УДК: 616-06
DOI 10.21886/2219-8075-2020-11-3-15-19

Mechanisms of fertility disorders in obese women

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Obesity is a common problem among women of reproductive age. Overweight is known to negatively affect a woman's fertility. So, women of reproductive age who are obese may experience menstrual irregularities, endometrial pathology and, ultimately, infertility. The pathogenetic mechanisms of reproductive dysfunction in obesity remain actively studied issues. It was established that leptin synthesized by adipose tissue inhibits granulosis, cell steroidogenesis and interferes with the ovulation process, which can directly affect reproductive function. Insulin resistance and compensatory hyperinsulinemia, which accompany obesity in women, can contribute to menstrual irregularities, ovulation and, ultimately, fertility. Obesity is also characterized by a state of «relative functional hyperandrogenism», which can affect ovarian function, contributing to the development of infertility. Moreover, obesity is characterized by a state of hyposomatotropinism, which can affect fertility, through changes in ovarian and endometrial function. Weight loss is most likely able to restore fertility in most cases, but there are no practical guidelines that would help the clinician choose the best method to reduce body weight from increased physical activity, dietary restrictions, drug therapy and bariatric surgery.

Keywords: obesity, impaired fertility of a woman, infertility, overview

For citation: Volkova N.I., Degtyareva Yu.S. Mechanisms of fertility disorders in obese women. *Medical Herald of the South of Russia.* 2020;11(3):15-19. DOI 10.21886/2219-8075-2020-3-15-19.

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Механизмы нарушения фертильности у женщин с ожирением

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Ожирение — распространенная проблема среди женщин репродуктивного возраста. Известно, что избыточная масса тела оказывает негативное влияние на фертильность женщины. Так, женщины репродуктивного возраста с ожирением могут столкнуться с нарушением менструального цикла, патологией эндометрия и, в конечном счете, бесплодием. Патогенетические механизмы нарушения репродуктивной функции при ожирении остаются активно изучаемыми вопросами. Установлено, что лептин, синтезируемый жировой тканью, ингибирует гранулезу, клеточный стероидогенез и вмешивается в процесс овуляции, что напрямую может оказывать влияние на репродуктивную функцию. Инсулинорезистентность и компенсаторная гиперинсулинемия, которые сопровождают ожирение у женщин, могут способствовать нарушениям менструального цикла, овуляции и, в конечном счете, фертильности. Ожирение также характеризуется состоянием «относительного функционального гиперандрогенизма», которое может влиять на функцию яичников, способствуя развитию бесплодия. Более того, ожирение характеризуется состоянием гипосоматотропинизма, которое может влиять на фертильность, посредством изменения функции яичников и эндометрия. Потеря веса, вероятнее всего, способна восстановить фертильность в большинстве случаев, но нет практических указаний, которые бы помогли клиницисту выбрать наилучший метод по снижению массы тела из увеличения физической активности, диетических ограничений, медикаментозной терапии и бариатрической хирургии.

Ключевые слова: ожирение, нарушение фертильности женщины, бесплодие, обзор.

Для цитирования: Волкова Н.И., Дегтярева Ю.С. Механизмы нарушения фертильности у женщин с ожирением. *Медицинский вестник Юга России.* 2020;11(3):15-19. DOI 10.21886/2219-8075-2020-11-3-15-19.

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Mechanisms of impaired fertility in obese women

Introduction

Obesity is a common problem among women of reproductive age. According to the World Health Organization, 60% of women in the United States and most European countries are overweight, 30% are obese [1]. Obesity affects more than 20% of women of reproductive age [2]. In Russia, according to official statistics, the prevalence of the disease is somewhat lower, but the problem of obesity is no less acute than in other countries. According to Federal State Statistics Service data obtained in December 2019, 24.5% of women in Russia are obese, 34.7% are overweight [3].

The negative effect of excess weight on various types of metabolism, many organs and systems is known. Thus, women who are obese may face menstrual irregularities, endometrial pathology and, ultimately, infertility [2]. A cohort study of 1.2 million nulliparous women showed that overweight mothers have an increased risk of having children with birth defects [4].

Despite the fact that the clinical effect of obesity on fertility in women has been studied, the pathogenetic mechanisms of impaired reproductive function in overweight are still actively studied.

Adipokines and impaired fertility

Adipose tissue is equated with endocrine organs due to the secretion of bioactive cytokines called adipokines, which play an important role in the regulation of reproduction, immune response, glucose and lipid metabolism. If we talk about reproductive function, then adipokines are of decisive importance in this matter: normal levels of adipokines are necessary to maintain the integrity of the hypothalamus-pituitary-gonad axis, to regulate ovulatory processes, successful implantation of embryos and, in general, physiological pregnancy.

It has been established that leptin has a stimulating effect on the impulses of gonadotropin-releasing hormone (GnRH), thereby controlling reproductive function [5]. Leptin levels are directly related to the amount of adipose tissue in the body. When underweight, there is a decrease in leptin levels, which in itself suppresses fertility, while excess body weight is associated with increased secretion of leptin, but, nevertheless, this does not guarantee normal fertility. Probably, impaired fertility with an increased level of leptin is due to the fact that most forms of obesity are characterized by a state of resistance to leptin at the central level by suppressing the expression of the receptor [2], while maintaining sensitivity to it in other tissues. So, in the ovaries, it suppresses granulosis, the production of steroid hormones and interferes with the ovulation process, which can directly affect the reproduction of women, worsening it [6].

Insulin resistance and impaired fertility

It is known that obesity, mainly of the central type, is characterized by the presence of a state of insulin resistance (IR) and compensatory hyperinsulinemia, which is caused by the influence of free fatty acids (FFA), leptin, cytokines, androgens [5]. It should be noted that IR with excess body weight is not expressed in all tissues. Thus, musculoskeletal and adipose tissue lose their sensitivity to insulin, which leads to compensatory hyperinsulinemia. At the same time, an excessive level of insulin has a stimulating effect on the ovaries and adrenal glands, which have not lost their sensitivity to it, which leads to an increase in the synthesis of androgens and the development of hyperandrogenism [6]. These androgens are aromatized at a high rate into estrogens at the periphery (the high rate of aromatization is also due to the presence of excess adipose tissue). An excess of androgens affects the production of gonadotropin according to the principle of negative feedback, leading to impaired follicular formation and anovulation [2]. The liver also remains susceptible to insulin, and in the presence of its excess, the liver suppresses the production of sex hormone binding globulin (SHBG), which leads to an increase in free fractions of androgens [6].

In addition, insulin can interact with IGF-I receptors, resulting in a decrease in the synthesis of proteins that bind insulin-like growth factors in the liver, which increases the bioavailability of IGF-I and leads to increased androgen production by interstitial and stromal theca cells and inhibition of growth hormone production. [6].

Among other things, insulin also enhances the activity of luteinizing hormone (LH) on granulosa cells, which promotes the activation of steroidogenesis and inhibition of mitosis and leads to inhibition of terminal differentiation of these cells. As a result, follicle growth is blocked, which clinically also manifests itself in the form of menstrual irregularities and oligoanovulation [6]. Through these mechanisms, IR can contribute to menstrual irregularities, ovulation, and ultimately fertility.

Obesity and sex hormones

It is known that adipose tissue directly synthesizes androgens and converts them into estrogens, in connection with which it becomes obvious that the level of estrogens and androgens increases in obesity in women. In addition, in obesity, a decrease in the level of SHBG is noted, which is associated with a subsequent increase in the bioavailability of androgens and estrogens for target tissues. It is logical that the ability of adipose tissue to accumulate sex steroids leads to an increase in the steroid pool in women with overweight [5].

Obesity and growth hormone

Growth hormone (GH) is known to be essential for normal fertility. Thus, GR stimulates the growth of small follicles and prevents their atresia, together with gonadotropins, it participates in the stimulation of the late stages of follicular maturation and luteinization, and promotes the development of the dominant follicle. GH has a stimulating effect on the endometrium and myometrium of the uterus, and in the ovaries it increases the synthesis of estrogen and progesterone, in other words, it plays an important role in the reproductive health of women.

It has been established that obesity is characterized by a state of hyposomatotropinism caused by a decrease in GH secretion and an increase in its clearance. Factors responsible for the decrease in growth hormone levels include dysregulation of the somatotropin-releasing hormone, somatostatin and ghrelin pathways, increased plasma insulin levels, and excess circulating FFA. An increase in the level of total and free IGF-1 in obesity

entails inhibition of GH secretion in a negative feedback loop [5]. Thus, hyposomatotropinism observed in obesity [7] may become another serious factor that negatively affects a woman's fertility.

Obesity and ovaries

The function of the ovaries in obesity may change due to the influence on them of factors such as hyperinsulinemia, hyperandrogenism and hyposomatotropinism [5-7]. In addition, obesity can also directly affect the eggs, leading to a deterioration in their quality. Thus, when comparing unsuccessfully fertilized oocytes of patients with severe obesity and normal weight, it was found that in women with obesity, the prevalence of "irregular meiotic spindles with misaligned chromosomes" is significantly higher [8]. One of the proposed mechanisms underlying the altered oocyte quality in obese women is the change in the activity of mitochondria, which, in fact, perform numerous regulatory functions during oocyte maturation, fertilization, preimplantation, and normal embryonic development [5]. In addition, lipotoxicity, which occurs when an excess intake of free fatty acids (FFA) from the diet, can have a negative impact on the quality of the egg. FFA in the form of triglycerides accumulate not only in adipocytes, but also in other tissues, provided that they continue to be excessively supplied with food. In tissues not suitable for storage of triglycerides, FFAs have a toxic effect known as lipotoxicity. Thus, lipotoxicity leads to damage and apoptosis of many cells, including oocytes [9]. This phenomenon is closely associated with chronic inflammation, as evidenced by increased levels of circulating C-reactive protein, lactate and triglycerides in follicular fluid and increased expression of genes for pro-inflammatory and oxidative stress [6].

Obesity and endometrium

In obese women, there is a decreased susceptibility of the endometrium, which is primarily due to relative hyperestrogenism, a decrease in glycodelin due to hyperinsulinemia, and an excess of leptin. In addition, overweight women have impaired endometrial decidualization [10], which may be due to the presence of endothelial dysfunction, which arose under the influence of circulating pro-inflammatory cytokines and reactive oxygen species [11], as well as haptoglobulin (in women with obesity and recurrent miscarriages there is an increased expression of haptoglobulin in the endometrium) [12]. In addition, it was found that ERK signal transduction, which belongs to the MAPK / ERK pathways required for trophoblast invasion into the endometrium, is suppressed during implantation in obese women [5]. Thus, these mechanisms may be responsible not only for impaired reproductive function by reducing implantation, but also for the high frequency of miscarriages in obese women.

Weight loss and fertility

Obesity can rightfully be called one of the most easily diagnosed, but difficult to treat diseases. At the same time, weight loss in obese and infertile women is essential for the restoration of reproductive function. A recent study found that weight loss of 6.9% of initial body weight is sufficient to increase pregnancy rates [13]. Earlier evidence suggests that weight loss of 5-10% of body weight can definitely improve fertility rates [6]. Diet, behavioral modification therapy, medication and surgery are currently available for the treatment of obesity. Which weight loss method is most preferred for restoring fertility remains to be seen. There is evidence that bariatric surgery improves fertility in severely obese women, but there is no consensus on the role of bariatric surgery in treating obesity-associated infertility. The beneficial effect of bariatric surgery on anovulatory infertility was demonstrated in a survey study of 195 obese women with anovulation. In 71% of cases, ovulation was restored after surgery [14]. However, a recent pilot study demonstrated that short-term intensive weight loss intervention in severely obese infertile women resulted in improved ovulation similar to bariatric surgery [15]. More research is needed to confirm these results, which may determine an algorithm for the management of obese infertility patients. Regardless of the chosen treatment for obesity in infertile women, weight loss is the most inexpensive and most physiological method of restoring fertility, with no side effects and other health benefits, and therefore should be the first line treatment for women with obesity and anovulatory infertility. However, the decision to postpone fertility treatments in order to reduce weight often results in a further increase in maternal age in women. The effect of weight loss on fertility recovery appears to decrease with age, and in women 36 years and older, weight loss may lead to ineffectiveness in influencing a woman's fertility [6]. Maternal age is probably one of the most significant factors in choosing a weight loss method to restore fertility in obese women.

Conclusion

Obesity is associated with infertility in women. Leptin, FFA and cytokines, can influence both ovarian and endometrial function, with a final change in oocyte maturation and endometrial susceptibility. Due to the development of peripheral insulin resistance, obesity causes a state of functional hyperandrogenism and hyperestrogenism, which contribute to the occurrence of anovulation and reduce the susceptibility of the endometrium and, therefore, are involved in the occurrence of infertility. All these data support the opinion that obesity can lead to impaired ovulation, a decrease in the quality of oocytes and embryos, and, consequently, to infertility, which is also supported by an unfavorable intrauterine environment and impaired endometrial susceptibility. Weight loss is likely to restore fertility in most cases, but there are no practical guidelines to guide the clinician in choosing the best weight loss method from increased physical activity, dietary restrictions, drug therapy, and bariatric surgery. Undoubtedly, the age of a woman is important in determining the tactics of treating infertility in obese women, but more qualitative research is needed to address this issue.

Finansing. *The study did not have sponsorship.*

Финансирование. Исследование не имело спонсорской поддержки.

Conflict of interest. *Authors declares no conflict of interest.*

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

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All authors made a significant contribution to the preparation of the article, read and approved the final version before publication.

Вклад авторов

Все авторы внесли существенный вклад при подготовке статьи, прочли и одобрили финальную версию перед публикацией.

Получено / Received: 21.05.2020
Принято к печати / Accepted: 08.06.2020