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## MODERN ASPECTS OF ETIOLOGY, MECHANISMS, PATHOGENESIS AND DIAGNOSTICS OF OVARIAN FORMATIONS

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## СОВРЕМЕННЫЕ АСПЕКТЫ ЭТИОЛОГИИ, МЕХАНИЗМОВ, ПАТОГЕНЕЗА И ДИАГНОСТИКИ ОБРАЗОВАНИЙ ЯИЧНИКОВ

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*Abstract.* This review focuses on ovarian lesions. Ovarian tumors occupy the 3rd place among all tumors of the female genital organs, and 7th in the overall structure of malignant tumors, so the problem of timely diagnosis and treatment of ovarian lesions remains relevant. The share of benign ovarian tumors accounts for 70–80%. Among benign ovarian lesions, epithelial lesions are most common — taking up to 16% and cystadenoma up to 22.8%. Histogenesis of ovarian formations is not fully understood, which explains the contradictions in the origin of a particular tumor. For the first time, features of the mechanisms of neoplasm formation have been described by A. Knudson et al., his team was one of the first to develop and publish the theory of ‘double strike’, interpreting the mechanisms for implementing sporadic and hereditary forms of neoplasms. Ovarian cancer — both on the part of the etiology and the clinical picture of a heterogeneous genetically determined pathology. The basis of the emergence of this group of tumors is the mutation of the genetic apparatus of the cell. Yes, indeed, the diagnostic search for ovarian masses is difficult, and there is a perception that it may also be delayed due to an asymptomatic or asymptomatic course of the disease. The complex of diagnostic measures for ovarian formations should include interviewing patients with anamnesis data collection, clinical and special examination. Thus, in modern conditions, the diagnostic algorithm for searching ovarian formations requires an integrated approach to identify ovarian formations at early stages of development, as well as to conduct differential diagnostics with subsequent determination of the morphological structure of the tumor.

*Аннотация.* Данный обзор посвящен образованиям яичников. Опухоли яичников занимают 3-е место среди всех опухолей женских половых органов, и 7 в общей структуре злокачественных новообразований, поэтому проблема своевременной диагностики и лечения образований яичников остается по-прежнему актуальной. На долю доброкачественных опухолей яичников приходится 70–80%. Среди доброкачественных образований яичников наиболее часто встречаются эпителиальные образования — тератомы до 16% и цистаденомы до 22,8%. Гистогенез образований яичников изучен не до конца, чем и объясняются противоречия в происхождении той или иной опухоли. Впервые особенности механизмов возникновения новообразований были описаны А. Knudson, его команда одна из первых разработала и опубликовала теорию «двойного удара», интерпретирующую механизмы реализации спорадических и наследственных форм новообразований. Рак яичников — как со стороны этиологии, так и клинической картины гетерогенное генетически детерминированная патология. Основа возникновения данной группы опухолей — мутации генетического аппарата клетки. Диагностический поиск образований яичников сложен, и бытует мнение, что возможно является и запоздалым ввиду малосимптомного или бессимптомного течения заболевания. Комплекс диагностических мероприятий при образованиях яичников должен включать в себя интервьюирование пациенток со сбором данных анамнеза, общеклиническое и специальное обследование. Таким образом, в современных условиях диагностический алгоритм поиска образований яичников требует комплексного подхода для идентификации овариальных образований на ранних стадиях развития, а также проведения дифференциальной диагностики с последующим определением морфологического строения опухоли.

*Keywords:* ovarian formation, etiology, pathogenesis, mechanisms, diagnosis.

*Ключевые слова:* образования яичников, этиология, патогенез, механизмы, диагностика.

The problem of diagnosing and treating tumors and tumor-like formations of the ovaries is complex and extremely relevant, since ovarian tumors are a common gynecological pathology [1, p. 237]. Ovarian tumors occupy the 3rd among all tumors of the female genital organs, and the 7th among all malignant tumors. Most ovarian tumors are benign, accounting for 70-80%. Ovarian cancer is 4-6% among all malignant neoplasms. The frequency of ovarian tumors over the past ten years increased from 5,8-11,1% to 18,7-25,3% of all genital tumors [2, p. 200]. It has been established that over 170,000 new cases of ovarian tumors are recorded annually in the world. In the structure of the total gynecological morbidity, ovarian cancer takes 6-7 place [1, p. 240].

Among benign ovarian lesions, epithelial lesions are most common — cystadenoma up to 22.8% and teratoma up to 16% [3, p. 23].

Ovarian cysts make up an average of 18% in the structure of all ovarian formations, of which the number of follicular ones is 85-90%. A special group consists of paraovarian cysts — 4.9% and serozocle — 5,2%. They do not belong to the new ovaries, but it is difficult to distinguish them from ovarian tumors before surgery, so they were included in the group of ovarian formations [4, p. 218]. A certain group of tumor-like formations of the ovaries is made up of tubo-ovarian formations of inflammatory genesis. Inflammatory diseases of the uterus, significantly affect the health of women of reproductive age. In the past few years, there has been a clear trend towards an increase in the incidence of inflammatory diseases of the uterus. Very sad is the picture of the survival of patients with ovarian cancer. One-year survival of women with verified ovarian cancer is 60% during the first year, i.e. every 3rd patient dies; three-year survival is 43%; five-year survival is less

than 34%. One of the probable circumstances of such a low survival rate is the almost asymptomatic course of the disease in its early stages, the absence of pathognomonic signs, and ineffective treatment, especially in cases of relapse.

Thus, according to various authors, inflammatory processes of the internal genital organs make up 60-65% among outpatients, and up to 30% among inpatients [5, p. 560]. Up to 15-25% of women acute inflammatory processes occur with complications. Often the development of tubo-ovarian formations, the formation of abscesses is the result of irrational pharmacotherapy. Purulent inflammatory diseases of the uterus can develop at any age, but they are significantly more common in women of childbearing age, with the highest incidence occurring at 31-40 years of age. According to the International Agency for Research on Cancer, more than 200,000 cases of ovarian cancer are reported every year in the world. In Russia, ovarian cancer is detected in more than 12,000 women. Due to the late diagnosis of 60-72% of women, ovarian cancer is detected already in the later stages, when the use of radical methods of treatment is almost impossible. This is due to the lack of clear pathognomonic symptoms characteristic of the early stage of the disease. A significant proportion of ovarian tumors develop in women in the age group of 30-60 years, significantly more often among women older than 40 years. This pathology often leads to impaired menstrual, reproductive, sexual function and often leads to disability of the woman. These changes are one of the main causes of disability, which causes tremendous medical and social significance.

Differential diagnosis of tumors and tumor-like formations of the ovaries is extremely important, since it determines the tactics of patient management in each particular case.

In modern conditions, one of the leading places among the methods for diagnosing tumors of the pelvic organs is ultrasound, which, in combination with Doppler sonography, allows us to differentiate the types of appendage formations with great accuracy and evaluate the characteristics of the blood flow in them. In the past few years, immunoassay methods have been firmly introduced into clinical practice, allowing to detect specific proteins synthesized by tumors of various origins, the so-called tumor-like markers BRCA1, BRCA2, P53, STK 11, RAD51C, DICER, CA-125, CEA, CA-50 and a lot others. The most commonly used in gynecology practice is the CA-125 marker, the definition of which can act as a screening method that allows monitoring the results of treatment.

Today, there are two main approaches to the diagnosis and treatment of tumors and tumor-like formations of the ovaries: laboratory and laparoscopic. In recent years, endoscopic methods of research and treatment of ovarian tumors have been increasingly introduced into clinical practice. Among endoscopic methods, special importance is attached to laparoscopy, as the most informative study.

But, despite the progress made in identifying ovarian tumors, the pre-operative determination of the true nature of ovarian education still encounters considerable difficulties, which may entail the use of irrational patient management tactics. To this day, the development and improvement of methods for visualizing ovarian formations continues.

Thus, in modern conditions of diagnosis of tumors and tumor-like formations of the ovaries can not be based on one method of research, but requires an integrated approach to identify ovarian formations in the early stages of development, as well as the differential diagnosis of benign or malignant process and determination of the morphological structure of the tumor.

Ovarian cancer — both from the etiology and clinical picture of a heterogeneous genetically determined disease. The basis of the emergence of this group of tumors is the mutation of the genetic apparatus of the cell.

The mechanisms of the origin of tumors were first described in 1971. A. Knudson, he was one of the first to propose the theory of "double blow", interpreting the mechanism of the occurrence of hereditary and sporadic forms of malignant neoplasms. For the occurrence of a tumor, 2 events are

required: a mutation in germ-line cells and a mutation in a somatic cell. Today, the concept of the genetic nature of malignant neoplasms is widely recognized. It has been proven that tumors have a monoclonal origin.

The causes of most ovarian tumors are still unknown. Histogenesis of ovarian tumors, including benign ones, is not fully understood, which explains the controversy about the origin of a particular tumor.

In recent years, the role of genetic factors in the etiology of ovarian tumors has been revealed. The study of heredity leads to the conclusion about the unusual complexity of the interaction of genetic factors and the environment. Genetic factors that cause the control of enzyme activity, immune and hormonal status, affect the degree of DNA damage. Hereditary defects predisposing to the occurrence of malignant tumors are those associated with DNA repair, they are extremely rare. The concept of genetic predisposition to hormone-dependent tumors means inheritance of constitutional and endocrine-metabolic features, such as disorders of ovulation and steroid sex hormone metabolism, metabolic syndrome, diabetes mellitus, by recessive type.

The individual's ability to metabolize carcinogenic substances into the body affects the risk of tumors. The most studied enzymes that affect the metabolism of carcinogenic substances are enzymes encoded by the genes of the cytochrome P450c17A family catalyzing steroidogenesis, namely 17A hydrolase and 17, 20-lyase.

According to one theory, the risk of developing ovarian tumors is directly dependent on the number of ovulatory cycles throughout a woman's life. The intestinal epithelium of the ovary, from which most tumors develop, undergoes proliferation and repair after each ovulatory cycle. The greater the number of ovulations, the higher the potential risk of abnormalities in reparative processes, which leads to tumor transformation.

Direct evidence of the mutational nature of ovarian cancer is the discovery of proto-oncogenes, oncogenes, and suppressor genes. Transformation of proto-oncogenes into oncogenes occurs as a result of the mutation coding sequence of the proto-oncogene, which leads to the formation of increased expression of the proto-oncogenes, in addition to this, inhibition of suppressor gene initiation (anti-oncogenes) occurs — proteins inhibiting and preventing tumor growth. Unlike oncogene, mutant alleles of suppressor genes are recessive.

The effect of physical activity on the occurrence of tumors of the reproductive system was studied. Persons who are not involved in sports, get sick 2-5 times more often than actively engaged. The latter indicates the need for active physical training in the period of adolescence.

In the history of patients with benign ovarian tumors, a high frequency of chronic inflammatory processes and surgical interventions on the pelvic organs. Back in the early 2000s, Cottreau C. & Ness R.B. hypothesized that the basis of the impact of most risk factors are inflammatory processes. Inflammation leads to potentially mutagenic processes, such as DNA repair, oxidative stress, receptor desynchronization, which in turn is associated with an increase in the titer of pro-inflammatory cytokines, which also leads to negative effects. The identification of inflammatory cytokines, growth factors and chemokines in ovarian tumors confirms the above.

Significant achievements include the discovery of the BRCA genes 1, 2, which determine the hereditary predisposition to ovarian cancer. The BRCA 1 gene was detected at the chromosome 17q21 locus. To date, over 800 mutations have been identified [6, p. 27].

Analysis of concomitant extragenital pathology in case of ovarian tumors showed that its frequency increases with the age of patients. Of the conditions of the body, most often leading to the occurrence of ovarian tumors, are often metabolic syndrome, diabetes mellitus and thyroid pathology. In this connection, it is justified to form risk groups for the development of ovarian tumors, which include women with menstrual disorders, not having sex, not pregnant, not giving

birth, long-term dispensary patients with chronic inflammation of the uterus, with burdened heredity.

In the occurrence of ovarian tumors, an important role is played by changes in hormonal relationships, as many studies have noted that quantitative disturbances in the ratio of hormones lead to tumor growth.

Tropic hormones of the anterior pituitary gland regulate the work of the sex glands. In turn, the production of tropic hormones is stimulated by the releasing hormones of the hypothalamus. The hormones in the ovaries and the correlation with the hypothalamic-pituitary system are in direct communication, and proceed according to the laws of positive and negative feedback. Sex hormones, depending on their concentration and ratio with other hormones, suppress or initiate the production of the corresponding tropic hormone of the pituitary gland. This mechanism actually allows maintaining the titers of hormones of peripheral endocrine glands in the blood within the physiological balance.

The early hypothesis of the alternate functioning of + and — feedback was predominant: in the follicular phase there is + feedback that ensures the growth of the dominant follicle, and only in the luteal phase are the feedback mechanisms activated. It is now known for certain that the cyclical nature of work is a property of the ovaries themselves, and not of the regulatory centers, and both the positive and negative feedback mechanisms function continuously. Negative communication is regulated at the level of the hypothalamus and is manifested by increased secretion of GnRH with a decrease in the level of estrogen in the blood below threshold values [7, p. 3]. A positive connection is manifested by a brief increase in the secretion of gonadotropins by the pituitary gland in response to a sharp increase in the level of estrogen in the blood.

Hormonal status is a factor in determining the risk of many tumors, especially the ovaries. A tumor is formed in the process of excessive (increased) hormonal stimulation of an organ, the normal growth, development and function of which is under the control of one or another steroid or polypeptide hormone.

The mechanism of tumor formation can be represented as follows: the primary weakening of ovarian function with a decrease in estrogen levels, a compensatory increase in the level of pituitary gonadotropins, primarily FSH [8, p. 1139]. In the conditions of a prolonged increase in the secretion of FSH in the ovaries, first diffuse then focal hyperplasia and proliferation of cellular elements occur, which can result in the formation of a tumor.

The implementation of these processes is due to the exceptional interaction with steroid receptors. Hormonal receptors are highly specific protein structures of the respective target tissues that bind certain hormones. Binding of hormones to receptors is a starting stage in the realization of the hormonal effect [9, p. 30]. So, according to modern concepts, hormones do not directly lead to tumor transformation, because they do not change the primary structure of DNA. Hormones can trigger the activation of tumor growth. In intact ovaries, the target tissue of the action of estrogen is granulosa cells of the follicles. They contain estradiol and progesterone receptors. In addition, they contain membrane receptors of FSH, which stimulates the secretion of estrogen. The highly consistent receptors of steroid hormones in target tissues confirm the role of hyperestrogenism in the complex mechanisms and pathogenesis of hormone-dependent tumors.

Tumor formations of the ovaries represent a separate group and, by their structure, these are cysts that form in preformed cavities and cause a significant increase in the ovary, follicular cysts are formed in women with endocrine-metabolic disorders, against which hyperestrogenism and anovulation (single-phase menstrual cycle) develop. Yellow cysts occur only during a two-phase menstrual cycle, due to impaired blood and lymph circulation in the corpus luteum. A characteristic feature of cysts is that they are not capable of proliferation.

Speaking about the formations of the ovaries, it is impossible not to touch upon the aspects of diagnosis. Yes, indeed, the diagnosis of tumors and tumor-like formations of the ovaries is difficult and possibly belated due to an asymptomatic or asymptomatic course of the disease.

The complex of diagnostic measures for benign tumors and tumor-like formations of the ovaries includes the collection of anamnestic data, general clinical and special examination.

With a two-handed gynecological examination, it is possible to identify the tumor and determine its size, consistency, mobility, sensitivity, location in relation to the pelvic organs, the nature of the tumor surface. Palpation can only identify a tumor that has reached a certain size when it increases the volume of the ovary. Tumors during a bimanual examination are defined as a round or ovoid-shaped mass, located laterally or posteriorly from the uterus, a tight elastic texture, mobile or restricted, mobile, sensitive or painless on palpation, 5–20 cm in diameter [10, p. 590].

When vaginal examination in patients with purulent inflammatory formations of the pelvic organs is determined by the formation of fuzzy contours, uneven consistency, complete immobility and severe pain. Most often, the formation is in a single conglomerate with the uterus, palpation and the definition of which is difficult.

Considering that a pelvic examination is not informative with a small tumor and its atypical location, during examination of patients, preference should be given to additional diagnostic methods, such as ultrasound with color Doppler mapping and laboratory methods, namely tumor markers. For example, now the definition of the CA-125 tumor marker in the serum is considered non-informative, as a screening method [11, p. 182]. This marker is not a true tumor marker, as it is synthesized by both normal and malignant cells. The increase in serum CA-125 in patients with benign and especially malignant tumors, as well as with other diseases, is probably determined by the increase in the number of rapidly dividing cells synthesizing it. It is argued that the average CA-125 levels are different for women belonging to different ethnic groups, but the data obtained by independent research groups contradict each other. The level of CA-125 in the serum of women varies significantly throughout the menstrual cycle. It increases during menstruation, then there is a gradual decrease in the titers of this marker. According to some researchers, the concentration of CA-125 is equally low follicular and luteal phases, while others believe that a gradual decrease in its level to border values only in the luteal phase.

As a pre-morphological diagnosis of benign and malignant ovarian tumors is performed on the basis of transvaginal echography and the cumulative determination of CA-125 and HE4 with index calculation (ROMA). Oncomarkers CA-125 is a marker of malignant tumors of the ovaries and epithelial tumors of other localization. As an additional marker, HE4 shows the best results, which is more sensitive and specific. Than CA-125, its specificity reaches 73-75%. Oncomarkers specific for germ cell tumors of the ovary are: human chorionic gonadotropin, alpha-fetoprotein, lactate dehydrogenase. At present, the role of additional tumor markers has not been proved: cancer embryonic antigen, CA 72-4, CA 19-9, beta chorionic gonadotropin.

Laparoscopy has a high diagnostic value. Diagnostic laparoscopy is used in cases when difficulties arise in the differential diagnosis of a tumor and tumor-like formation of the ovary, since in this case it is possible to directly visualize the internal organs. During laparoscopy, the initial localization of the formation is determined, the degree of spread of the pathological process, differential diagnosis is made between tumors of the uterus and its appendages, between the retroperitoneal and ovarian formations. According to various authors, the accuracy of diagnosis of ovarian tumors using laparoscopy is in the range of 70-100%. At the same time, the maximum number of erroneous conclusions is connected with the adhesive process, which makes it difficult or impossible to inspect the pelvic organs and to obtain material for cytological and histological examination.

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