

OBESITY AS A RISK FACTOR FOR RECURRENT POLYCYSTIC OVARY DISEASE

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Abstract. Obesity is a recurrent polyetiological disease. 30-60% of women of reproductive age are overweight, and 25-27% are obese. By 2025, 50% of the world's women are expected to be obese. Obesity in women of reproductive age is accompanied by a high frequency of anovulation, hyperandrogenism syndrome, menstrual irregularities, endometrial pathology, infertility. During pregnancy, this group of women has a higher risk of loss in the short term, including pregnancy as a result of assisted reproductive technologies. An increase in body weight and the development of obesity can lead to decreased fertility in women. The body mass index of a woman of reproductive age negatively affects the course of pregnancy, namely: the risk of gestational diabetes, increased blood pressure, eclampsia, pathological course of labor, and pathology of the newborn increases. Obesity is a woman of reproductive age is an independent risk factor for cancer: breast cancer and endometrial cancer, and also leads to a decrease in the survival rate for ovarian cancer. Obesity often accompanies polycystic ovary syndrome, which occurs in every 10th patient of reproductive age. The combination of these diseases increases the risk of cardiometabolic conditions such as impaired glucose tolerance, type 2 diabetes, and dyslipidemia. Weight loss in such patients is a necessary component of complex therapy aimed at improving reproductive potential.

Keywords: obesity; overweight; woman; reproductive age; polycystic ovary syndrome; endometrial cancer; breast cancer; infertility; miscarriage; diabetes mellitus; liraglutide.

Introduction. Obesity is a chronic recurrent multifactorial neurobehavioral disease in which an increase in body fat contributes to adipose tissue dysfunction and

biomechanical effects of adipose tissue on surrounding tissues with the development of metabolic and psychosocial health consequences [1].

In 2019, a number of authors made the assumption that obesity is an evolutionary mechanism against hunger in humanity [2], however, at the moment, all the reasons for the increase in the number of overweight / obese people on the planet have not been completely clarified.

Obesity is an important risk factor for other chronic non-communicable diseases (diabetes mellitus, arterial hypertension, musculoskeletal disorders and some types of cancer (mainly endometrium, breast and colorectal)) [3, 4].

According to 2016 data, in the world 39% of adults over 18 years old (39% of men and 40% of women) were overweight, about 13% of the world's adult population (11% of men and 15% of women) were obese [5]. According to the WHO, by 2025, 50% of women on our planet will be obese. An increase in body weight, the development of obesity can lead to a decrease in fertility [6]. Even Hippocrates in the 4th century BC. noted: "Both obesity and thinness should be condemned. The uterus is unable to receive semen and menstruation irregularly. " Weight problems (overweight or obesity) can explain 14% of all cancer deaths in men and 20% in women [7].

Being a risk factor for the development of cardiometabolic disorders, obesity in women of reproductive age is accompanied by a high frequency of violations of ovulatory function of the ovaries (anovulation), hyperandrogenism syndrome, menstrual irregularities, infertility, endometrial pathology (hyperplastic processes), an increased risk of developing endometrial and breast cancer, and poor survival rate for ovarian cancer [8–13].

According to the WHO definition, reproductive health is characterized as a state of complete physical, mental and social well-being in all issues related to the reproductive system, its function, reproductive processes and harmony in psychosexual relationships in the family. Preservation and restoration of reproductive

health is one of the important tasks, the successful solution of which determines the possibility of reproduction of the species and the preservation of a healthy gene pool. Thus, the reproductive health of obese women is not only a medical, but also a social problem [14].

According to the WHO, the risk of developing diseases of the reproductive system directly correlates with the presence of an increase in the body mass index (BMI) in the patient.

- Overweight (25-29.9 kg / m²): increased risk.
- Obesity I degree (30-34.9 kg / m²): high risk.
- Obesity II degree (35–39.9 kg / m²): very high risk.
- Obesity grade III (≥ 40 kg / m²): extremely high risk [15].

Obesity has a negative effect on the hypothalamic-pituitary-ovarian axis, disrupts the rhythm and ratio of gonadotropic hormones, reduces the intensity of folliculogenesis and provokes a decrease in progesterone levels [16-18].

Menstrual irregularities are more common in obese women and progress (up to amenorrhea) with an increase in BMI [19, 20].

Of great importance in the risk of developing menstrual irregularities in women with overweight or obesity is not only BMI, but also the size of the waist circumference (WC) in a woman. It is known that women of reproductive age with an OT of more than 80 cm are more likely to have chronic anovulation syndrome in comparison with those who have the same BMI, but an OT of less than 80 cm [21, 22].

However, be aware of women with high BMI who have regular and ovulatory menstrual cycles. In such women, over time and in the absence of actions to modify the lifestyle, fertility will decline [20, 23–27].

Obesity in a woman of reproductive age can have a negative impact on the course of the preconception period, pregnancy, and the postpartum stage [28–31].

According to the clinical protocol of The Canadian Fertility & Andrology Society (2018), obesity is a risk factor for infertility, the main cause of which should be considered the formation of chronic anovulation syndrome [27].

Obesity in a woman of reproductive age is a risk factor for pregnancy loss at a short time [32, 33].

Maternal obesity before pregnancy increases the incidence of general maternal morbidity (adjusted odds ratio [OR] 1.34; 95% CI 1.14–1.59) and severe maternal morbidity during pregnancy (OR 2.07; 95% CI 1.61–2.65) [34].

An increased BMI (especially corresponding to obesity) in a mother before conception may be a risk factor for the pathological course of pregnancy. Obesity increases the risk of obstetric complications:

- threats of miscarriage (32.5%);
- premature (10.8%) and late (6.0%) births;
- abnormalities of labor (30.1%);
- birth trauma (45.7%);
- functional disorders of the fetoplacental complex with the development of intrauterine fetal hypoxia (60%) and fetoplacental insufficiency (10.8%), macrosomia of the newborn (18.1%) [29].

Obese pregnant women are more likely to require abdominal delivery and the use of surgical aids during labor [29, 31].

Obese women have a higher risk of having a baby with macrosomia or congenital malformations than the general population [27]. Severe perinatal outcomes are more common in obese women than in women with normal weight (Table 1) [35].

The health of the unborn child of an obese mother is subject to the following risks:

- the birth of a large fetus (weight > 4 kg) [36];
- development of disorders of the nervous system in children (attention deficit hyperactivity disorder and autistic disorders) [37].

A high BMI before pregnancy is largely associated with a violation of the psychological status of a woman throughout pregnancy: an increased risk of antenatal depression and anxiety [38].

Obesity reduces the incidence of biochemical and clinical pregnancy during the assisted reproductive technology (ART) protocol: implantation, the incidence of biochemical pregnancy and the incidence of clinical pregnancy are inversely proportional to the increase in BMI in the ART protocol [39–42]. Complications of ART protocols and peculiarities of the course of pregnancy in obese women are:

- ovarian hyperstimulation syndrome;
- multiple pregnancy;
- ectopic pregnancy;
- gestational diabetes;
- an increase in the frequency of caesarean section operations;
- small gestational age [43–46].

According to a study by Kouhkan et al. (2019), among women undergoing ART treatment for infertility, the risk of gestational diabetes is 3.27 times higher in the overweight group, and 5.14 times in the obese group ($p < 0.002$) compared with women with normal body weight [47].

Experts from The Canadian Fertility & Andrology Society (2018) recommend that clinicians take into account the following postulates for managing an obese woman within the framework of the ART protocol:

- Obese women have fewer eggs during the ART protocol (strong recommendation, moderate quality evidence);
- the higher the BMI, the worse the implantation, the lower the incidence of clinical pregnancy and fertility (strong recommendation, moderate quality evidence);
- up to 24 weeks' gestation in obese women, the risk of pregnancy loss increases in direct proportion to the increase in BMI (strong recommendation, moderate quality evidence);

- fertility decreases by about 0.3–0.4% for every 1 kg / m² increase in BMI (strong recommendation);

- obese women using an egg donor should be advised to lose weight before entering an ART protocol (strong recommendation, moderate quality evidence);

- obesity is a risk factor for complications during the ovarian follicle puncture procedure (strong recommendation, low-quality evidence) [27].

There is also evidence that obesity can affect the expression of endometrial genes during the period of implantation both in the natural cycle and in ART cycles, including even during the procedure using a donor egg in a woman with an increased BMI [48–50].

Obesity is an independent risk factor for sexual dysfunction (every second obese patient has no satisfaction with sexual life), which can lead to a violation of the psychological status of a woman and be a factor in the non-occurrence of pregnancy due to a decrease in the frequency of sexual intercourse and a decrease in sexual desire [51, 52] ... Is it important to talk about sexuality with a woman at the reception? Yes, since sexuality is the driving force of human social activity, since it is aimed at achieving not only sexual satisfaction, but also a socio-psychological state, designated as "happiness." Sexuality is one of the important factors in human cognition of the surrounding world. And most importantly, sexuality is a factor that induces people to create a family and bear children [53].

In addition to the risk of infertility, the pathological course of pregnancy and the postpartum period, obesity is a risk factor for endometrial pathology, including endometrial cancer [56]. Experts believe that the possible reasons are:

- deficiency of progesterone;
- chronic anovulation syndrome accompanying an obese woman;
- an increase in peripheral hyperestrogenism [57-59].

In addition to the threat of endometrial pathology, obesity is a risk factor for breast diseases, including breast cancer [60].

Polycystic ovary syndrome (PCOS) is a polyendocrine syndrome characterized by dysfunction of the ovaries (chronic anovulation) and hormonal secretion of the endocrine glands [13, 14]. As a syndrome, PCOS consists of several important components (metabolic, reproductive, cardiovascular, psychological, etc.) [15], the course of which forms the pathophysiology of the disease. The main clinically important signs of the disease are hyperandrogenism (clinical and / or biochemical) and chronic anovulation [53, 55].

PCOS is of great social and clinical importance due to its high prevalence in women of fertile age and is one of the most common endocrinopathies. PCOS occurs in every 10th patient of reproductive age [53].

Obesity cannot be called a mandatory clinical symptom of PCOS, however, the number of patients with obesity and PCOS reaches, according to various authors, 45%, which is significantly higher than in the population (up to 30%) [56]. Obesity actually potentiates the development of metabolic disorders. The combination of PCOS and obesity is a powerful risk factor for the development of cardiometabolic conditions: impaired glucose tolerance (IGT), type 2 diabetes mellitus (DM), and dyslipidemia. And it is important to note that the frequency of these conditions is high both in PCOS itself and increases significantly in the presence of obesity in a woman [53]. Overweight / obesity as a diagnostic criterion for PCOS should be critical, since the effectiveness of treatment in patients with PCOS and obesity is largely determined by progress in weight loss [53, 54].

The incidence of obesity is increasing and has a tremendous impact on the course of PCOS. The risk of developing metabolic syndrome in women with PCOS is 14 times higher and proportionally increases with an increase in BMI [57].

The risk of developing endometrial cancer in women with PCOS is 2–6 times higher before menopause, while the risk factors for endometrial pathology are prolonged amenorrhea, abnormal uterine bleeding, and overweight [53].

In PCOS, psychological status disorders such as moderate to severe anxiety and depressive disorders are more common. The aggravating factors of these disorders are obesity, pregnancy failure, hirsutism, and hormonal drugs [53].

Finally, factors affecting fertility rates, reproductive response, and pregnancy outcomes in women with PCOS are:

- blood glucose level;
- woman's weight;
- blood pressure level;
- smoking;
- alcohol abuse;
- emotional and sexual health [53].

The “poor” response to stimulation of ovulation with clomiphene citrate in women with PCOS is associated with the patient's BMI: the higher the BMI, the lower the number of oocytes obtained and the worse the quality of the embryos [58].

Pregnancy in women with PCOS is more complicated than in the population [53–55]. In addition to the generally recognized complications (gestational diabetes, increased blood pressure, preeclampsia and eclampsia [59, 60]), according to the literature, it is with PCOS that:

- pathological weight gain during pregnancy;
- increased risk of premature birth;
- higher gestational age, lower birth weight.

And it is with an overweight mother with PCOS at the time of conception that the risk of developing these complications is associated [51].

According to The international evidence-based guideline for the assessment and management of polycystic ovary syndrome (2018), a balanced diet and regular exercise should be recommended for all women with PCOS to achieve and / or maintain a healthy weight, optimize hormonal imbalance, overall health and improving the quality of life by all specialists. Weight loss from 5 to 10% within 6

months in overweight patients will clinically lead to improved laboratory parameters. But it is worth remembering that without correcting the psychological status (in case of eating disorders, for example), optimization and adherence to a correct lifestyle will not be achieved [53].

Therapeutic tactics in obese women during the reproductive period are the same as in the general population. According to The Canadian Fertility & Andrology Society (2018), moderate intensity weight loss with lifestyle modification improves the metabolic profile for pregnancy planning (strong recommendation, moderate quality evidence) [27]. Weight loss itself is one of the most important recommendations for infertility therapy [8, 22].

Overweight women are advised to reduce their weight by 5-10% within 3-6 months before pregnancy in order to increase the percentage of fertility. According to the Clinical Protocol of the National Institute for Health and Care Excellence, a woman planning a pregnancy with a BMI ≥ 30 kg / m² should be the first line of therapy recommended for weight loss [23]. Experts in the latest clinical protocol from The Canadian Fertility & Andrology Society (2018) recommended the following positions for an overweight / obese woman of reproductive age:

- 1st line of therapeutic tactics: non-drug therapy (lifestyle changes through dietary adjustments and increased exercise) (strong recommendation, low quality evidence);
- 2nd line of therapy - prescribing drugs registered as medicines for the treatment of obesity and bariatric surgery (if indicated) (strong recommendation, moderate quality evidence);
- Pregnancy planning after bariatric surgery is only possible after 1–2 years (strong recommendation, low-quality evidence). Women after bariatric surgery have higher risks of low gestational age, but lower risks of fetal macrosomia, gestational diabetes, and hypertension (strong recommendation, good quality evidence) [27].

At the planning stage of pregnancy, weight loss will prevent complications of gestation, delivery and improve perinatal prognosis [31].

If a patient with endometrial pathology (especially with a recurrent course) is overweight / obese, then one of the preventive measures to reduce the risk of endometrial cancer is to recommend her to reduce body weight [22, 24].

The problem of overweight in women with PCOS has also been clarified in a structured approach in the International Clinical Protocol for the Management of Women with PCOS. The first stage of PCOS treatment is lifestyle changes and weight loss [53, 55].

Lifestyle modification based on the correction and development of a balanced diet and increased physical activity is the most important aspect of the treatment of obese patients. However, not all patients manage to change their dietary and lifestyle habits and achieve significant positive results in treatment. Pharmacological therapy of obesity allows you to achieve a more effective reduction in body weight, helps to comply with dietary recommendations and the development of new eating habits, thereby contributing to the long-term stabilization of the reduced body weight. Since obesity is a chronic relapsing disease requiring long-term life-long treatment and follow-up, short-term therapy is ineffective [56].

Prescription of drugs for the treatment of obesity is recommended for BMI ≥ 30 kg / m² or BMI ≥ 27 kg / m² in the presence of risk factors and / or comorbid diseases [57].

The prescription of food supplements or dietary supplements is not recommended due to the lack of data on their effectiveness and safety in the treatment of obesity in women of reproductive age.

Conclusion

Despite the fact that the relationship between obesity and impaired reproductive health in women has been known for almost a century, the most important stage - weight loss - in the framework of individual counseling, not enough

attention is paid to doctors of all specialties. Only in the presence of comorbid pathology in a patient, a column on the need to comply with lifestyle modifications appears in the list of recommendations [51]. Repeatedly conducted studies in the Russian Federation and foreign colleagues have shown that weight loss improves reproductive function in overweight and obese women. For women with overweight or obesity of reproductive age, especially with menstrual irregularities, non-pregnancy, burdened obstetric and gynecological history, visiting specialized specialists, it is fundamentally important to receive a set of recommendations aimed at weight loss. Among them - the need to modify the lifestyle, the expansion of physical activity, pharmacotherapy of obesity. And these recommendations will be as basic as, for example, therapy for menstrual irregularities or endometriosis therapy by a gynecologist. Weight loss is most often achieved through dietary changes and increased physical activity. In recent years, weight loss drugs and bariatric surgery have become more widely used. And these data should be fully owned by specialists to whom an overweight patient can come (for example, a therapist, gynecologist), because a doctor of any specialty can recommend all 3 possible stages (lifestyle modification, increased physical activity, pharmacotherapy) for weight loss.

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