive age (mean age 31.3 ± 5.13 years) was conducted. The main group (1 group) consisted of 100 women with obesity and a violation of reproductive function. The average body weight of the examined patients was 94.7 ± 2.76 kg, the average BMI was 33.2 ± 0.82 kg / m2. Overweight (BMI <30 kg / m2) was diagnosed in 6 (20%) patients, obesity of the 1st degree (BMI 30-35 kg / m2) in 10 (33%) patients, obesity of the 2nd degree (BMI-35- 40 kg / m2) - in 9 (30%) and obesity of III degree (BMI> 40 kg / m2) - in 5 (16.7%) of women. The average waist circumference of the patients included in the study was 98.3 ± 2.28 cm, the circumference of the hips was 117.6 ± 2.11 cm. In the vast majority of patients, 24 (80%) had an index reflecting the ratio of the circumference of the waist to the hip circumference (OT / OB), exceeded 0.8, which indicated the presence of abdominal obesity. The OT / OB index averaged 0.84 ± 0.01. The comparison group consisted of 60 women with reproductive failure, but without obesity.

The study of the content of hormones in the blood serum was performed by an enzyme immunoassay using standard commercial reagent kits. A quantitative assessment of the total cholesterol, high-density lipoprotein cholesterol and triglycerides in the blood serum was performed using enzymatic calorimetric methods using Abris reagent kits (Russia). Determination of biochemical parameters of blood serum was performed on a spectrophotometer of the company "Beckmann" (USA).

The ultrasonic examination was performed by a high-resolution Siemens ultrasound unit "Sonoline SL-250" using a sector sensor with a frequency of 3.5 MHz. The normal size of the ovaries was 25-40 mm long, 15-30 mm wide, 10-15 mm thick, and no more than 8 cm3 ovary. The volume of the ovary was calculated according to the formula: volume of the ovary = length of the ovary × width × thickness × × 0.524. The presence of ovulation was evaluated by tests of functional diagnostics.

To automate predictive calculations based on the STATISTICA 6.0 (StatSoft) program, a computer program was created that allows calculating the probability of developing gynecological diseases after entering individual parameters of the patients under study.

RESULTS AND THEIR DISCUSSION

A screening study of women of reproductive age (from 17 to 44 years) found that the frequency of obesity in the population is 31.02%. Among women with obesity, the neuroendocrine form (NEO) was found in 60.4%, and the alimentary-constitutional obesity (ACH) is 39.6%. The family predisposition to obesity was 67.9% of patients of the I1 group and 22.1% of the women - group II.

Using the questionnaire method it was determined that in childhood the frequency of occurrence of excess body weight among the examined women in 2 groups was 8.2%, while in 1 group 45.5% of women reported excess weight in childhood. Further, during sexual development, the frequency of pronounced weight gain in group 2 was 7.4%, and in group 1, 54.5% of women reported a sharp increase in body weight. Consequently, for the majority of women in group 1, the accumulation of adipose tissue was noted already in the childhood and adolescent ontogenesis.

In patients of group 1, menarche was significantly earlier than in group 2, at 12.7 ± 1.3 years and 13.5 ± 1.4 years, respectively (p = 0.005). In women with obesity, a longer period of menstrual cycle was established, 5.6 ± 4.4 years, in the 2nd group 3.1 ± 1.6 years (p = 0.015). The duration of the menstrual cycle, on average, was greater in group I and was 33.2 ± 10.1 days, in the 2nd group - 28.1 ± 2.6 days (p = 0.004).

Violations of the menstrual cycle were recorded in 60% of women in group 1 and in 17.4% in the 2 groups examined (p <0.001). On average, the occurrence of menstrual irregularities in Group 1 was observed at 4.4 ± 1.8 years after menarche, in Group 2 much later - at 8.9 ± 4.6 years (p <0.001). In the structure of the NMC, hypomenstrual syndrome (23.0%) and a mild rhythm disorder (18.6%) prevailed among women of the 1st group, algomenorrhea (21.7%) in group 2 and irregularities in menstruation (13.0%). In women of the II group, there was no hypominstral syndrome (p = 0.023). Spontaneous abortions were much more frequent in group 1 - 21.5%, in group 2 4.2% (p = 0.046). In the 1st group, 30.3% of women suffered from infertility, in 2-7.7% (p = 0.009).

According to ultrasound of the genitals, the volume of the uterus in obese patients was significantly higher than in the comparison group due to the length and thickness of the uterus (p = 0.018). The average size of the uterus in group 1 was - 5.04 x 3.6 x 4.9 cm and in the second group - 4.6 x 3.4 x 4.2 cm. The thickness of the endometrium in group 1 was significantly higher than in 2 group (p <0.001). Patients in group 1 had a statistically significant increase in both the right and left ovary volume, compared with those in group 2 (p <0.001).

Diffuse small-cystic inclusions (4-8 mm in diameter) were statistically significantly more frequent in Group 1 patients (52.5%) than in women of the 2nd group (8.7%) (p = 0.001). The data of ultrasound of genital organs (increase in the volume of the ovaries, IAM, small-cystic inclusions, absence of the dominant follicle) in combination with an increase in the ratio of LH / FSH, LH, testosterone, and progesterone decrease suggest the formation of polycystic ovaries in 52.5% of patients with obesity.

The level of PRL in women with obesity is 2.8 times higher than in women without obesity. The concentration of FSH in group 1 is also higher than that of women in group 2, but there is a decrease in grade III obesity. The concentration of FSH correlates with the level of PRL in groups 1 and 2 (r = + 0.8749 and r = + 0.8619, respectively, P <0.01). The concentration of LH in obese patients is higher for ovulatory patients and lower for anovulatory cycles and NLF (7.8, 5.6, 4.8 IU / L, respectively), while in women with NEO, the level of LH in ovulatory is lower than in the anovulatory cycles and NLF (4.8, 6.9, 5.8 IU / L, respectively).

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The concentration of LH in group 1 with grade III obesity correlates with the level of PRL (r = +0.9168, P <0.001) and FSH (r = + 0.8999, P <0.001). The difference in the content of progesterone in women of groups 1 and 2 in the anovulatory cycles is 52.9%, which confirms the opinion of several authors about the leading role of increasing these hormones in the formation of polycystic ovaries in obesity.

An analysis of some anamnestic data is of interest: in women with menstrual dysfunction, the incidence of prematurity in the structure of the pathology of pregnancy and childbirth in mothers of patients was significantly higher than in the group of women with normal menstrual function (Table 1).

Table 1: Frequency of pathology of pregnancy of mothers of the surveyed women

	1st group		2nd group	
	n	%	n	%
Pathology of pregnancy and childbirth	16	24,2	9	17,6
Early and late gestosis	5	7,6	6	11,8
Asphyxia at birth	4	6,1	4	7,8
Prematurely bornness	1	1,5	7	13,7

The state of lipid metabolism in patients of reproductive age with obesity, in contrast to the comparison group, was characterized by higher serum levels of atherogenic lipid fractions: cholesterol - 5.4 ± 0.9 and 4.5 ± 0.9 mmol / l (p = 0.001), LDL cholesterol - 3,5 ± 0,8 and 2,6 ± 0,9 mmol / l (p <0,001), TG - 1,8 ± 0,8 and 0,8 ± 0,3 mmol / l (p <0.001) and low indices of antiatherogenic fractions of HDL cholesterol - 1,2 ± 0,4 and 1,5 ± 0,5 mmol / l (p = 0,005). In obese women, normoglycemia was significantly less frequent than in group 2, at 70.5 and 95.7%, respectively (p = 0.023).

At the next stage, as a result of the stepwise discriminant analysis, the most significant potential predictors or classification functions that were used as the basis for the computer program determining the prediction of violations were selected. An analysis of the relationship between a single qualitative feature-the presence of obesity, acting as a dependent, resultant index, and a subset of quantitative and qualitative traits, was conducted using a logistic regression model with a step-by-step algorithm for including and excluding predictors. The results of the estimation of the logistic regression equations are represented by a set of regression coefficients (Table 2), achieved significance levels for each coefficient, as well as an assessment of the agreement indicator of the actual belonging of the patient to a particular group and the theoretical membership obtained by the log-regression equation.

Table 2: Classification functions (KF) of discriminant model of estimation of risk of development of reproductive violations

№		KF patients with obesity	KF patients without obesity
1	Pelvic of fruit at birth	–0,786	–2,556
2	Obesity from little up	147,383	100,968
3	Gynaecological diseases are in anamnesis	5,590	8,246
4	Violation of menstrual function	19,468	29,066
5	Megascopic volume of ovary	–13,215	–10,037
6	Violation of food behavior	–67,610	–52,571
7	Libra at birth > 4 kg	46,854	24,089
8	Early and late gestosis	29,066	19,468
9	Asphyxia at birth	–121,543	–91,814
10	Prematurely bornness	5,590	8,246
	Constant	–635,201	–559,6

Ranking of the selected predictors by the degree of connection with the dependent variable was made by sorting the predictors by the module of standardized coefficients of regression. As a result, the forecasting system included 11 factors determining the risk of developing reproductive disorders in women of fertile age against obesity.

As a result of statistical processing, the parameters of linear regression equations were obtained: y = a + b1, * x1, + b2 * x2, where y is the value of the logistic regression function; a is the free term of the equation; b1, b2 - regression weights reflecting the contribution of factors x1, x2 to the result of classification of patients.

To predict the development of reproductive disorders, two regression equations were obtained with a fairly high percentage of correct reclassification:

$$\beta_1 = 0.98\text{-}1.15 \times V30 + 1.03 \times V24\text{-}4.4 + 0.84 \times V13 + 0.68 \times V16$$

Concordant = 68.3% Somers' D = 0.369 R2 = 0.2136 Max-rescaled R2 = 0.2406 where: 0,98 - free member, V30 - the age of menarche; V24 - obesity since childhood (0 - no, 1- there); V13 - asphyxiation at birth; V16 - eating disorders.

$$\beta_2 = 2.63\text{-}0.27 \times V22 + 1.64 \times V12 + 1.06 \times V16$$

Concordant = 62.2% Somers' D = 0.335 R2 = 0.3819 Max-rescaled R2 = 0.4227 where: 2, 63-free member; V22 - menstrual dysfunction V12 - birth weight> 4 kg; V16 - eating disorders.

For the equations obtained, the significance level of the consent test was 0.681 and 0.628, respectively, i.e. The models created are adequate.

To assess the quality of the models obtained, in addition to the percentage of correct assignments, the ROC curve was used. The area under the ROC curve was estimated to be 0.869 and 0.765, respectively. The obtained area values indicate the high quality of these mathematical models for predicting reproductive dysfunction in obese women.

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