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RISK FACTORS AND CLINICAL ASPECTS OF RECURRENT INVASIVE CERVICAL CANCER (REVIEW)

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Cervical cancer (CC) is the leading cancer in the structure of morbidity and mortality among women and remains one of the important medical and social problems in economically developed countries. According to official statistics, the overall cancer incidence worldwide tends to increase. Russia, including the CIS countries are also no exception, so for the first decade of the XXI century, the incidence of CC increased by 1,5 times. According to IARC, more than 12 million new cases of cancer and about 6,2 million deaths from it are registered annually in the world. The annual growth rate of malignant neoplasm (MN) is about 2%, which is 0,3-0,5% higher than the growth of the world population.[2,3,4,5] IARC calculations in Europe showed an annual increase of 2,9 million new cases and 1,7 million cancer deaths.

Morbidity and mortality from MN also remains one of the global problems in Uzbekistan. According to the state statistics Committee of the Republic of Uzbekistan, the incidence of MN in 2016 was 4,6 per 100 000 population. As well as all over the world among MN occurring in Uzbekistan there is a gender difference, which is expressed in high figures of morbidity and mortality among women: breast cancer (morbidity / mortality - 9,5/4,4) for several years occupies the first position in the structure of MN among women. The following ranking places belong to stomach cancer (5,9/5,1) CC in the third place (4,6/2,5).

The steady growth of neglected cases, as well as the increase in the incidence of CC among young people dictate the need to develop new, more advanced methods of combined and complex treatment of patients with this pathology.

Despite the emerging trend to reduce the incidence of invasive CC due to the widespread use of preventive examinations and cytological screening, mortality rates from CC still remain high: the total five-year survival rate of patients with preinvasive, microinvasive CC and I stage reaches 98%, at II stage 78,4-94,9%, at I - II stages-54,5 - 68%, at III stage – 18,4-53,5%, at IV stage – 6,3-22,9%, respectively.[1,5,7,9] In most countries, the peak incidence of CC occurs in the age groups older than 50-60 years, but in developing countries, 80% of cases of this disease are detected at the age of 35 years and older. Recurrence of cervical cancer after special treatment, often occurs after 12-20 months. After the start of treatment, their frequency ranges from 3,3% to 40%. 78,3% of all relapses are detected in the first 2 years after the start of treatment.[6,8,11] These circumstances determine the need to search for additional markers that can be used in clinical practice as factors that determine the prognosis of disease.

Detection of the tumor process in the cervix at the initial stages of its development is also essential for the organ-preserving treatment of breast cancer, which is a new direction in modern oncogynecology.[13,15] The peak incidence of patients with CC is on average 55 years, preinvasive and microinvasive - 36 years. The age of patients with cervical epithelial dysplasia varies significantly - from 26 to 45 years. It is alarming that, according to the results of the screening of breast cancer, in many countries (Netherlands, Germany, Czech Republic)[6,10,12], as well as in Ukraine in recent years, the incidence of CC among young women has increased. In such patients, almost half of the total number of diagnosed tumors (about 48%) is characteristic of the initial forms of CC, the detection of which was made possible by a comprehensive examination of women using methods of colposcopy, cytology, molecular biology.[6,7,14]

Timely diagnosis and prevention of CC is one of the most pressing problems of Oncology. The first studies on the epidemiology of CC appeared in the XIX century. Rigoni-Stern, in 1842 published data based on the study of the register of deaths in Verona from 1760 to 1830y. he noticed that CC was much more often the cause of death of married women and widows and did not occur in virgins and nuns. This circumstance allowed the

scientist to state a hypothesis about the infectious origin of cervical cancer. Of particular interest are the data published by F. Gagnon (1950) - in the study of 13 000 medical histories of nuns in Montreal and Quebec, where CC has not been detected once. The author attributed this to the low incidence of inflammatory cervical diseases in nuns. A review by Mogaji (1973) showed that histologically confirmed squamous cell carcinoma in virgins is extremely rare, this data is confirmed by studies by Kessler (1976) and Skoqg (1982). The results of epidemiological studies have been published, which determined the importance of such factors as: early onset of sexual life, early first pregnancy, frequent change of sexual partners, as well as sexually transmitted infections.[5,7]

In the analysis of a number of works devoted to the problems of etiopathogenesis of pathological conditions of the cervix, an important role in the emergence of this process of exogenous factors, in particular genital papillomavirus infection – human papilloma virus (HPV) is noted. This infection has features that distinguish it from many other sexually transmitted viruses, since these viruses are tumor-like, i.e. capable of causing benign, and some types-malignant tumors of the cervix.[8,11] In cervical tumors, the genetic material of papilloma viruses is detected in 90% of samples. When infected with oncogenic viruses type 16 and 18 in women in 20-150 times the risk of developing CC.

CC is a malignant tumor, the most common among oncopathology in women, in the occurrence of this pathology, the oncogenic type of HPV plays an undoubted role.[6,8,9] From 9 to 13% of the world's population are carriers of HPV, while the degree of infection depends on the geographical location. Despite the availability and visualization of the organ, most patients are admitted to specialized clinics in advanced cases, this is due to the insufficient level and organization of early diagnosis, the lack of effective screening programs, prevention, as well as standard diagnostic methods using oncogenes typing, liquid Cytology, modern cancer markers. The oncogenic potential of papillomaviruses varies significantly; according to the ability to initiate dysplastic (precancerous) changes and cancer, papillomaviruses are conditionally divided into groups of "high" and "low" risk of tumor transformation of the infected epithelium. HPV types 6,11, 42, 43, 44 were classified as low-risk types of cancer, types 16, 18, 48, 56 - high risk. Thus, HPV types 6 and 11 are the cause of genital warts, are often identified in mild to moderate dysplasia and are rarely associated with cervical tumors. HPV types 16 and 18 prevail over other types of papillomaviruses in CC, so HPV type 16 is detected in 50-70% of cases, in 10-20% HPV type 18 is detected, the other types of high-risk HPV are detected much less often.[6] The most common identified type 16 virus, which is detected in 21% of cases in CIN-I and 57% of cases in CIN-II-III. 67-93% of CC cases are associated with infection of type 16 and 18 viruses, and type 18 virus is detected about 2 times less often than type 16.[8] Papilloma virus type 18 is associated with the development of adenocarcinoma, which has a higher oncogenic potential, which is associated with a rapid rate of tumor progression, a low level of differentiation of the infected epithelium, an unfavorable prognosis in comparison with other oncogenic types.

According to the literature, the increase in the incidence of CC may be associated not only with untimely diagnosis, but also with unsatisfactory efficiency of treatment of patients with cervical pathology, especially cervical intraepithelial neoplasia (CIN), which precedes CC and is most often detected at a young age.

According to the literature, 13-38% of young healthy women are carriers of HPV, it was found that HPV infection does not correlate with the age of patients, the age of the beginning of sexual life. According to, HPV type 16 and 18 were found in 27,6% of healthy women, in 44-87% of patients with epithelial dysplasia (I-III degree), but most often in patients with preinvasive and invasive CC, respectively, in 93,2 and 96,7%. Similar data on significant infection of patients with CIN-3 and CC are given by other researchers. HPV type 16 is also found in cervical warts. The Association of pointed and flat warts, in the pathogenesis of which HPV infection is important, with dysplasia of the cervical epithelium in 17,1-52,4% of young women is observed.[6,8] It has been shown that HPV carriers have an increased risk of developing CIN compared to women without HPV infection.

Despite the prevalence of HPV, CC does not occur in every carrier and, obviously, other, as yet unknown factors may be important in the pathogenesis of CIN.[40] Although HPV is considered an etiological agent in the development of dysplasia and CC, yet some researchers believe that HPV alone is not enough for the development of CIN. In such a complex process as the initiation of tumor growth, other factors can play a role - comutagens, which do not cause mutations on their own, but enhance the mutagenic effects of other factors. These include pathogens of genital infections (viruses of the family Herpes Viridae (herpes simplex viruses type 1-2-HSV type 1-2 and cytomegalovirus - CMV, Chlamydia trachomatis), which often recur, do not cause persistent immunity and in recent years have become widespread throughout the world. It was found that HSV is detected in patients with CC in 2 times more often than in healthy women.

With herpes infection in the form of monoinfection or mixed infection with virus persistence, as with other chronic diseases, transient secondary immunodeficiency develops, due to the insufficiency of different immunodeficiency units and their inability to eliminate the virus from the body. With the progression of immunosuppression, the activity of the virus becomes

more frequent, and in severe immunodeficiency, generalization of the process is observed.[15] However, until this time, the role of infectious factors both concomitant and modifying the development of CIN and primary CC has not been definitively determined, despite the fact that the Association of HPV, HSV infection with precancerous and CC is displayed in a number of papers.

The mechanism of influence of viruses on the development of cancer in humans is related to their type: some viruses, like HPV, have their own transforming genes; other viruses have a transactivating potential on genes that control the processes of cell proliferation. The integration of the viral genome into the cell genome makes the expression of virus genes independent of control antiviral mechanisms. For HPV, 192 individual integration loci were determined mainly in fragile chromosome sites, in oncogenes loci, which leads to microsatellite instability and destabilization of the genome of the cell population. The integration of HPV type 18 at the site of localization of C-myc oncogene in the development of cervical carcinoma was established.[15] Integration into fragile chromosome sites is typical not only for highly oncogenic HPV types 16 and 18, but also HPV types 45 and 67, which was demonstrated in an experiment on cervical cancer cell lines.

On the basis of comparison of clinical, morphological and virological studies, the following stages of cervical pathology development in women infected with HPV are proposed: HPV infection, virus persistence, cellular dysregulation, severe CIN invasive CC. Factors such as low levels of folates, antioxidants, beta-carotene, vitamins C and E, tissue hypoxia can translate latent HPV infection into subclinical forms of damage and contribute to the development of CIN.[8] Long-term persistence of HPV is an indicator of possible recurrences of pathological processes of the cervix. The persistence of infection can be induced by immune factors-macrophages, interferons, interleukins.[11] Hereditary factors and immune status can also influence the variations of HPV infection in patients with dysplastic and tumor processes. In General, most researchers strongly indicate that HPV persistence induces cervical carcinogenesis.

The depth of tumor invasion, lymph vessel and node damage, parametral and vaginal infiltration do not depend on molecular genetic determinants of HPV infection.

In a one-factor analysis according to J. H. Tavares et al.[14] the relationship between the occurrence of recurrent CC among socio-demographic and clinical variables, in which only the number of previous pregnancies exceeding four were significant, was shown. Among histopathological variables, associations were found between the occurrence of relapses and the number of metastatic pelvic nodes; the depth of tumor invasion and the intensity of the inflammatory response in the cervix, while not one variable associated with treatment showed no connection with relapse.

During the multivariate analysis, independent risk factors for recurrence of CC were identified: the number of metastatic lymph nodes; the depth of penetration of the tumor into the cervix and the presence or absence of an intense inflammatory reaction of the cervix.

Thus, the available data on the occurrence of recurrence of CC in the literature are contradictory, as in some studies there is no connection between the identified risk factors in other studies with the occurrence of recurrence of CC. Given the inconsistency of the literature data, further research is needed to determine and identify the clinical and morphological signs of recurrence of CC, which will continue in subsequent works.

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