WAYS TO CORRECT MENSTRUAL DYSFUNCTION IN WOMEN WITH OBESITY

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Abstract. *According to the World Health Organization, the prevalence of obesity among women of reproductive age ranges from 1.8 to 25.3% in different countries [1]. Obesity has a negative impact on women's reproductive health. Disorders of the menstrual cycle in the context of obesity require special attention. This paper presents an analysis of methods for correcting menstrual dysfunction in obese women.*
Keywords*: obesity, menstrual cycle disorders, infertility.*

At present, obesity is a serious healthcare problem in all countries due to its prevalence and significant health consequences associated with high morbidity and mortality rates. According to the WHO, approximately 1.5 billion adults worldwide are affected by excess weight. Around 30% of women of reproductive age suffer from obesity, and another approximately 25% of women in this group are overweight [2]. According to WHO data, by 2025, an increase in the frequency of obesity diagnosis among the female population to 50% is expected [3].

According to the classification developed in accordance with WHO recommendations, a body mass index (BMI: kg/m2) of 25-30 is considered overweight, BMI of 30-35 is considered obesity, BMI of 35-40 is considered obesity of the second degree, and obesity where BMI exceeds 40 is defined as morbid obesity [4]. In studies of another degree of evidence, waist circumference is accepted as a criterion, and it is claimed that women with a waist circumference of more than 80 cm have excess visceral fat [5].

It is known that adipose tissue plays a role in regulating the menstrual cycle, as female sex hormones are also synthesized in it. Increased amount of adipose tissue (more than 15-20%) leads to disruption in the "hypothalamus-pituitary-ovaries" system and can be a factor in the development of polycystic ovary syndrome (PCOS), endometrial hyperplastic processes, infertility, miscarriages, preeclampsia, fetal growth restriction. According to various authors, the timely onset of menarche in women with various forms of obesity and reproductive dysfunction is observed in only 31% of cases [6].

The onset of menstrual function significantly affects the reproductive system. Some researchers consider the early age of menarche not only as a reproductive factor but also as an independent predictive factor for increasing body mass index (BMI) [6]. The most unfavorable for further reproductive function disruption is late menarche and a prolonged period of menstrual rhythm formation.

In alimentary obesity, menstrual dysfunction is noted 6.1 times more often, and primary infertility is almost twice as common [7]. There is a direct relationship between weight gain and the severity of ovarian disorders, accompanied by anovulation and inadequate luteal phase. Therefore, one of the main methods in the initial treatment of women with obesity is weight reduction. Under these conditions, the hormonal profile changes, resulting in the restoration of menstrual function in 80% of women and an average increase in pregnancy rates by 29% [8].

Weight loss is most often achieved by changing diet, following a specific diet, and increasing physical activity levels. In recent decades, pharmaceuticals for weight loss and bariatric (metabolic) surgery have become more widely used. Let's consider modern methods of weight loss that are widely used at present.

Conservative methods for restoring reproductive health:

Several studies have shown that lifestyle changes, including weight loss, have been an effective measure to reduce undesirable metabolic consequences of obesity [9]. Several studies have demonstrated the benefits of lifestyle changes in normalizing ovulation and overall reproductive function. For example, A. Clark et al. [10] showed that impressive improvements in reproductive function and ovulation and pregnancy rates can be achieved by lifestyle changes in obese women compared to a group of patients who failed to adhere to the diet and maintain the required level of physical activity [10]. However, weight loss is difficult to achieve through diet and exercise alone. In most cases, after weight loss, it is regained. In such cases, there is a need to complement treatment with medication therapy [11]. Currently, indications for pharmacological treatment of obesity include [12]: - BMI > 30 kg/m2 if weight loss during 3 months of dietary treatment is less than 10% of the initial body weight; - BMI > 27 kg/m2 in combination with abdominal obesity, genetic predisposition to type 2 diabetes, and the presence of risk factors (dyslipidemia, arterial hypertension, and type 2 diabetes). Currently, in pharmacological treatment of obesity in women of reproductive age, preference is given to centrally acting drugs for correcting eating behavior – selective serotonin and norepinephrine reuptake inhibitors (sibutramine) and selective serotoninergic antidepressants (fluoxetine) [13]; peripheral acting drugs (orlistat and acarbose) for controlling fat and carbohydrate intake, biguanides (metformin) for reducing insulin resistance and metabolic disorders, treatment. When using the above-mentioned drugs in women, in addition to weight loss, positive dynamics of the lipid profile of the blood are noted, basal hyperinsulinemia normalizes, insulin sensitivity increases, hemodynamics, hormonal parameters, eating behavior improve, ovulatory menstrual cycles restore. In scientific literature, the drugs mentioned most often for improving reproductive function in obese women are metformin, clomiphene citrate, and aromatase inhibitors. Metformin is a first-line drug in the treatment of type 2 diabetes; however, it also has potential in the treatment of reproductive function disorders associated with obesity [14]. The action of the drug is aimed at increasing tissue sensitivity to insulin and inhibiting gluconeogenesis in the liver, and it is widely used in the treatment of this category of patients. According to a meta-analysis conducted in 2003 [14] about the use of medications aimed at increasing insulin sensitivity, which included over 500 patients with polycystic ovary syndrome (PCOS), it was found that metformin increases ovulation frequency by 4 times compared to placebo, and that the drug effectively increases the frequency pregnancy when combined with clomiphene [14]. In the systematic review and meta-analysis conducted by T. Siebert [15] and J. Xiao [16], a comparison was made between metformin and clomiphene as ovulation inductors in women with obesity and PCOS. Clomiphene is a non-steroidal anti-estrogen compound that acts by specifically binding to estrogen receptors in the ovaries and pituitary gland. In small doses, it enhances the secretion of gonadotropins - prolactin, FSH, and LH, stimulating ovulation. The results showed that clomiphene was more effective than metformin in terms of both ovulation and pregnancy rates. Furthermore, the authors concluded that the side effects of Metformin hinder its use as a first-line drug for ovulation induction in such patients. Overall, the conclusions reached by the authors confirm the results of previous meta-

analyses and systematic reviews of randomized studies comparing Clomiphene citrate and Metformin as first-line treatments for anovulatory infertility in patients with PCOS and obesity. The results of another meta-analysis conducted by M. Misso, M. Costello, M. Garrubba in 2013 could not identify differences between Metformin and Clomiphene in terms of improving ovulation, pregnancy rates, live births, and miscarriages. S. Palomba, evaluating the effectiveness of preconception use of Metformin in women with PCOS and a high risk of complicated pregnancy, did not find a therapeutic effect of the drug based on the analysis of 17 randomized studies conducted in this patient population. Given such results, it is not surprising that the medical community and committees responsible for developing national guidelines in countries such as the USA and the UK are cautious about the use of Metformin for this condition.

Surgical treatment methods

Bariatric surgery is increasingly being used to treat women of reproductive age suffering from obesity (BMI 35 kg/m2 and higher) who have been unable to lose weight through diet, lifestyle modifications, and physical exercise. In cases of morbid obesity, surgical treatment is indicated and performed without any prior conservative therapy. Among the arsenal of bariatric interventions currently used, only a few modern laparoscopic surgeries are applied. These interventions are conditionally divided into several types. Restrictive procedures include adjustable banding and sleeve gastrectomy. These operations aim to reduce the intake of nutrients into the body, allowing the patient to form a new eating and lifestyle pattern, resulting in effective weight loss. Another type of operation is called combined, involving various gastric bypass procedures. These operations act on metabolism through two principles: restricting nutrient intake in the body (severe restriction of food intake by reducing the stomach) and malabsorption (reducing the absorptive surface by reconstructing the small intestine). For example, in the Roux-en-Y gastric bypass, a "small" stomach is created and anastomosed with a distal part of of the small intestine. Sleeve gastrectomy involves forming a thin tube from the stomach along its lesser curvature. These are mainly the most commonly used bariatric surgeries today. There are studies showing that women with menstrual cycle disorders or anovulation experienced normalization of their menstrual cycles and an increase in pregnancy rates after bariatric interventions. R. S. Lergo attempted to demonstrate that weight loss following Roux-en-Y gastric bypass surgery leads to improved reproductive function.

Significant differences in outcomes depending on the type of intervention were not found statistically, however, a limitation of this study should be considered the lack of data on infertility causes or ovulatory status. To determine which operation has the maximum effect on the variable of interest, a comparison was made between patients who underwent gastric bypass [24] and women who had an intragastric balloon placed. Thanks to this, a significant difference in pregnancy rates was identified after gastric bypass (29%) compared to intragastric balloon placement (70%). The difference is explained by the authors [25] based on the difference in baseline BMI values in patients who underwent these types of surgical interventions. Moreover, in obese women who underwent gastric bypass, the baseline BMI was higher than in patients who had the balloon placed (40.8 vs. 50.1 kg/m2, p=0.001). Several studies have focused on changes in sex hormone levels before and after surgical treatment for obesity. Bariatric interventions lead to normalization of luteinizing hormone, follicle-stimulating hormone, pregnandiol glucuronide, sex hormone-binding globulin, and gonadotropin-releasing hormone levels. In women with obesity and subclinical hypothyroidism, there is also a reduction in TSH levels in the postoperative

period without the use of hormone replacement therapy. Regarding anti-Mullerian hormone – a marker of ovarian reserve – no such effect occurs. The level of anti-Mullerian hormone in women with obesity is significantly lower. It is interesting to note that after surgical intervention, the level of anti-Mullerian hormone decreased in women under 35 years old, while in perimenopausal and postmenopausal women, it remained unchanged. Observation of patients with metabolic syndrome for 48 months after bariatric interventions showed a significant improvement in fasting glycemia, a reduction in insulin resistance, and a decrease in the area under the concentration-time curves for glucose and insulin. It should be noted that bariatric surgery is an economically viable method of treating this patient group, especially considering the costly therapy for metabolic disorders and diabetes, as well as the high cost of using assisted reproductive technologies. Additionally, research results indicate an improvement in emotional well-being, greater satisfaction with appearance, and an enhancement in the quality of life for patients after bariatric interventions.

Conclusion: Based on the literature analysis, it can be concluded that bariatric surgery leads to effective weight loss, regression of obesity-related diseases, resulting in improved reproductive function in women, including stabilization of the menstrual cycle, hormonal balance, and increased desired pregnancy rates. However, obesity should be addressed by first regulating dietary habits and increasing physical activity. Bariatric surgery should only be considered in cases where no results can be achieved by other means. Bariatric surgery is effective in achieving significant and sustainable weight loss in women with morbid obesity. Continuous research and randomized controlled trials are necessary to fully understand the role of obesity and the impact that conservative and surgical obesity treatment methods have on correcting menstrual dysfunction outcomes. It is especially important for women with this condition visiting specialists to receive necessary support and recommendations aimed at weight loss.

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