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CERVICAL INTRAEPITHELIAL NEOPLASIA: THE CURRENT STATE OF THE PROBLEM IN YEKATERINBURG

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ЦЕРВИКАЛЬНАЯ ИНТРАЭПИТЕЛИАЛЬНАЯ НЕОПЛАЗИЯ: СОВРЕМЕННОЕ СОСТОЯНИЕ ПРОБЛЕМЫ В Г. ЕКАТЕРИНБУРГЕ

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Objective. To determine the frequency of cervical intraepithelial neoplasia among female citizens in Yekaterinburg.

Materials and methods. The retrospective analysis of the report forms of the cervical pathology office in Yekaterinburg Perinatal Center from January to September 2022 was carried out. Statistical data processing was conducted using descriptive statistical methods in the Excel programme.

Results. 255 cases of precancerous cervical diseases and 7 cases of cervical cancer were revealed within 9 months of monitoring, among them 24 patients with precancerous pathology and 4 with cervical cancer had previously been followed up by a specialist. Most cases of cervical pathology were revealed in patients over 40.

Conclusions. The women's consultations of Verkh-Isetsky and Leninsky districts refer patients to the specialized cervical pathology office most actively. Patients of the cervical pathology office are provided with the full range of therapeutic and diagnostic procedures, with colposcopy being most often performed (27 % of cases). The dispensary group of patients of the cervical pathology office is mainly represented by women with cervical dysplasia of the 2nd degree (HSIL, CIN II) – 43.5 %.

Keywords. Cervical intraepithelial neoplasia, cervical cancer, biopsy, colposcopy, excision.

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Цель. Выявить частоту цервикальной интраэпителиальной неоплазии среди жительниц г. Екатеринбурга.
Материалы и методы. Проведен ретроспективный анализ отчетных форм кабинета патологии шейки матки Екатеринбургского перинатального центра в период с января по сентябрь 2022 г. Статистическая обработка осуществлялась с применением описательных методов статистики в программе Excel.
Результаты. За девять месяцев наблюдения было выявлено 255 случая предраковых заболеваний шейки матки и 7 случаев рака шейки матки, при этом 24 пациентки с впервые выявленной предраковой патологией и 4 с раком шейки матки ранее уже наблюдались у специалиста. Больше всего случаев патологии шейки матки было обнаружено у пациенток старше 40 лет.
Выводы. Наиболее активно направляют пациенток в специализированный кабинет патологии шейки матки женские консультации Верх-Исетского и Ленинского районов. Пациенткам кабинета патологии шейки матки выполняется весь объем лечебно-диагностических мероприятий, но чаще всего осуществляется кольпоскопия – в 27 % случаев. Диспансерная группа пациенток кабинета патологии шейки матки преимущественно представлена женщинами с дисплазией шейки матки 2-й степени (HSIL, CIN II) – 43,5 %.
Ключевые слова. Цервикальная интраэпителиальная неоплазия, рак шейки матки, биопсия, кольпоскопия, эксцизия.

INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is an atypical transformation of squamous epithelium without stromal invasion and is a precursor of cervical cancer (CC). According to the literature, in women of reproductive age, CIN accounts for from 10.7 to 38.8 % in the structure of gynecological diseases. In addition, a number of studies show that pronounced cervical dysplasia progresses with the development of carcinomas in 0.2–0.4 % of cases within a year [1]. CC is the fourth most common cancer in women worldwide with an estimated incidence of 569,847 cases and 311,365 deaths according to the latest Globocan report [2]. In the Russian Federation, as of 2018, CC ranks 5th in the structure of oncopathology [1].

The leading role in the pathogenesis of CIN and CC development belongs to the human papillomavirus (HPV). More than 80 % of sexually active men and women become infected with HPV during their lifetime. Despite this, most cervical HPV infections resolve spontaneously; however, in a minority of women, the virus persists and progresses to cervical dysplasia and cancer. Known risk factors for the development of CIN are: early onset of sexual activity, a large number of sexual partners, long-term use of combined oral contraceptives, smoking, presence of mixed infections associated with herpes simplex virus type 2 or human immunodeficiency virus, as well as other sexually transmitted infections, bacterial vaginosis, history of vulvar and anal dysplasia [3].

Based on the extent of tissue involvement, CIN can be classified as CIN I (poorly differentiated neoplasia), CIN II, and CIN III (the most severe form). Although CIN I can regress, it can also progress to high-grade dysplasia and, even worse, to CC [1]. According to the World Health Organization (WHO), 99 % of high-grade intraepithelial lesions and invasive forms of CC can be detected at an early stage using well-organized screening programs [4]. WHO has approved three main methods: virological, cytological and visual [5]. Cervical cytology is the pre-

ferred method of screening for CC and its precursors in many countries, as it is a cheap and accessible test. Despite its high specificity, it has low sensitivity. False-negative results can be caused by inadequate collection and fixation of material [4]. Double staining for p16 and Ki67 helps identify truly malignant cells. Compared with HPV testing or single p16 staining, the sensitivity of double staining for detecting CIN II and above is significantly increased while maintaining the same specificity. Women with HPV+/p16+ were at high risk of developing CIN III+ after three years of persistent infection. Data from a large Italian screening study suggested immediate referral for colposcopy in women with HPV 16/18+ in combination with double staining of positive p16 and Ki67 tests. This may reduce the rate of false-positive HPV testing and allow effective identification of patients with HPV who require surgical treatment to prevent CC.

Persistent infection can lead to integration of the HPV genome into the host chromosome, causing cessation of the normal viral life cycle and overexpression of E6 and E7 oncoproteins through methylation of the 5'-C-phosphate-G-3' CpG sites. HPV integration often occurs early in CIN. PCR-based testing of E6/E7 mRNA not only provides a quantification of viral load, but also indicates its transcriptional activity, meaning that E6/E7 mRNA testing has prognostic value. It is a biomarker of significant dysplasia and CC [5]. In 2012, the American Society of Colposcopy and Cervical Pathology (ASCCP) published guidelines for screening tests for CC and precursors of cancer, which introduced a new concept: using a patient's risk of cancer progression and chance of recovery from HPV based on age and HPV subtype (HPV-16, HPV-18 and other high-risk HPV strains) for clinical decision-making when referring for colposcopy and planning follow-up. These recommendations were summarized in algorithms that began with cytology results. In April 2020, the ASCCP published 2019 guidelines for screening tests for CC and cancer precursors of cancer, which require a full shift to risk-based decision making and address the growing evidence that persistent HPV infection is a leading cause for CC developing risk. Colposcopy is now recommended for “any combination of history and current test results that gives a 4 % or greater chance of detecting CIN III or worse.” The biopsy should target any lesion present on the cervix, for example, 2–4 targeted biopsies (i.e., biopsies of tissue with abnormal appearance or acetowhite epithelium) within the squamous-glandular junction improve detection of CIN II or others. Targeted biopsies are 8 to 12 times more likely to detect CIN III and more severe lesions than random biopsies. If there are no lesions or visible squamous metaplasia at colposcopy, random biopsies or biopsy samples at the squamous-glandular junction should be considered for patients at greatest risk of CIN II or worser. When the colposcopy biopsy is abnormal, random biopsies at the squamous-glandular junction from unse-

lected quadrants should be considered, in addition to the recommended 2 to 4 targeted biopsies. The ASCCP does not recommend random biopsy in low-risk patients with a normal colposcopic biopsy and no squamous metaplasia (squamous metaplasia is normal but may be confused with changes in the acetowhite epithelium) [6].

Identified diseases are subject to conservative and surgical treatment methods in the form of ablation, excision and cervical conization, however, the latter can have a negative impact on fertility, the incidence of premature birth, and bacterial infection of the endo- and exocervix. In addition, it was found that women with CIN who underwent surgical treatment were still at risk of CC. Currently, therapeutic measures are carried out differentially depending on the stage of damage to the cervical epithelium and the woman's reproductive plans [7].

The purpose of the study is to identify the frequency of cervical intraepithelial neoplasia among female residents of Yekaterinburg.

MATERIALS AND METHODS

To achieve this purpose, we conducted a retrospective analysis of the report forms of the cervical pathology office in Yekaterinburg Clinical Perinatal Center (ECPC) from January to September 2022.

From March 16, 2022, by order of the Ministry of Health of the Sverdlovsk Region, patients with suspected and diagnosed CIN I–II degrees are subject to observation in the cervical pathology office of the ECPC. Doctors at antenatal clinics in Yekaterinburg have the opportunity to refer the patient to the office to perform colposcopy, cervical biopsy, excision of the transformation zone, cervical conization, polypectomy, hysteroscopy and some other manipulations. Patients with suspected CIN III, CC are subject to routing to the Regional Oncology Dispensary.

After surgical treatment of cervical pathology at the ECPC, patients are subject to dispensary observation at the antenatal clinic at their place of residence.

Statistical processing was conducted using descriptive statistical methods in Excel. Fisher's test was used; differences were considered significant at $p < 0.05$.

RESULTS AND DISCUSSION

In the ECPC cervical pathology office for the period from January to September 2022, a total of 255 cases of precancerous cervical diseases and 7 cases of cervical cancer were revealed. Among them, 24 patients with newly diagnosed precancerous pathology and 4 with CC had previously been followed up by a specialist. Primary cervical pathology most often occurred in patients over 40 years old – 93 cases (38 %), least often – in patients under 20 years old – 5 cases (2 %). There were no statistically significant differences in the incidence of CIN in women under 40 years old ($p > 0.05$).

But after 40 years, the prevalence of precancerous diseases is significantly higher than in patients under 20 years of age ($p = 0.017$), from 21 to 25 years ($p = 0.0017$) and from 26 to 30 years ($p = 0.017$). The age distribution of patients with precancerous cervical diseases is presented in Fig. 1.

The largest number of cervical diseases cases was identified in the Verkh-Isetsky district of Yekaterinburg – 68, the fewest cases of cervical pathologies were in the Oktyabrsky district and in the Sverdlovsk region – 3 (Fig. 2). Districts of Yekaterinburg, where the detection of precancerous diseases is low (such as Oktyabrsky and Kirovsky), have a full range of capabilities (cervical pathology office, appropriate equipment and trained personnel) for carrying out therapeutic and diagnostic procedures in women with CIN and patients are sent only in extremely difficult cases. The remaining areas of the city have the opportunity to provide medical care with equal interest and need. According to the routing order, only patients living in the territory of Yekaterinburg are subject to medical care. This explains the small percentage of patients from the Sverdlovsk region in the ECPC cervical pathology office – 1.5 % (3 people), in comparison with the Verkh-Isetsky and Leninsky districts of Yekaterinburg, this figure is significantly lower ($p < 0.0001$).

The Kirovsky and Oktyabrsky districts of the city referred patients to the cervical pathology office significantly less often ($p = 0.01$ and $p < 0.001$, respectively) (compared to the Verkh-Isetsky district) due to the presence of a well-equipped operating room on the basis of these institutions and highly qualified obstetrician-gynecologist.

Among the manipulations performed in the ECPC during this period, the predominant ones were (Fig. 3): colposcopy – 27 % (832), biopsy, excision and cervical conization – 21 % (652), ablative treatment procedures – 20.2 % (619), cervical argon plasma coagulation – 15.5 % (475), ultrasonic cavitation of the vagina – 14.6 % (450); the most rear manipulations were cervical diathermocoagulation – 0.2 % (4), removal of intrauterine devices and condylomas – 0.1 % (2 cases each).

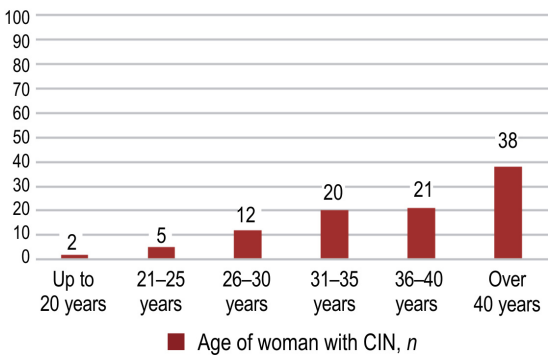

Fig. 1. Distribution of patients in the cervical pathology office by age groups, %

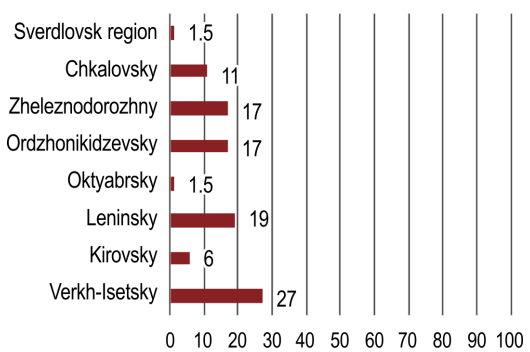

Fig. 2. Distribution of cervical pathologies cases detected for the first time by district of Yekaterinburg for the period from January to September 2022, %

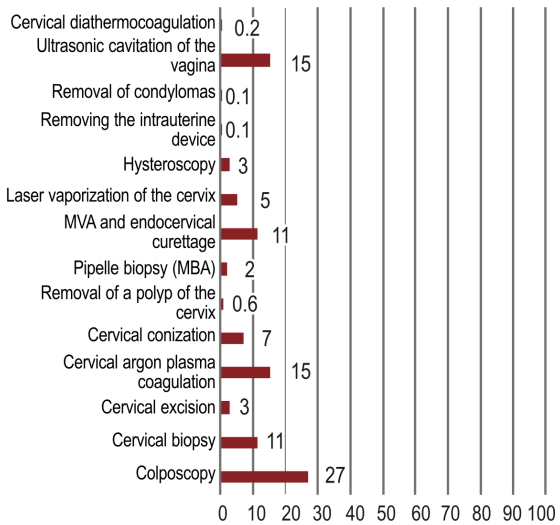

Fig. 3. Manipulations carried out in the ECPC cervical pathology office for the period from January to September 2022, %

By the end of September 2022, 258 women were registered at the cervical pathology office (Fig. 4). The largest dispensary group was patients with CIN II – 43.5 % (112), a slightly smaller group of women with CIN I – 28 % (71), patients with CIN III accounted for 17 % (45). 2.7 % (7) of patients were registered with cervicitis, VIN, CC, 2.3 % of women – with cervical leukoplakia (6). The smallest dispensary groups are patients with cervical ectopia 0.7 % (2) and polyps of the cervix 0.4 % (1).

The study confirmed the literature data on the high percentage of CIN (38 %) in patients over 40 years old [1]. However, it is also noteworthy that there are cases of precancerous cervical diseases in young patients, and even if this is only 2 % of cases (which in absolute terms corresponds to 5 patients), we understand that in the future these women remain at risk for the development of cervical cancer within two years after surgical treatment, they may have an increased rate of miscarriage (in particular, due to the development of isthmic-cervical insufficiency), labor activity anomalies (secondary uterine inertia) [8].

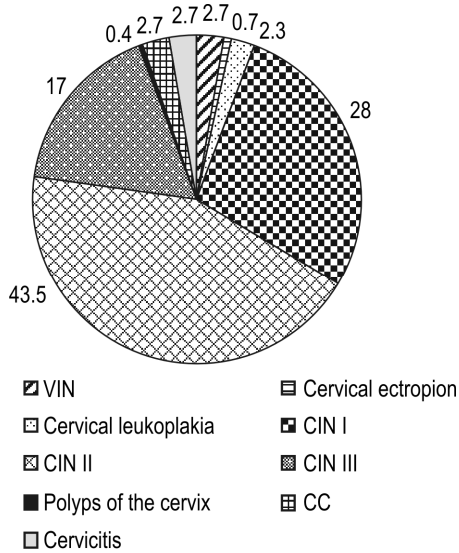

Fig. 4. Distribution of patients with cervical pathology within the dispensary group

The order on the work of antenatal clinics in Yekaterinburg made it possible to centralize patients with CIN in one institution for a full diagnosis and adequate surgical treatment if necessary. All antenatal clinics in the metropolis refer patients to the cervical pathology office according to the order. At the same time, we see that in the city institution (ECPC) patients with CIN began to appear, living in the Sverdlovsk region (1.5 %). Currently, this is only a small part of those living in these settlements, but we understand that in the future it may be necessary to form similar structures with the possibility of centralizing specialized

medical care in offices in the cities of the Sverdlovsk region.

Most often, precancerous diseases of the cervix in residents of Yekaterinburg are detected at stage CIN II (43.5 %), slightly less often at stage CIN I (28 %). CC was detected in 2.7 % (n = 7). Thus, we believe that the main goal of creating a cervical pathology office on the basis of the ECPC in the metropolis has been achieved: the centralization of patients with CIN has been carried out, the identification of precancerous cervical diseases in the early stages for the purpose of timely treatment and prevention of the CC development [9–11].

Conclusions

1. Most often (in 38 % of cases) precancerous cervical diseases are detected in the group of women over 40 years old.

2. All districts of Yekaterinburg refer patients to a specialized cervical pathology office; antenatal clinics in the Verkh-Isetsky and Leninsky districts are especially active.

3. Patients in the cervical pathology office are provided with the full range of therapeutic and diagnostic procedures: biopsy, cervical excision and conization – in 21 % of cases, colposcopy – in 27 %, ablative treatment procedures – in 20.2 %, cervical argon plasma coagulation and ultrasound vaginal cavitation – 15.5 and 14.6 %; the most rear manipulations was cervical diathermocoagulation – 0.2 % (4).

4. The dispensary group of patients of the cervical pathology office is mainly represented by women with CIN II – 43.5 %, with CIN I – 28 % and with CIN III – 17 %.

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