PRECANCER CERVICAL DISEASES AND PREGNANCY

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Abstract. *The purpose of the review: to summarize the current knowledge on the diagnosis and treatment of precancer of the cervix during pregnancy. The article presents a review of the literature on epidemiology, classification, developmental risk factors, symptoms and diagnosis, principles of treatment of precancerous diseases of the cervix, management of pregnant women with this pathology.*

Keywords: *precancer and cervical cancer, etiology, risk factors, pregnancy, principles of management.*

The problem of studying pathological conditions of the cervix, their diagnosis and treatment, especially during pregnancy, remains relevant in protecting women's health. It is well known that oncological processes of the reproductive system occupy a significant place, occurring in 10-15% of women of reproductive age. Cervical cancer (CC) ranks second after breast cancer and in advanced stages (III-IV) is diagnosed in 25-40% of cases of malignant neoplasms of the female genital organs and mammary glands. CC ranks third in the world [21,42] and third place in the Russian structure of gynecological oncological morbidity [4-6]. In the Russian Federation, in 2016, the incidence of cervical cancer over the previous 30-year period reached its maximum value - 15.45 per 100,000 women [6] in the age groups 25-29 years and 30-34 years (cervical cancer ranks 1st place - 19.82% and 23.31%, respectively [4].

During pregnancy, CC is detected in the early stages three times more often than in the general population. CC ranks first in prevalence among tumors of the reproductive organs detected during pregnancy. In Russia, the frequency of detection of cervical cancer during pregnancy ranges from 1:2000 to 1:5000, preinvasive carcinoma in situ - 1:770 pregnant women [10]

Cervical cancer detected within 6 months after termination of pregnancy and 12 months after childbirth is classified as pregnancy-associated tumors, because clinical and morphological manifestations of the tumor process are already present during pregnancy. Among patients with cervical cancer, the frequency of combination with pregnancy is 1-3%. The average age of patients with cervical cancer in combination with pregnancy is 30 years [9].

According to foreign literature, cervical atypia (ASC-US, ASC-H, SIL) during pregnancy varies between 0.13% and 6.8% [13,44].

Cervical intraepithelial neoplasia, CIN) II, III degrees, Ca in situ, equivalent according to modern classification to severe dysplasia (HSIL, high grade squamous intraepithelial lesions), is a preinvasive cervical cancer with a risk of progression to an invasive process in pregnant women from 1.1 to 3.6% [26]

Prevalence of CIN in pregnant women as opposed to invasive cancer cervix is higher and is 13.0 cases per 10,000 [13].

The problem of choosing different types of diagnosis and treatment of cervical pathology and the impact of this pathology on the course and outcome of pregnancy is of paramount importance. In the majority of first-time mothers, benign diseases of the cervix, including cervical

intraepithelial neoplasia (CIN), are discovered only during pregnancy. The incidence of CIN is observed in 5–8% of pregnant women [14,19].

The main place in clinical practice is prevention, early diagnosis and improvement of treatment methods for patients with benign and precancerous diseases, as well as pre-invasive cervical cancer.

Benign diseases are diseases of different morphology and etiology that do not pose a threat to a woman's health and are not accompanied by the appearance of cellular atypia and impaired stratification of the epithelial layer.

Benign diseases include ectopic columnar epithelium, polyps, papillomas, endometriosis, true erosion, cervicitis, cicatricial deformation of the cervix, leukoplakia [7].

Precancer is a disease characterized by proliferation, atypia of cells of the epithelial layer and disruption of its stratification (layering).

There are several classifications of cervical diseases. In the International Statistical Classification of Diseases (ICD), 10th revision (1992), the pathology of cervical cancer is presented as follows:

ICD 10 classification

N72 Cervicitis

N84.1 Cervical polyp

N86 Erosion and ectropion of the cervix, included decubital (trophic) ulcer, cervical eversion, excluded connection with inflammatory disease of the cervix, including cervicitis, endocervicitis, exocervicitis (N72)

N88.0 Leukoplakia of the cervix

N87 Cervical dysplasia (cervical intraepithelial neoplasia), carcinoma in situ of the cervix excluded (D06)

N87.0 Mild cervical dysplasia, cervical intraepithelial neoplasia grade I (CIN I).

Low grade squamous intraepithelial lesions (LSIL).

N87.1 Moderate cervical dysplasia, includes cervical intraepithelial neoplasia grade II (CIN II)

N87.2 Severe cervical dysplasia, not included in other specified groups of diseases, excludes cervical intraepithelial neoplasia grade III (CIN III) with and without indication of severe dysplasia and carcinoma in situ of the cervix (D06)

D06 Carcinoma in situ of the cervix

However, the term cervical erosion and cervical pseudo-erosion are still used. Currently, the term "pseudo-erosion of the cervix" has been replaced by "ectopia". Precancerous diseases of the cervix include:

N87 cervical dysplasia (carcinoma in situ of the cervix is excluded);

N87.0 Cervical intraepithelial neoplasia grade 1 (CIN 1, mild cervical dysplasia);

N87.1 Cervical intraepithelial neoplasia grade 2 (CIN 2, moderate cervical dysplasia);

N87.2 Cervical intraepithelial neoplasia grade 3 (CIN 3, severe cervical dysplasia);

D06 Dysplasia with keratinization; carcinoma in situ of the cervix.[1].

Histological classification of dysplasia [15, 24].

Cervical intraepithelial neoplasia (CIN) is divided into:

♦ CIN I - mild dysplasia; ♦ CIN II - moderate dysplasia;

♦ CIN III - severe dysplasia and pre-invasive cancer.

Precancerous diseases of the cervix are a number of pathological conditions that, under certain conditions, can transform into cervical cancer. A distinctive feature of precancerous diseases of the cervix is that they occur with epithelial dysplasia - its hyperplastic transformation, proliferation, impaired differentiation, maturation and exfoliation. However, unlike cervical cancer, all of these cellular changes are limited to the basement membrane.

Dysplasia (atypia of the cervical epithelium) is characterized by intense proliferation of atypical cells. There are mild (CIN-I), moderate (CIN-II) and severe (CIN-III) dysplasia. With mild dysplasia, cells of the deep - basal and parabasal - layers are affected (less than 1/3 of the thickness of the stratified epithelium); There are no atypical cells. Moderate dysplasia is characterized by changes in 1/3-2/3 of the thickness of the epithelial layer; no atypia is observed. In severe dysplasia, hyperplastic cells account for more than 2/3 of the thickness of the epithelial layer; cells of atypical structure are found

Moderate and severe dysplasia more often degenerates into cancer. The frequency of transition of pronounced untreated dysplasia to pre-invasive and invasive cancer is 20-30%. Thus, the precancerous condition of the cervix (dysplasia) is borderline and has the ability to transform into invasive cancer.

Precancer and subsequently cervical cancer is formed against the background of benign non-tumor disorders of the stratified squamous epithelium.

All risk factors for cervical diseases are traditionally divided into exogenous (environmental) and endogenous (genetic).

Hereditary factor Features of the formation of menstrual function. With early menarche and early puberty, the risk of developing cervical diseases increases by 5-7.5 times. Features of sexual history. Early onset of sexual activity during puberty or before age 18; having multiple sexual partners; and having a male partner who has had multiple sexual partners, all of which increase a woman's risk for reproductive system infection. The latter aggravates the course of background diseases and therefore serves as a factor in carcinogenesis.

Reproductive function of a woman In this case, traumatic injuries to the cervix that occur after childbirth or abortion are important (the predisposing factor is a violation of trophism and innervation of tissue), as well as barrier contraceptives and vaginal tampons such as Tampax. With high reproductive activity (many pregnancies with different outcomes) in young women (under 30 years of age) and early menopause (before 45 years of age), the risk of developing cervical cancer increases.

Inflammatory diseases of the genitals create a background for the occurrence of precancerous conditions. The human papillomavirus (HPV) is of particular importance in the occurrence of cervical dysplasia. V.A. Ershov [3] proved the leading role of HPV genotype 16 in the genesis cervical neoplasia in women of St. Petersburg. It has now been proven that cervical cancer is an HPV-associated disease. to high cancer risk - 16, 18 and 31 types of virus. HPV types 16 and 18 have the highest oncogenic potential and are the most virulent.

The state of hormonal homeostasis and its disorders. increased gonadotropic function, changes in estrogen metabolism with a predominance of estradiol, an increase in oxygenated forms of 17-keto steroids. Use of COCs with a high content of gestagens.

Immune disorders are characterized by an increase in the level of cytotoxic T-lymphocytes. The degree of dysplasia is proportional to the level of immunosuppression. Women receiving

immunosuppressive therapy for autoimmune diseases, cancer, or organ transplantation are at increased risk of cervical dysplasia, which progresses to cervical cancer [18, 11].

Age-related changes in the genital organs. Smoking increases the risk of developing many types of cancer, including cervical cancer [40], and quitting smoking reduces the risk of developing CIN III and cervical cancer [39].

Body weight. Overweight women had a 25% increased risk of developing cervical cancer, while moderately obese women had a 70% increased risk [31].

Symptoms and diagnosis of precancerous diseases of the cervix. A feature of precancerous diseases of the cervix is the asymptomatic or nonspecific clinical manifestations; Sometimes watery leucorrhoea, contact or intermenstrual bleeding is observed. Early diagnosis is the detection of a tumor in the intraepithelial stage. Prognosis and timely diagnosis of the oncological process gives patients a chance to completely recover from this pathology. It is important to correctly assess complaints, medical history, conduct bacterioscopic and bacteriological examination of discharge from the vagina, cervical canal, urethra, colposcopy, cytological and histological examination.

The standard classification of cytological examination of cervical smears according to Papanicolaou includes 5 classes:

Class 1 - no atypical cells;

Class 2 - changes in cellular elements are caused by an inflammatory process in the vagina or cervix;

Class 3 - there are single cells with an altered ratio of nucleus and cytoplasm; a repeat smear or biopsy is required, followed by cytological examination;

Class 4 - cells with signs of malignancy were found: with enlarged nuclei, basophilic cytoplasm, uneven distribution of chromatin;

Class 5 - the smear contains numerous atypical cells.

Bethesda classification [24]:

• low grade of intraepithelial lesions (LSIL-squamous Intraepithelial lesions low grade), which corresponds to CIN I;

• high degree of intraepithelial lesions (HSIL-squamous Intraepithelial lesions high grade), which corresponds to CIN II-III;

• ASCUS (atypical squamous cell of undetermined significance) - squamous epithelial cells with atypia of unknown significance. Additional examination or follow-up is recommended.

WHO [41] recommends HPV testing, cytological and visual examination using acetic acid as screening at least once for every woman in the target age group: 30-49 years.

According to global recommendations, prenatal care includes cytological monitoring, colposcopic examination with targeted biopsy if an invasive process is suspected and is safe and a reliable method, according to foreign and domestic experts. Cone biopsy during pregnancy is associated with complications such as miscarriage, bleeding, premature birth.

Colposcopic assessment during pregnancy is difficult due to physiological, pregnancy-related metaplastic changes, which may resemble the appearance of intraepithelial lesions of the cervix after the use of acetic acid. Typical changes during pregnancy include cervical cyanosis and hypertrophy and swelling of the endocervical glands. In addition, extensive immature metaplasia often causes intense acetowhite staining after application of acetic acid.

The main purpose of colposcopy for pregnant women is rule out invasive cancer and delay biopsy and definitive treatment until postpartum. During pregnancy the best method diagnosis is only cytological and colposcopic examination without histological confirmation. According to the recommendations of the NHSCSP (The National Health Service of Cervical Screening Programme), women who have cytologically detected LSIL during pregnancy should have a repeat colposcopy 3 months after birth. If there is a suspicion of HSIL, colposcopy is recommended at the end of the second trimester, but if the gestational age has passed the 2nd trimester, then the study should be carried out three months after delivery. If an invasive process is suspected clinically or colposcopically, a biopsy is recommended [35].

When comparing cytological and colposcopic studies within the same severity level, the correspondence was 91%, when comparing colposcopic and histological diagnosis - 95%.

Colposcopic targeted biopsy has been shown to be safe and a reliable method in pregnant women [23]. In Europe, cervical biopsy is regulated in cases where an invasive process is suspected, both clinically and colposcopically [35]. According to American Society of Colposcopy guidelines and cervical pathology (American Society for Colposcopy and Cervical Pathology, ASCCP) for pregnant women with CIN 1, in whom CIN2+ is cytologically or histologically excluded at initial colposcopy, postpartum observation is recommended. Additional colposcopic or cytological examination is not necessary. In cases of CIN 2-3 and the exclusion of an invasive process, colposcopic and cytological examinations are recommended at intervals of no more than 12 weeks. A repeat biopsy is performed if the clinical picture worsens or if invasive cancer is suspected cytologically. Once invasive cancer has been excluded, treatment is considered inappropriate and re-evaluation is recommended 6 weeks after delivery [33]. The literature notes that if the excisional biopsy depth is less than 10 mm, the relative risk of preterm birth before 37 weeks is significantly lower than if the excision depth is greater than 10 mm [29]. Ortoft G. et al. noted a 2.8-fold increase in perinatal mortality after one conization and a 10-fold increase in preterm birth after two conizations [37].

Treatment of cervical diseases

Mild dysplasia such as CIN I or LSIL may resolve without treatment, but close monitoring at regular intervals, usually 6–12 months, is necessary, and treatment should be given if changes persist or worsen over time [12].

HPV immunotherapy has recently been proposed.

It has been proposed to use high doses of vitamin D in the form of vaginal suppositories. High consumption of green tea and vegetables has been associated with a reduced risk of developing cervical cancer or CIN II or III. Folic acid is an essential factor in the proper functioning of DNA, and thus possibly preventing cancer formation [32].

Multivitamins B12, C, E and beta-carotene significantly protect against cervical neoplasia. Higher blood levels of vitamin E and alpha- and gamma-tocopherol compounds were associated with a reduction in the risk of developing CIN III by almost 50%.

Enzymatically modified rice bran. Using enzymatically modified rice bran has been shown to increase NK cell activity, which may also help women with cervical dysplasia or those who want to prevent the condition.

Surgical treatment includes the following methods:

Local destruction: chemical destruction, diathermosurgical method, cryodestruction, laser destruction, argon plasma ablation, radio wave surgery

Radical surgical intervention: excision of the cervix, amputation of the cervix, reconstructive plastic method, hysterectomy.

The generally accepted standard for all women during the first examination is a cytological examination in combination with colposcopy. In recent years, when CIN II, III was detected in a pregnant woman, aggressive treatment and diagnostic tactics were replaced by conservative-expectant ones. Excision may lead to an increased risk of preterm birth [30], but others have suggested that there is no significant negative effect. The European Society of Medical Oncology considers excisional biopsy a safe method of research: in young pregnant women with CIN II–III, careful observation is optimal, and only if cervical cancer is suspected, excision is indicated [33]. The active use of a surgical method for the treatment of intraepithelial changes in the cervix in young women, serves as one of the factors in the development of isthmic-cervical insufficiency, leading to complications of pregnancy up to its termination in the second trimester [22].

Russian authors recommend performing a targeted biopsy (in some cases conization) if CIN II–III is present in smears [8].

Intervention for CIN during pregnancy is dangerous due to the risk of its interruption, and delaying treatment may carry the risk of disease progression. This dilemma dictates the need to identify predictive factors that can adequately determine the prognosis of CIN in order to develop treatment tactics.

The regression rate of CIN 1 ranges between 32% and 69%, CIN 2-3 from 16.7% to 70% [16, 26].

In pregnant women diagnosed with HSIL, the rate of progression to invasive cancer has been documented in some studies to range from 1.1 to 3.6%, while other authors have reported higher rates from 5.4 to 13.6% [16,17].

In pregnant women under 25 years of age, there is evidence of progression to CIN2/3 not received [17]. However, over the age of 25 years, progression of CIN2/3 to invasive cancer was observed in 2.5% to 22% of cases [34]. The regression rate among young patients was 52.6% versus 26.2% among those over 25 years of age. Patients with HSIL over 25 years of age had a 2-fold increase in progression and persistence rates than those under 25 years of age [17].

The issue of regression of cervical dysplasia depending on from the route of delivery. Do not demonstrate the benefits of performing a cesarean section [43]. Regression after vaginal birth occurred in 60%-69%. According to Paraskevaidis E. et al. the frequency of CIN regression prevailed after vaginal birth, which the author explains by trauma to the cervix during the passage of the fetus through the birth canal and, as a consequence, desquamation of the altered epithelium, postpartum local reparative immune response [38,43]. Regression for CIN II and III occurs in 68% and 70% of cases, respectively. Only 7% of pregnant women progress to CIN I to CIN III in the postpartum period [16]. The most significant level of regression was observed in women who gave birth through the birth canal. In CIN II–III, repeated diagnostic procedures can be postponed until the postpartum period, since regression is observed in 35% of cases during the first year after pregnancy, and the risk of developing invasive carcinoma is 0.45–1/1000 [28]. A feature of the treatment tactics for women with CIN identified during pregnancy, if they wish to continue the pregnancy, is cytological monitoring, delivery per vias naturales, repeated cytological examination 8 weeks after birth (the frequency is progressive invasive cancer 0.9%); if you do not want to continue the pregnancy, conization of the cervix 2 months after a medical abortion.

ASCCP recommends that if LSIL is present on smears during pregnancy, the patient may not be monitored. Pap test and colposcopy are recommended to be performed through 3–4 months after birth, since in 86% of cases postpartum regression of LSIL occurs [33]. Performing a biopsy while pregnant may be associated with high risk complications. Some authors recommend taking a biopsy only with colposcopic signs indicating possible cancer [16]. However, other authors indicate that cervical cancer can be missed with this approach. Therefore, experts recommend taking a biopsy from the most changed areas. Due to severe edema and increased vascularization of the cervix, bleeding may develop after a biopsy, in which hemostasis is achieved without difficulty. The results of a meta-analysis showed an increased risk of complications after conization for CIN [25]. A number of studies have demonstrated that if the depth of the removed cone is 10–12 mm, then the likelihood of preterm birth is high [27]. Other authors believe that, despite varying degrees of cervical shortening, conization does not lead to obstetric complications [36,20]. According to the latest ASCCP recommendations. Conization should be performed only if cervical cancer is suspected, since this procedure is associated with bleeding in 5–15% of pregnant women and spontaneous abortion in more than 25% of them. In the first trimester of pregnancy with carcinoma in situ, it is recommended to terminate the pregnancy and perform a cone-shaped excision of the cervix. In the second and third trimesters, it is possible to prolong pregnancy against the background of colposcopic and cytological control; 8–12 weeks after delivery, cone-shaped excision or amputation of the cervix is indicated T.N.Bebneva [2] notes the importance of cytological screening in the prenatal period or when registering a woman for pregnancy. “Pregnancy is accompanied by structural and morphological changes, which must be taken into account when interpreting the data of colposcopy, cytological and histological studies. Their implementation requires the involvement of experienced specialists. Considering that the rate of progression of dysplastic lesions of the cervix during pregnancy is very low, and the risk of developing invasive cancer is insignificant, when managing pregnant women with cervical interepithelial dysplasia, preference is given to conservative tactics. Surgical intervention is indicated only in cases of suspected cervical cancer (CC), since the risk of obstetric complications remains high. If cervical cancer is excluded, all further diagnostic and therapeutic measures are carried out in the postpartum period.” Much attention in the literature is paid to the consideration of tactics and standardization of management of pregnant women with cervical pathology. In addition, predictive factors for prognosis of the disease during pregnancy, issues of additional methods diagnostics and treatment. An analysis of the literature on this topic allows us to conclude that the problem of cervical precancer associated with pregnancy remains relevant, gives rise to serious discussions and requires further research.

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