ETIOPATHOGENESIS OF DYSPLASTIC PROCESSES OF THE CERVIX

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Abstract: Cervical dysplasia (intraepithelial neoplasia) is a pathological change in the epithelium covering it. Atypical cells appear among healthy cells. They have an abnormal structure, size, shape, and development program. Such cells disrupt the structure of the epithelial layers. The peak incidence occurs at the age of 25-35 years. Dysplasia is considered a precancerous tissue change, but at an early stage the process is reversible. The disease is insidious - obvious clinical symptoms are absent for a long time. Simple screening, which is part of a preventive examination, helps to detect it at a safe stage.

According to WHO, the transition from dysplasia to cancer in situ lasts approximately 3-8 years, then microinvasive cancer develops within 10-15 years. Dysplasia of the cervix is detected during preventive examinations in 0.2-2.2% of cases, while the frequency of dysplasia against the background of ectopia reaches 8.5% [1, 3, 4]. In this regard, one of the main preventive measures in the complex to prevent the development of cervical cancer is the timely detection and treatment of non-neoplastic diseases of the cervix. General cytological screening is the most important condition for the early detection of cervical cancer [5]. Currently, the oncological aspect of gynecological diseases is considered inextricably linked with the endocrine function of the reproductive system [4]. Therefore, in recent years, data have appeared on the role of functional hormonal disorders in the pathogenesis of cervical cancer diseases.

In the 90s of the 20th century, research data were published confirming the role of absolute or relative hyperestrogenism in the genesis of cervical leukoplakia. An increase in the gonadotropic function of the pituitary gland, a violation of estrogen metabolism with a predominance of estradiol content, changes in the ratio of deoxygenated and oxygenated forms of 17-ketosteroids towards an increase in the content of the latter were shown. Progression of the degree of cervical neoplasia against the background of hyperestrogenemia was noted. Other studies have shown that

hyperestrogenism contributes to the development of cervical cancer, and progestins block the tumor initiation phase [6]. The main link that plays an exceptionally important role in the development of neoplastic processes in the so-called estrogen-sensitive tissues, including the cervical epithelium, are estrogens. Estradiol is one of the most active female sex hormones, has a high affinity for estrogen receptors and, interacting with them, has a significant effect on the metabolic and proliferative activity of cervical epithelial cells.

Thus, the trigger mechanism in the development of cervical pathology in diabetes mellitus is an autoimmune lesion of the ovaries with the formation of autoantibodies to their tissue. The content of estradiol naturally decreases, which leads to a decrease in the pulse secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus and, accordingly, the secretion of luteinizing and follicle-stimulating hormones (LH and FSH) by the pituitary gland. In this case, the effect of GnRH on FSH is less pronounced than on LH. Under these conditions, the sensitivity of the ovaries to FSH decreases, causing a secondary decrease in the release of LH, hypoestrogenism and anovulation. In this case, ovarian granulosa cells, under conditions of frequent exogenous insulin administration and often its overdose, intensively secrete and release inhibin, which suppresses the secretion of FSH and increases the LH/FSH ratio. And against the background of existing insulin resistance, all of the above leads to the emergence of secondary polycystic ovaries.

It should be noted that the ovaries, in addition to specific receptors for gonadotropins, also have receptors for insulin, the action of which through insulin-like growth factors enhances LH-dependent synthesis of androgens and reduces the production of testosterone-estrogen-binding globulin. At the same time, the level of free testosterone in the blood increases, and the developing resistance to insulin independently stimulates the conversion of estrogens into androgens, leading to even more pronounced hypoestrogenism and hyperandrogenism . In addition, poorly controlled diabetes is often accompanied by an increase in the level of counter-insular hormones, such as cortisol, somatotropic hormone, ACTH, stimulating the function of the adrenal glands and manifestations of hypercorticism. The cytochrome P-450

enzymatic system ensures the conversion of estradiol into two main metabolites: 16a-hydroxysterone (16a-OH) and 2-hydroxysterone (2-OH). The first of these belongs to the category of aggressive hormones that cause a long-term effect (there is evidence that 16a-OH is capable of forming covalent bonds with the receptor, i.e., interacting with it irreversibly).

The second metabolite, 2-OH, has moderate functions and normalizes cell growth. It has long been noted that tissue changes in the cervical canal caused by HPV are localized mainly in estrogen-sensitive zones. Moreover, it has been established that where there is active expression of HPV proteins, there is a high level of 16a-OH synthesis, comparable to that in breast cancer cells. It should be noted that normally, cervical epithelial cells are unable to convert estradiol into 16a-OH. Thus, active reproduction of HPV induces the formation of an aggressive metabolite in infected cells. Infected human keratinocytes exhibit proliferative activity in vitro, but do not have a tumor phenotype when examined microscopically. Addition of exogenous 16a-OH to the culture medium transforms the cells into typically cancerous ones. Based on this, it becomes clear that infection of epithelial cells with HPV is a necessary but not sufficient condition for cancerous degeneration. The following conditions are necessary for the formation of irreversible neoplasia: 1) active expression of the E6 and E7 genes of the virus; 2) induction of metabolic mechanisms of estradiol conversion to 16a-OH; 3) induction of multiple damages to chromosomal DNA in the infected cell, which completes the degeneration process. The key role of 16a-OH in the cancerous degeneration of HPV-infected cells is confirmed by direct studies on cervical epithelial cells and cervical carcinoma. According to some data [12], one of the main mechanisms of malignancy of HPV-infected cells is that the virus modifies cellular metabolism in such a way that the cell acquires the ability to convert estradiol mainly into 16a-OH, which is a direct activator of the E7 gene expression, responsible for the tumor transformation of cells. Thus, a vicious circle is formed, in which the virus (through the formation of an aggressive form of estradiol) creates favorable conditions for the development of a tumor, stimulating the synthesis of the oncoprotein E7. The latter, in turn, on the one hand, activates the mechanisms of pathological cell proliferation, and on the other, blocks the mechanisms of development of immune defense [2, 3, 9].

In addition, with prolonged estrogen deprivation, estrogen receptors change qualitatively, becoming more sensitive to estrogens and at the same time providing selective activation of certain genes, which confirms the hypothesis of the so-called impaired receptor sensitivity in target organs in women with endocrinopathies and, in particular, with diabetes.

Most researchers agree that tumor transformation (initiation) occurs under the influence of direct carcinogenic effects, while hormones can cause activation of tumor growth [1,6]. Based on the above, some researchers distinguish two types of hormonal carcinogenesis: promoter and genotoxic.

The first of them is in a certain sense "natural" and is realized in the case of excessive hormonal stimulation based on the physiological (often mutagenic) effects of hormones. In the genotoxic variant, hormones or their metabolic products behave as true carcinogens. According to modern concepts, the transformation of estrogens into catecholestrogens and subsequent metabolites during free-radical reactions is the basis for the implementation of DNA-damaging hormonal effects. The risk of the transition of the promoter variant to the genotoxic one increases when an enhanced hormonal signal is superimposed on the influence of certain environmental factors (for example, tobacco smoke).

According to researchers studying hyperplastic processes of hormone-dependent organs of the female reproductive system, the uniformity of the premorbid background in patients with various combinations of benign diseases of the female genital organs suggests similarity of the pathogenetic mechanisms of their development. This can probably explain the frequent sequential detection of these pathological conditions during a woman's life. Immunohistochemical studies conducted by the authors [7] showed that the unchanged epithelium of the cervix contains receptors to estrogens, which are localized in the nuclei of the basal and parabasal cell layers. It is known that the cells of these layers of the ectocervix have mitotic activity, which increases as the level of estrogens in the blood increases. In dyskeratosis of the cervix, a sharp increase in the number of cells with receptors to estrogens and pronounced expression of the

latter in the cell nuclei is noted, combined with hyperplasia of the parabasal layer cells and acanthosis phenomena with the formation of stromal papillary structures. Considering the fact that HPV requires actively proliferating cells of the parabasal epithelial layer for its introduction, the number of which increases sharply against the background of hyperestrogenism, this pathological condition should be considered as one of the factors contributing to the formation of neoplastic lesions of the cervix [17, 18, 20]. It should be noted that at the present stage, hormonal drugs (combined oral contraceptives - COCs, drugs for hormone replacement therapy) are often used to treat dysfunctional disorders in the female reproductive system. Hormonal contraceptives affect various parts of the reproductive system, including the cervix. However, studies devoted to the study of the state of the cervix during the use of COCs, although numerous, are very contradictory [4,8,12].

The results of some studies indicate a high risk of dysplastic changes in the ectocervix, others - the absence of this connection, and still others - the disappearance of even dysplastic changes with the use of COCs [10,13]. Apparently, such inconsistency is associated with the different contingent of those examined, the heterogeneity of the groups, failure to comply with clear inclusion and exclusion criteria, as well as the use of exogenously administered sex steroids of different composition and dose by the researchers. Along with numerous supporters of the concept of systemic hyperestrogenism, there are also supporters of the concept of local, or organ, hyperestrogenism. A group of scientists headed by G. A. Savitsky in 2001-2003 examined 600 patients who had undergone surgery for uterine fibroids. They compared the content of sex steroids in the blood from the cubital and uterine veins. In the examined subjects, the concentration of the main sex steroids in the general bloodstream was close to normal, while the level of estradiol and progesterone in the uterine veins exceeded the norm by 2-3 times.

In addition, the content of estradiol and progesterone in the blood from the tubal-uterine arterioles was determined several times. The content of sex hormones in these portions of blood was 2-8 times higher than in the blood from the cubital vein. From the point of view of R. Hunter (2004), the discovered differences in the concentration of sex

steroids in different vascular circuits are evidence of the existence of a countercurrent "transfer" mechanism of hormones from the ovarian veins to the arterial vascular circuits of the ovary and fallopian tube, which ensures the flow of high concentrations of hormones to certain areas of the internal genital organs. Thus, long-term clinical studies and experimental data suggest that in the female body there is a relatively independent subovarian system of regulation of tubal-uterine, in particular hormonal, homeostasis, associated with anomalies in the concentration-time parameters of specific hormonal regulation [2,6]. According to J. Liehr (2004), the source of qualitative changes in estrogen production, including the formation of catecholestrogens, can be the processes of local and/or intra-tissue metabolism [12, 13]. And disturbances in hormone sensitivity can be expressed both by shifts in the number of receptor molecules and by changes in their spatial configuration, as well as by features of conjugation with a significant number of post-receptor mechanisms [2,3].

At the present stage, the study of the role of endocrine factors in the mechanisms of cervical dysplastic processes is promising. Unfortunately, neither in domestic nor in foreign literature are there any studies devoted to the study of the development of cervical pathology in women with diseases of the endocrine glands.

In connection with the above and taking into account the accumulated factual material, this area, in our opinion, is of great scientific interest.

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