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EFFECT OF STRESS ON OVULATORY FUNCTION

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Annotation. *The article presents a review of the scientific literature that addresses the problem of the impact of stress on ovulatory function. Psychological stress is widespread among the population, and its health consequences have been a major topic of research in recent decades. It is considered a crucial factor in the onset, course and exacerbation of various diseases, such as depression, cardiovascular disease, immune disorders, and has been associated with higher overall mortality. Today, more and more doctors, including gynaecologists, are aware of the huge impact of various types of stress on women's health, including the reproductive system. The purpose of this analysis was to study the impact of stress on ovulatory function. A retrospective analysis of scientific literature from such scientific databases as Scopus, PubMed, ScienceDirect, UpToDate, and Web of Science was conducted. The following keywords were used to search for information on the relationship between stress and ovulatory function: stress, ovulation, hormones, menstrual cycle. When processing the search results, we selected the most recent publications (10 years) or the most recent publications on the subject (regardless of the time of publication). In total, 31 papers were included in the inclusion criteria and are presented in this review. The problem of the negative impact of stress on women's reproductive health in the practice of gynaecologists around the world is becoming more and more relevant every year, as the level of infertility, early pregnancy loss and fertility decline is increasing. These conditions have an even greater impact on women, worsening their psycho-emotional state and increasing their stress levels. Thus, understanding how to cope with stress is critical to developing clear algorithms for preventing the effects of stress on the body and providing medical care to patients after its impact in order to preserve reproductive health.*

Keywords: *stress, ovulatory function, menstrual cycle, hormones.*

Introduction

For a long time, the world's population has been exposed to chronic stress. Recently, the world was shaken by the COVID-19 pandemic, which, like previous epidemics and pandemics, caused significant stress [2]. Humanity did not have time to recover from this state, when a full-scale war began in the center of Europe, as a result of Russia's armed attack on Ukraine, which kills thousands of people, destroys lives and has a significant impact on the health and mental state of the entire population of Ukraine, especially the residents of the frontline and occupied territories of our state. In addition, large-scale man-made and natural disasters occur almost every day. All these conditions have a negative effect on the human body. Psychological stress is a pervasive aspect of life, and although stress affects all of us at some point, prolonged or uncontrolled stress can become harmful for some people, adversely affecting their health, including reproductive function [9, 27]. Stress and its consequences for health have been a major topic of research for the past decades. Psychological stress is considered a decisive factor in the onset, course and exacerbation of various diseases, for example, depression, cardiovascular diseases, immune disorders, and it has been associated with higher overall mortality [7] According to the results of a prospective population-based cohort study involving about 120 thousand individuals, it was established that long-term stress is significantly associated with mortality, deterioration of mental health and lower quality of life [19]. Although there is agreement that stress has a significant

impact on health, the conceptualization and assessment of stress, however, is not consistent. According to various definitions, the concept of stress has been evaluated from ecological, biological and psychological points of view [7] In addition to the ecological and biological approach, the psychological approach focuses on a person's assessment of the significance of the stressor (primary appraisal) and the individual's ability to cope with problems (secondary appraisal) within the framework of human-environment transactions [7].

Today, more and more doctors, including gynecologists, are aware of the enormous impact of various types of stress on a woman's health, particularly on the reproductive system. [18] It is important for a doctor to know what consequences they can lead to and to be able to prevent them and provide the necessary help in a timely manner.

The purpose of this analysis was to study the effect of stress on ovulatory function.

Materials and methods

A retrospective analysis of the scientific literature of such scientometric bases as Scopus, PubMed, ScienceDirect, UpToDate, Web of science was conducted. When searching for information on the relationship between stress and ovulatory function, the following keywords were used: "stress", "ovulation", "hormones", "menstrual cycle". When processing the search results, the most recent publications (10 years) or the latest publications on this issue were chosen (regardless of the time of publication).

In total, 31 works, which are presented in this review, fell under the inclusion criteria.

Results. Discussion

"Stress" itself has been a controversial concept since it was first described in physiology by Cannon and Selye at the beginning of the last century. However, a stressor (stimulus) can generally be considered an intense, non-standard challenge to homeostasis, which leads to a non-specific response, including general activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathomedullary systems [13, 25, 27].

Stress has many negative effects on health. Unfortunately, the relative lack of objective markers of chronic stress means that identifying people with chronic stress is clinically very difficult [4]. In women, phenotypic markers of chronic stress include menstrual irregularities, amenorrhea, and/or infertility due to hypothalamic hypogonadism [20]. Previous research on the link between stress and the menstrual cycle has yielded conflicting results. Some have found that stress is associated with longer cycles, others with shorter cycles, and still others have found no relationship between stress and cycle length [30]. It is interesting to note that the changes in the menstrual cycle observed during stress are sometimes similar to those experienced by perimenopausal women [30].

Humans and animals have a limited amount of energy for their activities. Therefore, if any activity is to be energetically prioritized, the energy for other activities will be suppressed. Although these changes may play a role in the regulation of homeostasis, they sometimes lead to negative consequences for normal physiological function and accelerate some diseases. Reproductive functions are often suppressed when large amounts of energy would be used for other physiological functions because such reproductive processes are not essential for individual survival. Certain conditions, such as infection, psychological stress, and excessive physical exertion are stressful for the body and are considered key causes of reproductive dysfunctions in humans and animals. As a rule, stress activates the hypothalamic-pituitary-adrenal axis, the synthesis of cortisol, prolactin and pro-inflammatory cytokines to regulate homeostasis. However, such changes simultaneously inhibit reproductive function [5].

Given the complexity of the interaction between stress and the reproductive axis, the relationships between stress, stress reduction approaches, and successful conception in humans are inconsistent. Similarly, efforts to isolate a single cause-and-effect relationship between stress and infertility have so far been unsuccessful and research is still ongoing. However, stress management has important potential to improve reproductive success rates, so it is important to determine why fertility may be markedly affected by stress in some and to a lesser extent in others

[27].

One of the effects of stress is an increased level of prolactin. It is a hormone that performs more than 300 functions in the body, its secretion is influenced by many environmental factors (for example, circadian rhythms or seasonal changes), prolactin also belongs to the group of hormones that are strongly regulated by stress. The results obtained on animal models showed that its secretion depends on the type and intensity of stress [3]. Prolactin receptors, along with growth hormone and interleukin-6 receptors, are members of the type I cytokine receptor family [8]. Prolactin suppresses reproductive function by suppressing gonadotropin-releasing hormones, thus inhibiting the release of gonadotropins, follicle-stimulating and luteinizing hormones, and impairing gonadal steroidogenesis in women and men [6]. S. Sonigo and co-authors demonstrated that subcutaneous infusion of prolactin in female mice resulted in hyperprolactinemia (with an average infusion of 260 ng/ml), which was then associated with loss of the estrous cycle, anovulation (reflected by a decrease in the corpora lutea of the ovaries), and decreased circulating levels of luteinizing hormone and follicle-stimulating hormone, as well as a decrease in the mRNA level of luteinizing hormone and pituitary follicle-stimulating hormone [28]. Persistently high levels of prolactin can lead to fertility problems, decreased libido, and amenorrhea because prolactin affects the reproductive organs. An increase in the level of prolactin in the blood reduces the secretion of gonadotropins, and the consequences of a high level of prolactin depend on gender. Abnormal menstruation is often observed in women, including irregular cycles, amenorrhea, oligomenorrhea, hypomenorrhea, hypermenorrhea, or shortened menstrual cycles (polymenorrhea) [14, 17, 24]. Ovulation disorders, including complete disappearance of ovulation, are common [3]. Additional findings may include galactorrhea, infertility, decreased libido, dyspareunia, acne, weight gain, obesity, and hirsutism [14, 17, 24]. Hyperprolactinemia causes abnormal frequency and amplitude of luteinizing hormone pulsations in women, possibly due to the positive effect of estrogen on midcycle luteinizing hormone release. There is evidence that hyperprolactinemia suppresses gonadotropin release, not its synthesis. In addition, elevated prolactin directly suppresses basal and gonadotropin-stimulated secretion of estradiol and progesterone by the ovaries [21]. In women, chronic hyperprolactinemia causes a decrease in the mineral density of bone tissue, especially against the background of significant hypoestrogenia [14].

Stress is known to especially affect women's health through hypothalamic-pituitary-gonadal (HPG) dysfunction and, as a result, ovulatory dysfunction.

Ovulation is the result of the coordinated action of the endocrine, paracrine and autocrine systems. Any violation of the finely coordinated interaction between the components of the hypothalamus-pituitary-ovary axis can

lead to ovulatory dysfunction [29]. Persistent disturbances of the ovulatory cycle can be associated with stress, as well as with endocrine, autoimmune, gynecological, genetic, nutritional and iatrogenic disorders. Although regular periods are usually considered an indicator of ovulation, they may actually be due to anovulation. Therefore, monitoring regular ovulation, and not just regular menstruation, is key in analyzing a woman's health [30].

Reproductive function is mainly regulated by the hypothalamic-pituitary-gonadal axis in humans and animals. Physical and psychological stressors inhibit HPG activity through inhibition of gonadotropin-releasing hormone (GRH) in both men and women, thereby reducing the release of luteinizing hormone and follicle-stimulating hormone from the pituitary gland [5]. Thus, the impact of stress is usually accompanied by a decrease in the production of gonadal steroids [22].

According to original research at the University of California, glucocorticoid stress levels alter multiple aspects of endocrine control necessary to maintain cyclicity and fertility. Specifically, corticosterone suppresses basal levels of luteinizing hormone, causing diestrus arrest in female mice, preventing proestrus from occurring, and prevents proper activation of kisspeptin neural circuits by elevated estradiol levels (which normally occurs in proestrus). Thus, scientists hypothesize that stressful levels of glucocorticoids may impair the basal pulsatile release of luteinizing hormone, which is necessary to stimulate the preovulatory increase in estradiol secretion necessary for the transition to proestrus when the surge occurs. It is also confirmed that glucocorticoids directly affect the neuroendocrine response to the positive feedback signal of estradiol both at the level of the hypothalamus and at the level of the pituitary gland. Thus, glucocorticoids apparently inhibit multiple aspects of the female neuroendocrine reproductive axis, preventing both the transition to proestrus and the proper activation of neuroendocrine circuits by estradiol signaling at the proestrus level [10].

When evaluating experimentally the relationship between stress and reproductive functions, inflammatory stress induced by the component of the cell wall of Gram-negative bacteria, lipopolysaccharide, and psychological stress induced by restraint stress are often used. Furthermore, it has been well established that certain stress-related endocrine, neuroendocrine, and inflammatory factors, such as proinflammatory cytokines, corticotropin-releasing hormone, and glucocorticoids/corticosterone, are enhanced during stress, and that these changes act to decrease secretion gonadotropin during stress. However, research results have been somewhat conflicting, and it has been suggested that some other factors may also be involved in the stress-induced inhibition of GRH activity [5].

Schliep Karen and colleagues in the 2005-2007 BioCycle prospective cohort study, which followed 259 premenopausal women from western New York state over

2 menstrual cycles, found that high daily stress was associated with lower total and free estradiol, luteinizing hormone, progesterone, higher concentrations of follicle-stimulating hormone and increased chances of sporadic anovulation compared to low stress. Although it has long been demonstrated that severe stress in experimental settings or among individuals with certain stressors can adversely affect female reproductive function, this is the first study to demonstrate that daily stress among healthy women without known reproductive disorders is associated with a change in reproductive function. Findings regarding daily, but not baseline, perceived stress indicate that it is the latter that has the greatest impact on menstrual cycle parameters, including ovulation function [26].

The connection of perceived stress with reproductive hormones and the function of ovulation has significant consequences for a woman's health. It is known that changes in gonadotropins and gonadal steroids affect a woman's chance of becoming pregnant [26].

The Environment and Reproductive Health study, conducted at the Massachusetts Institute of Technology from 2005 to 2019 and involving 520 women, found that increased perceived stress was negatively associated with antral follicle count and serum levels of antimüllerian hormone. These associations were modified by several socio-economic factors [16]. Also, as part of the Environment and Reproductive Health (EARTH) study (2005-2019), another observational study was conducted with the participation of 645 women, which assessed the impact of comorbidities on reproductive function. It showed that a history of neurological disorders was negatively associated with the number of antral follicles [15].

Only a few prospective epidemiological studies have thoroughly investigated the stress-fertility hypothesis, with mixed results. Epidemiological studies of the relationship between stress among women and fertility report conflicting results. Two preconception cohort studies found an inverse association between salivary α -amylase levels, but not cortisol, and fertility, whereas studies of questionnaire-based measures of stress and fertility reported an inverse association with luteal phase psychological distress, feedback association with follicular phase stress, but positive association with luteal phase stress [1] or weak association [11]. Discrepancies between studies may arise due to different methods and timing of stress measurement [31].

None of the studies compared the effects of stress on different periods of the menstrual cycle. If stress affects the process of ovulation or fertilization, then stress in the follicular phase (especially during the ovulatory window) can affect fertility [12, 27] It is likely that if stress prevents implantation, then stress during the luteal phase will affect fertility [23].

A prospective cohort study of 400 women investigated the relationship between self-reported stress and fertility during the fertile window of the menstrual cycle. High stress

during the expected fertile window was statistically significantly associated with a 46% reduction in fertility. This effect is large enough to be considered clinically significant, as it represents a delay in conception of more than 3 months. The results of this study support a significant reduction in the ability to conceive during the ovulatory window for women who experience higher levels of preconception stress [1].

Conclusion and prospects for further developments

1. Every day, stress affects our lives more and more often, and more and more factors provoke it. This has significant consequences for the human body on various organs and systems and on the body as a whole.

2. Stress affects women's health through dysfunction

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ВПЛИВ СТРЕСУ НА ОВУЛЯТОРНУ ФУНКЦІЮ

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Анотація. Продемонстровано огляд наукової літератури, який розглядає проблему впливу стресу на овуляторну функцію. Психологічний стрес є розповсюдженим серед населення, а його наслідки для здоров'я були основною темою досліджень протягом останніх десятиліть. Він вважається вирішальним фактором у виникненні, перебігу та загостренні різних захворювань, наприклад, депресії, серцево-судинних захворювань, імунних розладів, і це було пов'язано з вищою загальною смертністю. Сьогодні все більше лікарів, у тому числі гінекологів, усвідомлюють величезний вплив різних видів стресу на здоров'я жінки, зокрема на репродуктивну систему. Метою цього аналізу стало вивчення впливу стресу на овуляторну функцію. Було проведено ретроспективний аналіз наукової літератури таких наукометричних баз, як Scopus, PubMed, ScienceDirect, UpToDate, Web of science. Під час пошуку інформації з питання зв'язку стресу та овуляторної функції використовувалися такі ключові слова "stress", "ovulation", "hormones", "menstrual cycle". При опрацюванні результатів пошуку обирали найновіші публікації (10 років) або останні публікації з даного питання (не залежно від часу публікації). Загалом під критерії включення потрапило 31 робота, які представлені в даному огляді. Проблема негативного впливу стресу на репродуктивне здоров'я жінок у практиці лікарів гінекологів усього світу стає все актуальнішою з кожним роком, адже все більше зростає рівень безпліддя, ранніх втрат вагітності та знижується народжуваність. Ці стани ще більше впливають на жінок та погіршують психоемоційний стан, та посилюють рівень стресу. Таким чином розуміння способів боротьби зі стресом є критично важливим для формування чітких алгоритмів профілактики впливу стресу на організм та надання медичної допомоги пацієнткам після його впливу, з метою збереження репродуктивного здоров'я.

Ключові слова: стрес, овуляторна функція, менструальний цикл, гормони.