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COMPARATIVE CHARACTERISTICS OF THE STATE OF THE CERVIX DEPENDING ON THE METHOD OF CONTRACEPTION

Atakhodzhayeva F.A., Tashbaeva U.I.

Tashkent Medical Academy

Abstract: Cervical cancer remains one of the leading causes of cancer among women and is currently the fourth most common cancer worldwide. According to WHO estimates, 604,000 new cases of cervical cancer and 342,000 deaths from it were registered in 2020[1]. Cervical cancer is most prevalent in low- and middle-income countries, which is associated with low levels of vaccination and screening of vulnerable groups of women. It is known that the main cause of cervical cancer is the human papillomavirus (HPV), especially its highly oncogenic strains (16, 18, 31, 33, 35, 45, 52 and 58). The presence of these types of virus is mandatory, but is not sufficient for the development of the disease. Understanding the extent to which external factors contribute to the progression of oncogenic strains of the virus into cervical dysplasia and/or cervical cancer can help improve methods of preventing this disease.

Keywords: Cervical cancer, cervical dysplasia, cervical intraepithelial dysplasia, combined oral contraceptives, intrauterine device, contraception.

According to the United Nations Population Fund report for 2022, the number of unwanted pregnancies has reached more than 60% of the total number of pregnancies per year, for this reason, women's need for effective and safe methods of contraception is growing every year [16]. Combined oral contraceptives have proven themselves to be one of these methods and today more than 100 million women around the world prefer them. Until today, the composition, combination, and dose of COCs have undergone significant changes and improvements, which has contributed to reducing undesirable effects on women's health. However, according to the estimates of the International Agency for Research on Cancer, COC is considered as one of the causes of cervical cancer [3]. On the one hand, the cervix is an estrogen-sensitive tissue that quickly reacts to the effects of steroid hormonal contraceptives [5,10], on the other hand, estrogen is an inducer of HPV-dependent carcinogenesis of the cervix [5]. Steroid hormones can enhance the transcription of important HPV oncogenes, disrupting the normal cell cycle and eventually leading to cervical cancer [15].

The age-related incidence of cervical cancer increases after age 25 and peaks around age 40 in high-income countries, although in low-income countries it continues to rise until age 55-69, and therefore, the contribution of COCs to the lifetime incidence of cervical cancer will largely depend on the consequences later in life, when most women will have become former users. The long-term risk of cervical malignancies does not appear to increase among those who have ever taken the drug compared to those who have never taken it [8]. Nevertheless, an analysis of the duration of COC use shows that long-term or recent use (<5 years) is accompanied by an increased risk of developing malignant neoplasms of the cervix [8]. The reported risk decreases approximately 5 years after stopping COC use, and there is no indication that chronic users of COCs later in life will be at increased risk of developing cervical cancer.

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In the EPIC study, which involved more than 300,000 people who were observed for 9 years, it was also found that the risk of malignant neoplasms of the cervix increases with continued use and decreases after discontinuation of drugs, and this confirmed the recognized clear correlation between the use of oral contraceptives and precancerous and cancerous conditions of the cervix [14].

A study conducted in Denmark, which involved about 2 million women aged 15 to 79 years, revealed an increased risk of developing malignant tumors of the cervix (both adenocarcinoma and squamous cell carcinoma) among those who recently took COCs and those who are currently taking them. In this cohort, most women were not vaccinated against HPV, which may indicate that the COCs currently used have a similar effect on the condition of the cervix compared to older drugs [4].

The meta-analysis, which consists of 24 studies involving almost 17,000 patients with malignant neoplasms of the cervix and approximately 36,000 control groups, confirms the above effect of COCs. The risk of invasive malignant neoplasms of the cervix was increased among regular users of COCs with a long period of use. This increased risk decreased after discontinuation of the drug and within 10 years recovered to the level of those who had never used it. An identical risk model was identified for both invasive malignancies and in situ malignancies, as well as for high-risk HPV carriers [2].

The second method of contraception, which is of interest in studying its effect on the condition of the cervix, is the intrauterine device. More than 150 million women use IUDs worldwide. This growing popularity of the IUD is primarily due to its high efficiency, women's satisfaction, reversibility and ease of use. There are 2 types of IUD: hormonal (they contain levonorgestrel in their composition) and non-hormonal (copper-containing, silver-containing and gold-containing). The intrauterine device with levonorgestrel releases progestin, which causes endometrial depression and thickening of cervical mucus, while the main mechanism of action of the non-hormonal intrauterine device is to create a local inflammatory reaction to prevent fertilization.

Although previous studies have shown an association between hormonal contraceptive use and the risk of cervical cancer, there are controversial results regarding the association with intrauterine device (IUD) use. [7, 11,13,14].

Two meta-analyses have revealed that the use of an IUD is a protective factor that reduces the risk of developing cervical cancer. The first study noted a protective association for squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma, but not among women infected with HPV [7]. Another study claims that the use of an intrauterine device is safe for women and girls infected with the human papillomavirus, or at high risk of contracting the human papillomavirus, because IUD prevents the development of precancerous lesions of the cervix in women infected with HPV, or helps to eliminate identified precancerous lesions [13]. This effect is mainly associated with the activation of cellular immunity caused by the installation of an IUD. A second meta-analysis also revealed that invasive cervical cancer may occur about a third less frequently in women who have used an IUD. This possible advantage, unrelated to contraception, may be most useful in populations with extremely limited access to screening and concomitant high incidence of cervical cancer [6]. However, in these studies, only those who have ever used the IUD and

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those who have never used it could be compared. At the same time, the group of those who had never used contraceptives consisted of a heterogeneous group, including people who did not use them and people using other types of contraceptives, which makes it difficult to interpret the results.

Another study, which examined about 18,000 women from the Kaiser Permanente Healthcare System in Northern California for the risk of precancerous and cancerous cervical diseases with recent IUD use, found a weak association with the development of CIN2+, but no association with the risk of CIN3+ [11]. At the same time, only levonorgestrel containing IUDs were a relative danger, and copper-containing IUDs were not the cause of the development of precancerous conditions. The causal relationship between the use of IUD and CIN2+ is not accurate, because The observed association may be related to other uncontrollable factors (i.e. sexual activity and, consequently, a different risk of HPV infection) [11].

In a retrospective cohort study conducted at Columbia University Medical Center, 10,674 women were studied, of which 8,274 women used a copper-containing IUD (Cu-IUD) and 2,400 used a levonorgestrel IUD(LNG-IUD). 77 (0.9%) in the Cu-IUD group and 37 (1.5%) in the LNG-IUD group were diagnosed with grade II or III intraepithelial cervical neoplasia, which again confirmed that copper-containing IUDs pose a lower risk of developing cervical neoplasia.

Thus, it can be concluded that the use of COCs and IUDs were associated with an increased risk of developing CIN3+ compared to those who had never used them. However, for women with persistent HPV infection or with a high risk of HPV infection, preference should be given to the use of an IUD. Because this method of contraception, along with a minimal carcinogenic effect, also, to some extent, has protective properties against malignant neoplasms of the cervix. As for COC, the latest WHO guidelines on the use of contraceptives from 2015 state that the benefits of using COCs generally outweigh the risks. However, women at risk should remember that long-term and continuous (>5 years) intake can increase the risk of developing carcinoma in situ and invasive carcinoma [9].

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