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To Study Modern Approaches to the Management of Cervical Intraepithelial Neoplasia in Women of Reproductive Age in a Comparative Aspect

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Abstract Based on a retrospective study of outpatient records of 147 women of reproductive age, an analysis of various modern approaches to the management of cervical intraepithelial neoplasia was carried out. A comparative analysis of modern management strategies will allow us to identify priority effective approaches for the timely prevention of potential oncogenesis.

Keywords Gynecology, Benign and precancerous pathology, Cervical intraepithelial neoplasia, Cervical pathology, Wait-and-see approach, Surgical methods of treatment

1. Introduction

The most effective way to prevent cervical cancer is early diagnosis and timely treatment of preinvasive lesions of the cervical epithelium [1]. Cervical intraepithelial neoplasia (CIN) is characterized by potentially precancerous transformation and abnormal growth (dysplasia) of squamous epithelium on the surface of the cervix [2]. There are mild, moderate and severe cervical dysplasia (CIN 1, CIN 2 and CIN 3, respectively). Progression to invasive cancer occurs in about 1% of cases of CIN 1 detection, in 5% – with CIN 2 and at least in 12-15% of cases of CIN 3 [3].

The management of patients with mild CIN has changed dramatically over the past decade. It was believed that the treatment of patients with mild dysplasia was mandatory and prevented the development of cervical cancer. However, in recent years, this theory has been refuted by the results of studies in which it was shown that in women with a normal immune response and hormonal background, in the absence of a chronic inflammatory stroma reaction and low viral activity, spontaneous regression of mild CIN is observed in the vast majority of cases [4]. Thus, a wait-and-see approach to the management of mild CIN is the most preferable, since surgical methods of treatment have an adverse effect on reproductive function, and the probability of disease regression in the absence of treatment is very high [5,6].

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The purpose of the study was to study modern approaches to the management of cervical intraepithelial neoplasia (CIN) in women of reproductive age, in a comparative perspective.

2. Materials and Methods

A retrospective analysis was performed in groups of women of reproductive age with cervical intraepithelial neoplasia, who underwent various diagnostic and management approaches.

Outpatient follow-up records of 147 women were studied. The analysis was performed separately in groups of women who were diagnosed with cervical intraepithelial neoplasia of varying severity, confirmed by histological methods. In the group of women with mild CIN, with a histologically confirmed diagnosis, n=86 (58%), routine follow-up and retesting after 12 and 24 months were recommended. With positive screening results, after confirmation of the diagnosis of CIN by colposcopic method and histological verification in a biopsy of the cervix of CIN 2-3 n=61 (42%), treatment was recommended. The main purpose of treatment was to remove the transformation zone, and the choice of the appropriate technique depended on the individual case, the colposcopic picture, the depth and severity of the lesion, the type of transformation zone, the age of the woman, as well as the experience of the doctor and the availability of equipment.

3. Results and Discussion

The analysis in the studied groups revealed progression to CIN 1-2 within 24 months after diagnosis. With histological

confirmation of CIN 1, the risk of progression was about 11-13% within 24 months, and disease progression within 12 months was detected in only 6%. The observation of the patients included performing a cytological examination or determining the DNA of the human papillomavirus (HPV), depending on the availability of the procedure. Colposcopy was recommended every 12 months. If the HPV test was negative or two consecutive cytological smears were negative, the women remained on routine cytological screening. CIN 1 has not been treated. It is important to note that currently none of the methods of drug treatment of mild CIN are approved by the recommendations, since the effectiveness of these methods has not been proven, and they can also have a systemic toxic effect on the body [11]. With positive screening results, after confirmation of the diagnosis of CIN by colposcopic method and histological verification, treatment was indicated in the biopsy of the cervix of CIN 2-3. Surgical treatment of severe intraepithelial neoplasia is a recognized tactic worldwide. Considering that the majority of women with CING are patients of reproductive age, treatment should be effective and cause a minimal risk of recurrence of the disease and adverse effects on reproductive function. Most clinics around the world have now switched to using only excision methods, the most common of which is loop electroexcision (LEE) [5]. In the group of examined women, excision methods were used during surgical treatment, mainly loop electroexcision, n=46 (75%). An important difference between excisional and ablative methods of treatment is the possibility of obtaining material for subsequent histological examination and accurate assessment of the edges of resection. This helps to identify the presence of microinvasive cancer, which may be missed during biopsy. In addition, excisional treatment methods are characterized by a short duration of treatment, low cost and simplicity of the technique of performing the intervention [16]. Ablative methods lead to the destruction of the transformation zone and, therefore, exclude histological examination, which is a significant disadvantage of treatment and requires a preliminary biopsy. Conservative methods of treatment in this case have many advantages, such as relatively low cost, as well as the ability to perform them under local anesthesia and on an outpatient basis. The effectiveness of ablative and excision methods in the treatment of cervical dysplasia is almost the same and exceeds 90% [16].

Before using any form of ablative therapy, histological verification of the diagnosis is necessary to exclude an invasive lesion. In addition, the transformation zone should be fully visible during colposcopy, and the conclusions of cytological examination, colposcopy and histology should not differ. Ablative methods are contraindicated in the presence of glandular lesions of the cervix, inflammatory diseases, suspected invasion and repeated treatment of CIN. Cryotherapy is an effective treatment method for small lesions with a low degree of malignancy. Its effectiveness depends on the localization of the lesion, the extent of the lesion (more than two quadrants), the size of the cervix (more than 3-3.5 cm) and the severity of the lesion. It was revealed that when the lesion passes into the cervical canal, treatment is most often ineffective, which is mainly due to the freezing temperature that is not low enough for tissue destruction.

Electroconization of the cervix is an affordable treatment method and is capable of destroying the lesion up to 1 cm deep, however, the use of this method is associated with the risk of significant thermal necrosis of tissues. The advantages of laser treatment of the cervix are good control over the depth of destruction, good hemostasis, high efficiency of treatment with minimal damage to nearby tissues. Laser vaporization is usually performed under local anesthesia using one of the three most common techniques. The depth and area of resection depend on the severity and prevalence of the lesion. If the lesion captures a significant part of the cervix and goes into the canal, the use of a combined technique is indicated. The central part of the transformation zone is removed by laser conization, setting the appropriate depth of resection, and the peripheral part is removed by vaporization. This approach reduces the volume of removed tissue and minimizes the risks of early and late complications.

Excision treatment methods are indicated in cases of suspected invasion, in the presence of glandular lesions, an unsatisfactory colposcopic picture that does not allow visualization of the entire lesion area, repeated treatment of dysplasia, as well as in the presence of inconsistencies between cytology, colposcopy and histology results. LEE is the most widely used treatment technique. The effectiveness of LEE is comparable to knife biopsy and laser conization, and the result depends on the parameters of cytological examination of tissues along the edge of the resection zone. With a negative result, the probability of a complete cure was 95%, and with a positive result – about 70%. For many years, knife conization of the cervix remained the standard method of organ-preserving treatment of cervical dysplasia. However, currently this method is used relatively rarely and is increasingly being replaced by simpler methods — laser and loop conization. Hysterectomy for cervical dysplasia is currently performed extremely rarely, usually in elderly women and in the presence of concomitant gynecological diseases. Hysterectomy was also not recorded in the study groups.

Complications of surgical treatment of CING are quite rare, and the risk of their development depends on the chosen treatment tactics of the patient. Early complications after PEE included profuse bleeding and inflammation n=2 (3.3%). It has been shown that the risk of bleeding increases with the removal of a large fragment. Late complications are characterized by the development of bleeding and stenosis of the cervical canal. In 9% (n=5) of patients after PEE, the results of colposcopy were unsatisfactory and 1 patient developed cervical canal stenosis. According to most studies [11,15], the risks of early and late complications in the use of ablative treatment methods do not significantly differ from the risks of excision techniques. The greatest risk of complications is knife conization of the cervix. After this procedure, the transformation zone often shifts into the cervical canal, which subsequently makes it impossible to

evaluate it colposcopically. Currently, the effects of various CING treatments on women's fertility and the outcomes of future pregnancies are being actively studied. In several large meta-analyses conducted in recent years, it has been convincingly shown that excisional treatments for cervical dysplasia are significantly associated with a high risk of premature birth and low fetal birth weight. Moreover, it was found that this adverse effect is "dose-dependent": the probability of having a premature baby is higher the larger the tissue fragment is removed, and this factor, apparently, has a greater impact on outcomes than the specifics of a particular treatment method. Surgical treatment of CING also appears to have an adverse effect on pregnancy outcomes: the risk of premature birth at 24-27 weeks of gestation was 4.4%. Knife conization is most associated with the risk of premature birth (OR 2.59; 95% CI 1.80-3.72), low fetal body weight at birth (<2500 g; OR 2.53; 95% CI 1.19-5.36) and cesarean delivery (OR 3.17; 95% CI 1.07-9.40). Excision of a large fragment of the transformation zone is also statistically significantly associated with the risk of premature birth (OR 1.70; 95% CI 1.24-2.35), low birth weight (OR 1.82; 95% CI 1.09- 3.06) and premature discharge of amniotic fluid (OR 2.69; 95% CI 1.62-4.46). With regard to laser conization of the cervix, similar results were obtained, but with a significantly lower risk (risk of premature birth OR 1.71; 95% CI 0.93-3.14). In a recent systematic review of 30 studies, it was demonstrated that the risk of premature birth after cervical conization is 2.19 (95% CI 1.93-2.49), while after ablative treatment it is 1.47 (95% CI 1.24–1.74), which proves the association between ablative treatments and the risk of adverse perinatal outcomes. It was also revealed that the risk of premature birth in the case of multiple pregnancies after cervical conization is 1.58 (95% CI 1.16—2.14). In addition, it was shown that deep conization (when removing a tissue fragment of more than 10 mm) is associated with the highest risk of premature birth (OR 4.55; 95% CI 1.32-15.65) compared with healthy women. The risk of premature birth increases by 9.9 times after two conizations compared with women who did not undergo cervical treatment. A direct comparison of knife conization and PE revealed a greater risk of premature birth when using the first method (11% vs. 5%; p=0.04). According to the results of a recent meta-analysis, the rate of premature birth is higher with knife conization, although PEE and cryotherapy also increase the risk of premature birth. Thus, surgical treatment of cervical dysplasia is most associated with a worsening obstetric prognosis.

4. Conclusions

It was found that progressing to CIN 1 – 2 within 24 months after diagnosis is very rare. According to the recommendations, which was confirmed in our study, QIN 1 in the vast majority of cases does not require treatment for 2 years. Observation of patients includes performing cytological examination or DNA determination of human papillomavirus (HPV), as well as colposcopy at least once a year. In case of a negative result of an HPV test or two consecutive cytological smears, it is recommended to continue routine cytological screening. QIN 1 treatment is not required, and the decision on treatment should be based on a thorough medical history and should take into account the woman's further reproductive plans, the risk of obstetric complications and other risk factors. If treatment is necessary (after 2 years of follow-up), an excision procedure is recommended. It is important to note that currently none of the methods of drug treatment of mild QING are approved by the recommendations, since the effectiveness of these methods has not been proven, they can also have a systemic toxic effect on the body. With regard to surgical treatments, randomized trials have shown similar efficacy for loop electroconization of the cervix, laser vaporization, and cryotherapy in the treatment of CIN. Thus, the choice of treatment method remains at the discretion of the doctor.

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