RISK FACTORS FOR DIMINISHED OVARIAN RESERVE IN WOMEN: CURRENT STATE OF THE PROBLEM

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ABSTRACT

Ovarian reserve is the basis of female fertility. The main markers of ovarian reserve are the level of anti-Mullerian hormone and the number of antral follicles. In addition to the natural age-related loss of follicles, many women experience a premature diminished ovarian reserve associated with a number of factors. This can be caused by both various diseases and environmental factors, lifestyle, and social aspects.

The aim of this review *was to examine the influence of external factors on the ovarian reserve and women fertility. A systematic analysis of data from modern scientific literature, domestic and foreign sources was carried out. The search involved such resources as PubMed, MEDLINE, Science Direct, eLibrary, Scopus, Cyberleninka. A detailed analysis of the influence of environmental pollution, lifestyle (sleep, nutrition, physical activity), previous surgeries, bad habits, obesity, psychological and social factors on the ovarian reserve and reproductive function of women was carried out. Significantly diminished ovarian reserve was noted with low sleep quality, excessive physical activity, and an unbalanced diet poor with animal proteins. Regular consumption of alcohol, smoking and exposure to certain chemical environmental pollutants cause premature follicle apoptosis and the onset of menopause. Circadian dysrhythmia, chronic stress and obesity can lead to the ovarian menstrual cycle disorders and the development of infertility in women. Previous parovarium surgeries are a significant risk factor for diminished ovarian reserve. Further population-based studies are needed to determine the precise mechanisms of influence of various factors on female fertility.*

Key words: *ovarian reserve, follicles, menopause, fertility, infertility, lifestyle, smoking, environmental factors*

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ФАКТОРЫ РИСКА СНИЖЕНИЯ ОВАРИАЛЬНОГО РЕЗЕРВА ЖЕНЩИН: АКТУАЛЬНОЕ СОСТОЯНИЕ ПРОБЛЕМЫ

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РЕЗЮМЕ

Овариальный резерв – основа женской фертильности. Основными маркерами овариального резерва являются уровень антимюллерова гормона и количество антральных фолликулов. Помимо естественной возрастной потери фолликулов, многие женщины сталкиваются с преждевременным снижением овариального резерва, связанным с множеством факторов. Причинами данного явления могут стать как различные заболевания, так и факторы внешней среды, образ жизни, социальные аспекты.

***Целью настоящего обзора** стало рассмотрение влияния внешних факторов на овариальный резерв и фертильность женщин. Проведён систематический анализ данных современной научной литературы, отечественных и зарубежных источников. В поиске были задействованы такие информационные ресурсы, как PubMed, MEDLINE, Science Direct, eLibrary, Scopus, Cyberleninka. Проведён подробный анализ влияния загрязнения окружающей среды, образа жизни (сон, питание, физические нагрузки), перенесённых операций, вредных привычек, ожирения, психологических и социальных факторов на овариальный резерв и репродуктивную функцию женщин. Отмечено существенное снижение овариального резерва при низком качестве сна, чрезмерных физических нагрузках, несбалансированной диете, обеднённой животными белками. Регулярное употребление алкоголя, курение табака и воздействие некоторых химических загрязнителей окружающей среды приводят к преждевременному апоптозу фолликулов и наступлению менопаузы. Циркадианная дизритмия, хронический стресс и ожирение могут приводить к нарушениям овариально-менструального цикла и развитию бесплодия у женщин. Перенесённые операции на придатках являются существенным фактором риска снижения овариального резерва. Для выяснения точных механизмов воздействия различных факторов на фертильность женщин необходимы дальнейшие популяционные исследования.*

Ключевые слова: *овариальный резерв, фолликулы, менопауза, фертильность, бесплодие, образ жизни, курение, экологические факторы*

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INTRODUCTION

According to Russian and international associations of human reproductive science and embryology, the incidence of infertility among married couples has increased in recent decades, while the average age of its onset has decreased. Today, infertility in couples is a common problem among young women and men. Environmental pollution, various somatic diseases, lifestyle, psychological stress, and social aspects are factors that negatively affect reproductive function. While men can completely renew their sperm pool in a relatively short period of time, for women the impact on eggs can be irreversible in some cases and significantly affect their ability to conceive [1].

The reproductive lifespan of women begins at puberty and ends at menopause, after the depletion of the ovarian follicle reserve [1]. Ovarian reserve is the basis of female fertility. In clinical practice, it is usually assessed using parameters such as the woman's age, antral follicle number, Anti-Müllerian hormone (AMH) level, and basal levels of sex hormones, including follicle-stimulating hormone (FSH), luteinizing hormone, and estradiol [2].

Numerous studies have identified a number of determining factors that can have a negative impact on ovarian reserve and fertility in women, but most factors should be considered in combination due to their interaction with each other and the complexity of interpretation [2]. This review examines in detail such risk factors for decreased ovarian reserve as environmental, social, psychological factors, lifestyle (sleep, nutrition, unhealthy habits, physical activity), obesity, and previous surgeries on the pelvic organs. Multicenter and population-based scientific studies are needed to study the impact of each factor in more detail.

ENVIRONMENTAL FACTORS

A growing number of epidemiological studies and experimental animal models suggests that exposure to a number of ubiquitously distributed reproductively toxic environmental chemicals (RTECs) may contribute to earlier menopause and premature ovarian failure. These include lead, mercury, toluene, perchlorates, bisphenol A and some phthalates, pesticides, perfluorochemicals, polychlorinated biphenyls, and polybrominated diphenol ethers [3, 4].

The negative impact of toxic substances on the ovaries can occur in three ways: disruption of the endocrine system; induction of oxidative stress; epigenetic changes [4, 5]. Depending on the moment of exposure to ovarian ontogenesis, the effect of RTECs on ovarian function can be temporary or permanent. This effect causes the greatest harm prenatally, affecting the ontogenesis of the ovaries in the female fetus at the time of follicle development, and affects the reproductive function of girls whose mothers were exposed to RTECs during pregnancy [6].

Environmental toxicants can trigger the formation of reactive oxygen species such as free radicals, oxygen ions, and hydrogen peroxide in the body cells. Oxidative stress is induced by cellular oversaturation with reactive oxygen species (ROS), when cellular machinery and endogenous antioxidants that regulate ROS levels are overloaded by exogenous reactive oxygen species. There is strong evidence that ROS are involved in the initiation of antral follicle apoptosis [7]. The role of oxidative stress in the pathogenesis of premature ovarian failure has been confirmed [7, 8].

Epigenetic modifications can occur as a result of environmental pollutants affecting DNA methylation, which can alter ovarian function. For example, bisphenol A, which is used in the manufacture of plastics, can destroy methyl groups and inhibit enzymes responsible for DNA methylation [5].

A number of scientific papers have shown the impact of chemical pollutants of the environment on any stage of follicle formation, as well as on the development of the ovaries in general. Evidence has been found that exposure to RTECs in the prenatal, neonatal, prepubertal periods and even in adulthood leads to disruption of ovarian function and a reduction in the duration of reproductive function in female rodents [3].

Due to their similarity to natural ligands, many environmental compounds have the ability to bind to sex hormone receptors (albeit with lower affinity) and can thus influence either the initial stages of ovarian reserve formation during fetal development or the maintenance of ovarian reserve in adults [9]. Exposure to chemicals can negatively affect ovarian reserve through aryl hydrocarbon or estrogen receptors. Thus, after binding to such an exogenous ligand, the aryl hydrocarbon receptor induces the synthesis of proapoptotic factors that promote follicular atresia.

Major international organizations, including the Endocrine Society [10], the World Health Organization and the International Pollutants Elimination Network [11], and the International Federation of Gynecology and Obstetrics [12], have noted an increase in chemical pollution in recent decades and emphasize the need for more detailed study of chemical impacts on the female reproductive system. For example, a study of the fertility of women living in the Aral Sea basin showed that they had a reduced number of antral follicles number compared to women of the same age living in a more ecologically favorable region [13]. The drainage of the Aral Sea has led to increased levels of various toxicants in the soil, water, and air, namely substances such as pesticides and heavy metals, which contribute to the development of various diseases among the local population. Cross-sectional studies show that exposure to certain environmental chemicals can compromise women's reproductive health and in some cases correlate with earlier onset of menopause [3]. However, in humans, adverse effects from chemical exposure are usually diagnosed after several years or decades, making it difficult

to determine the relationship between RTECs exposure and reproductive health [6].

Further epidemiological and experimental studies are needed to determine the direct and indirect effects of environmental chemical pollutants on ovarian function and to better understand their mechanisms of action.

LIFESTYLE

Sleep, nutrition and physical activity. Recently, more and more attention has been paid to the influence of a woman's lifestyle, diet, sleep and wakefulness patterns, and physical activity on the women reproductive function. Today, more and more women are into various diets, therapeutic fasting, extreme physical activity, and equally with men choose «difficult professions» with shift work schedules and high stress levels. Researchers have shown that intense physical exercise and poor sleep quality have a significant negative impact on the antral follicles number in women aged 31 to 36 years [14]. Excessive physical activity leads to menstrual irregularities, decreased ovulation frequency, disruption of endometrial development, and in some cases, amenorrhea and subfertility. The probable cause of these conditions is dysregulation of the hypothalamic-pituitary-ovarian axis due to a decrease in systemic stimulating signals for the release of gonadotropin-releasing hormone and impaired secretion of gonadotropins [15].

Adherence to a certain type of diet in some cases can also affect the ovarian reserve. Thus, it was shown that the transition to an exclusively plant-based diet without animal components, containing sugar and not supplemented with folic acid and vitamin B12, is associated with the risk of early menopause, while a "healthy" plant-based diet, additionally enriched with a vitamin complex, did not affect the timing of menopause [16]. In another study, the authors conclude that giving up vegetarianism contributes to longer-term preservation of fertility [17]. In a sample of more than 2,000 women, a relationship between regular consumption of dairy products and a reduced risk of early menopause was found [18]. Today, this is of particular importance, since adherence to veganism, which entails the rejection of dairy products, is widespread among modern women.

Long-term fasting can also have a negative impact on women's reproductive function. Thus, a diet violation leads to a decrease in the amplitude of the pulse secretion of thyroid-stimulating hormone: a decrease in its basal concentration in the blood serum, as well as a decrease in its peak level at night [19], which in turn leads to dysfunction of the thyroid gland and indirectly affects female fertility.

Misalignment of the biological clock with the sleep-wake cycle as a result of long and frequent flights, shift work, and stressful situations underlies the phenomenon of circadian dysrhythmia [20]. Circadian dysrhythmia is associated with a higher body mass index (BMI), obesity [21], and an increased risk of developing metabolic syndrome and type 2 diabetes [22]. The production of thyroid-stimulating hormone is also associated with circadian rhythms. Thus, in a study that included an examination of more than 5,000 patients, an increased risk of subclinical hyperthyroidism was found in patients who slept little (less than 7 hours per day), in contrast to people who slept more than 8 hours per day [23]. Hypothyroidism, in turn, is often the cause of endocrine infertility, as it is accompanied by increased prolactin levels, anovulatory menstrual cycles, luteal phase defects and changes in sex hormone levels [24, 25].

Circadian dysrhythmia can also have a direct effect on the secretion of reproductive hormones, leading to anovulation, and in some cases is combined with insulin resistance [26].

Smoking. According to numerous scientific studies, tobacco smoking has a number of consequences that are potentially harmful to a woman's reproductive function, as it can have an adverse effect on ovarian function, cause mutations in germ cells, and increase the risk of early miscarriages and adverse outcomes of assisted reproductive technology cycles [27].

Tobacco toxins have been shown to have a detrimental effect on the follicle pool and increase the rate of follicular atrophy and atresia, leading to a decrease in their number, changes in sex hormone levels, and ultimately to a decrease in fertility [2, 28]. Smoking has been found to be associated with a decrease in estradiol and estriol concentrations, an increase in testosterone levels, and a tendency toward an increase in serum FSH levels [29].

Other negative effects of tobacco toxins include increased rates of apoptosis as well as necrosis in various human tissues and increased apoptosis in primordial germ cells differentiated from human stem cells *in vitro* [30]. These effects may also manifest as increased rates of follicular apoptosis or ovarian dysfunction. Indeed, polycyclic aromatic hydrocarbons in cigarette smoke are toxic to follicles, which has been demonstrated in both animal models and numerous human studies [2, 28].

Smoking is associated with an increased rate of follicle loss in Caucasian women. In 14,620 middle-aged women in the Study of Women's Health across the Nation, smoking was associated with an earlier age at menopause (0.3–1.2 years earlier), but there was no dose-response effect with the number of cigarettes smoked per day [28]. Data were obtained indicating a higher incidence of early ovarian failure syndrome, reduced fertilization and implantation rates, pregnancy rates, and live birth rates in assisted reproductive technology programs in women who smoke [31, 32].

Among women of reproductive age, users of popular e-cigarettes have been found to have higher levels of several markers of toxin exposure (including nicotine metabolites, the tobacco carcinogenic biomarker

NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), lead, and volatile organic compounds) [33]. This study showed that exclusive use of e-cigarettes may reduce exposure to some toxins compared with smoking combustible cigarettes, but e-cigarettes result in greater exposure to toxicants compared with quitting smoking completely. Even reduced levels of tobacco toxins in e-cigarette users may lead to potentially harmful reproductive health consequences [33, 34].

Alcohol is also one of the risk factors for decreased female fertility. The biological mechanisms of the negative impact of alcohol on reproductive function are still poorly understood. One hypothesis is that alcohol can reduce fertility by changing the concentration of endogenous hormones [35]. Another theory suggests a direct negative effect of alcohol on egg maturation, early blastocyst development, and implantation [36].

A group of researchers from Denmark showed on a cohort of more than 6 thousand women that regular consumption of 14 servings of alcohol per week is associated with an increase in estrogen concentration, which reduces the secretion of FSH, resulting in the suppression of folliculogenesis and ovulation, as well as the amount of bioavailable forms of estrogen. In this work, the «serving» of alcohol was calculated depending on its strength (beer – 330 ml, wine – 120 ml, hard liquor – 20 ml) [35].

Alcohol consumption is combined with the consumption of other toxins present in alcoholic beverages, such as ethyl carbamates, tetra-beta-carbolines or food additives, which have a toxic effect on oocytes, including through the development of oxidative stress, accelerating follicular apoptosis [36]. To date, researchers agree on the negative impact of alcohol consumption on female reproductive function.

Data from univariate and multivariate analyses [2] conducted in China on a cohort of 1,513 women showed a significant negative correlation between alcohol consumption and AMH levels in both the 20–30 and 31–36 age groups. In 2017, a group of scientists from China conducted a dose-response meta-analysis based on 19 studies with a total of more than 98 thousand women and established a linear dose-dependent relationship between a decrease in the ability to spontaneously conceive and an increase in the dose of alcoholic beverages consumed per 12.5 g of ethanol per day (relative risk – 0.98; 95% confidence interval: 0.97–0.99) [36]. The data from these studies demonstrate that abstinence from alcohol is important for maintaining reproductive function, which is especially important for young women under 36 years of age [2].

OBESITY

Obesity is a disease that is closely related to a person's lifestyle and is currently becoming increasingly global in scale. Today, over 2 billion people worldwide suffer from excess body weight and obesity [37]. Obesity has a negative impact on a woman's reproductive function, associated with changes in the regulation of the hypothalamic-pituitary-ovarian axis, a decrease in the quality of eggs and a disruption of the physiological processes of the endometrium, which has been proven in a cohort of over 47 thousand women from Denmark and is confirmed by data from Russian scientists [38, 39].

Obesity leads to ovarian-menstrual cycle disorders and an increase in the number of anovulatory cycles. It has been proven that decreased fertility in obese patients may be associated, in particular, with a decrease in ovarian reserve [40].

Depending on the degree of obesity, patients experience a progressive decrease in ovarian reserve parameters: AMH concentration levels, a decrease in ovarian volume and antral follicles number, in parallel with an increase in serum testosterone concentration [39, 40]. Other studies have shown that women of reproductive age with abdominal obesity against the background of insulin resistance have a decrease in ovarian reserve and accelerated aging processes of the reproductive system [41, 42]. Some researchers have observed an inverse correlation between AMH levels and BMI, including in polycystic ovary syndrome, which is also often associated with infertility, as shown in a sample of 489 women with infertility examined in the USA [43].

It is interesting that the body mass index in late adolescence is an important prognostic factor for fertility in the reproductive period: for example, women in the Nurses' Health Study, conducted in Boston, USA on a cohort of 1950 people [44], who were underweight at 18 years of age (BMI < 18.5 kg/m^2), needed on average 25 % more time to get pregnant than women with normal weight in adolescence. This suggests that the prepubertal period is a critical time for programming the implementation of reproductive function [15]. Large randomized multicenter clinical trials are needed to study in more detail the role of body mass index in reducing ovarian reserve, including women of different ages and races and comprehensively assessing the influence of concomitant factors.

LATE PREGNANCY PLANNING

One of the main factors influencing the ovarian reserve is age. Today, there is a worldwide trend towards an increase in the age of women giving birth for the first time. In Russia, from 1990 to the present, the average age of a mother at the time of the birth of her first child has increased from 22 to 26 years [45]; and in the USA, over the past 30 years, the proportion of women giving birth over 35 years has increased from 8 % to 18 % [46]. With age, women's fertility decreases, and the optimal age for the birth of a first child is from 20 to 30 years, while after 35 years, the ability to conceive spontaneously decreases, while the risk of giving birth

to a child with congenital malformations or chromosomal pathology increases [1].

On the other hand, social, cultural and economic factors, the use of contraception and the availability of assisted reproductive technologies shape the tendency in society to plan pregnancy at the age of 35 and older [47]. A study conducted in Spain on a sample of 326 women revealed that women who were in stable relationships became mothers at an older age (31.83 ± 0.29 years) than unmarried women. The average time required to achieve pregnancy increased with increasing maternal age and averaged 24 months for women around 35 years of age compared to 3 months or less for women around 29 years of age. Women 35 years of age and older were more likely to require medical assistance to achieve pregnancy [47]. At the same time, age-related decrease in ovarian reserve in combination with concomitant diseases (obesity, diabetes, etc.) often leads to the fact that by the time of pregnancy planning, a woman has less and less chance of spontaneous conception [1, 46].

PSYCHOLOGICAL FACTORS AND STRESS

Factors that have an adverse effect on the function of the endocrine system include chronic stress. Individual perception of increased physical and mental stress can affect the regulatory function through an increase in the level of corticosteroid hormones, and they in turn affect the functioning of the hypothalamic-pituitary-ovarian axis [48].

In 2015, an experimental study was published in animal models showing that stress-induced changes in neuroendocrine and immune responses lead to premature ovarian failure and early menopause [49]. The latest study by Chinese scientists has caused resonance: in animal models, it was shown that prolonged three-week stress consistently reduced plasma AMH and estradiol concentrations, induced loss of primordial and preantral follicles, increased granulosa cell apoptosis in growing follicles, and ultimately reduced litter size in rats. Based on these results, scientists suggest that in humans, chronic psychological stress also causes loss of ovarian reserve by accelerating activation of primordial follicles and destruction of growing follicles, leading to ovarian exhaustion and decreased fertility [50].

Some population studies have shown that the discovery of infertility in a family is a stress factor in itself and can lead to depression. According to the literature, infertile men and women are perceived by society as inferior, socially maladjusted, and negative social attitudes aggravate their plight. According to researchers from India, for both men and women, factors such as weak support from a spouse, financial constraints, and social maladjustment in the first years of marriage are stress factors in themselves [51]. Thus, patients find themselves in a "vicious circle" when infertility causes stress, which aggravates the course of the disease.

In the study of emotional state, a scale for assessing positive and negative affect is used [52]. Thus, a high level of positive affect is defined as a state of pleasant involvement, high energy and full concentration as opposed to despondency and lethargy. In a study of female fertility and stress on a sample of more than 1000 women from the USA, it was shown that women with a low level of positive affect may experience an accelerated decrease in antral follicle number, and, conversely, high positive affect may be a protective factor mitigating the negative impact of psychological stress on antral follicle number [53].

PELVIC ORGANS SURGERIES

Pelvic organ surgeries have a significant negative impact on the ovarian reserve, since surgical intervention involves the removal of part of the ovarian tissue and disruption of the blood supply to the reproductive organs. A univariate and multivariate analysis conducted in China on a cohort of 8,323 women confirmed that appendage surgeries have a significant negative impact on such ovarian reserve indicators as antral follicle number and AMH in women aged 20–30 and 31–36 years [42].

Appendage surgeries lead to disruption of the blood supply to the ovaries and maturation of antral follicles, and removal of ovarian tissue during enucleation of benign and malignant ovarian neoplasms leads to a decrease in the amount of ovarian cortex and, as a consequence, to a decrease in the ovarian reserve [54]. Many researchers associate the main traumatic effect on the ovary with the bipolar coagulation method, often used in surgical interventions, however, in the work of Korean researchers on a group of 125 patients [55], it was shown that the level of Anti-Müllerian hormone decreases after appendage surgeries, regardless of the method used in surgical hemostasis. It is also noted that repeated interventions on the ovaries are significantly more traumatic for the ovarian reserve than primary ones [56], and the postoperative decrease in AMH occurs much more intensively with initially reduced levels of this hormone. This should be taken into account when counseling and planning appendage surgery for women planning to have children.

Moreover, surgical interventions on the uterus do not have adverse consequences for the ovarian reserve; the antral follicles number or the level of Anti-Müllerian hormone do not change after myomectomy or other surgeries on the uterus [57].

Thus, when planning surgical intervention on the uterine appendages in women of reproductive age, it is necessary to conduct a thorough assessment of the ovarian reserve, as well as discuss possible methods of preserving fertility, for example, by performing superovulation stimulation and cryopreservation of oocytes before surgery, or alternative methods of surgical treatment, such as reduction

therapy for endometrioid ovarian cysts, instead of their resection, before entering into in vitro fertilization programs [58]. However, advocating for the preservation of the ovarian reserve of each woman of reproductive age, one should not lose sight of oncological vigilance, that is, in each specific case, use an individual approach.

CONCLUSION

The female reproductive system is a delicate mechanism that is influenced by many factors. Changes at any stage of gametogenesis can negatively affect the ability to conceive. Life in the modern world, environmental problems, social behavioral trends, psychological factors leave a certain imprint on the reproductive function in general and the ovarian reserve in particular. Although female fertility has a certain ability to adapt to a new lifestyle, environmental pollution, social behavior and other factors, age-related risk factors, surgical interventions on the appendages, intense physical activity, normalization of work and rest, as well as the use of toxins should be taken seriously. Scientific research shows that female fertility is more susceptible to the effects of external factors with age [2].

The ways to solve the problem of the risk of reducing the ovarian reserve include conducting conversations, education and competent prospective counseling of teenage girls and women of young reproductive age, which can prevent the negative impact of a number of factors and adjust the lifestyle and reproductive plans of women both in our country and around the world. If the influence of environmental factors is not always possible to identify and correct in time, then minimizing the impact of tobacco and alcohol toxins is possible for women striving to give birth to a healthy child.

The wide modern possibilities of "delayed childbearing" associated with cryopreservation of oocytes, embryos and ovarian tissue can partially solve the problem of age-related loss of ovarian reserve and late implementation of a woman's reproductive plans.

A balanced approach to the choice of method, volume and timing of surgical interventions on the uterine appendages, drawing up a correct plan for managing patients together with a gynecological surgeon and a reproductive specialist will help minimize the consequences of these surgeries in relation to the fertility of patients.

Giving up unhealthy habits, choosing a healthy lifestyle, stabilizing the sleep and wakefulness patterns, regular moderate physical activity and a balanced diet are the basis for the normal functioning of the hypothalamic-pituitary-ovarian system, and therefore ensuring the long-term preservation of normal reproductive function in women.

Conflicts of interest

No potential conflict of interest relevant to this article reported.

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