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Characteristics of cervical biopsy during pregnancy

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ABSTRACT

BACKGROUND: Abnormal cervical cytology results occur in two out of every 100 pregnant women, a rate comparable to that in their nonpregnant peers. Histopathological examination of biopsy specimens is warranted only in cases of suspected invasive disease. Overall, cervical biopsy during pregnancy is rarely performed and is indicated only under strict clinical criteria, typically carried out by an experienced specialist, often in a hospital setting.

AIM: To evaluate the procedural characteristics of cervical biopsy and the histopathological findings in biopsy specimens obtained during pregnancy.

MATERIALS AND METHODS: This study included 28 patients divided into two groups: group 1 (n=13), pregnant patients who underwent cervical biopsy, and group 2 (n=15), nonpregnant patients who underwent the procedure. The indications for biopsy and the procedural techniques were analyzed in both study groups. Comparative statistical analysis was performed using Microsoft Excel, with statistical significance assessed using Pearson's chi-square test. The results were considered statistically significant at $p < 0.05$.

RESULTS: Comparative analysis of histopathological findings revealed no statistically significant differences in the detection rates of CIN I, CIN II, or CIN III between the groups. However, cervical leukoplakia was significantly more common in group 2 (14 cases, 93.3%), whereas no cases were recorded in group 1 (p=0.003). Nabothian cysts were identified in four cases (30.8%) in group 1 but were absent in group 2 (p=0.045). Dyskeratosis was observed only in group 1 (5 cases, 38.5%), whereas no cases were reported in group 2 (p=0.027).

CONCLUSION: Cervical biopsy during pregnancy is distinguished by the absence of anesthesia, the frequent use of targeted rather than multifocal biopsy, the omission of cervical canal curettage, and the need for prolonged hemostasis. Moreover, cervical biopsy performed during pregnancy is more frequently associated with CIN III histopathological findings (61.5%).

Keywords: cervical biopsy; pregnancy; cervical intraepithelial neoplasia.

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Особенности проведения биопсии шейки матки при беременности

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АННОТАЦИЯ

Обоснование. Во время беременности у двух из 100 женщин встречаются аномальные цитологические результаты анализов с шейки матки, которые аналогичны результатам небеременных сверстниц. Только при подозрении на инвазивный процесс показано гистологическое исследование биоптата опухоли. В целом биопсия шейки матки во время беременности проводится редко, по строгим показаниям, опытным специалистом, зачастую в условиях стационара.

Цель. Оценить особенности проведения биопсии шейки матки и результаты морфологического исследования биоптатов во время беременности.

Материалы и методы. В исследовании приняли участие 28 пациенток, которых разделили на две группы: группа 1 — 13 пациенток, которым проведена биопсия шейки матки при беременности; группа 2 — 15 пациенток, которым проведена биопсия шейки матки вне беременности. Проанализировали показания и технику проведения операций у пациенток исследуемых групп. На основании полученных данных провели сравнительный статистический анализ с помощью Microsoft Excel. Для оценки статистической значимости применяли критерий хи-квадрат Пирсона. Данные считали статистически значимыми при p <0,05.

Результаты. Сравнительный анализ гистологических заключений в двух группах показал, что статистически значимых различий в частоте обнаружения цервикальной интраэпителиальной неоплазии (CIN) I, II, III получено не было. Лейкоплакия шейки матки статистически значимо чаще обнаруживалась у женщин группы 2 — 14 (93,3%), тогда как в группе 1 не было ни одного случая (p=0,003). Кисты наботовых желёз в группе 1 имели место в 4 (30,8%) случаях, в группе 2 — не встретились ни у одной из пациенток (p=0,045). Дискератоз по результату морфологического исследования был установлен только у пациенток группы 1 — 5 (38,5%) случаев, в группе 2 такого заключения не было (p=0,027).

Заключение. Техника выполнения биопсии шейки матки при беременности отличается отсутствием обезболивания, частым применением точечной биопсии (вместо мультифокальной), отсутствием выскабливания цервикального канала и более длительным гемостазом. Проведение биопсии шейки матки во время беременности чаще сопровождается получением заключения CIN III по результату морфологии (61,5 %).

Ключевые слова: биопсия шейки матки; беременность; цервикальная интраэпителиальная неоплазия.

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妊娠期宫颈活检的特征

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摘要

背景。在妊娠期间，每100名女性中约有2人出现异常的宫颈细胞学检查结果，其结果与非妊娠同龄女性相似。仅在怀疑浸润性病变时，才需进行肿瘤组织活检和病理学检查。总体而言，妊娠期宫颈活检很少进行，且需严格遵循指征，由经验丰富的专家在住院环境中完成。

目的。评估妊娠期宫颈活检的操作特征及其病理学研究结果。

材料与方法。本研究纳入28名患者，并分为两组：第1组（*n*=13）为妊娠期接受宫颈活检的患者，第2组（*n*=15）为非妊娠期接受宫颈活检的患者。分析两组患者接受活检的指征及手术操作方式。基于所得数据，使用Microsoft Excel进行统计学比较分析，并采用 χ^2 检验评估统计学显著性当$p<0.05$时，认为数据具有统计学意义。

结果。两组患者的组织学分析比较结果显示，在宫颈上皮内瘤变（CIN I、II、III）的检出率方面，两组之间无统计学差异。然而，宫颈白斑在第2组患者中更为常见（93.3%，14例），而第1组患者中未见宫颈白斑（$p=0.003$）。纳博特囊肿在第1组中检出4例（30.8%），而第2组中未发现（0%，$p=0.045$）。组织学结果显示，仅第1组患者存在角化异常（5例，38.5%），而第2组未见此现象（$p=0.027$）。

结论。妊娠期宫颈活检的技术特征包括：无需麻醉，较常采用点状活检（而非多点活检），不进行宫颈管搔刮术，且止血时间较长。妊娠期宫颈活检的组织学分析结果更常诊断为CIN III（61.5%）。

关键词： 宫颈活检；妊娠；宫颈上皮内瘤变。

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BACKGROUND

Cervical cancer (CC) is a significant problem in both gynecology and oncology, currently ranking as the second leading cause of mortality [1]. In the majority of cases, intraepithelial neoplasia is diagnosed in women of reproductive age who have not yet experienced childbearing [2]. The detection rate of CC at the level of cervical intraepithelial neoplasia (CIN) in Russia is 25.5%, which is significantly lower than in Europe and the USA [3].

Abnormal cervical cytology results occur in two out of every 100 pregnant women, a rate comparable to that in their nonpregnant peers [4].

Over the years, the management of CIN during pregnancy has evolved from an aggressive biopsy and treatment-based course to a more conservative and watchful waiting approach [4]. Currently, the primary aim of interventions to reduce the incidence of CC is early diagnosis of CIN using the golden method, which includes colposcopy with biopsy of endocervical and exocervical epithelium together with identification of high-risk human papillomavirus (HPV) [4, 5].

If CIN is detected during pregnancy and pregnancy is to be preserved, prolongation of pregnancy with regular cytologic monitoring under the supervision of an obstetrician-gynecologist and an oncologist is indicated. Immunocytochemical double staining is an additional method in the diagnosis and prognosis of CIN, especially in controversial cases. Histopathology of biopsy specimens is warranted only in cases of suspected invasive disease. The presence of CIN is not an indication for termination of pregnancy or cesarean section. In all women who remain pregnant, repeat examination with cytology two months after delivery followed by loop electrosurgical excision is recommended. If CIN resolves after delivery, cervical conization is indicated because of the risk of CIN recurrence (up to 12.0%). However, it is possible to postpone conization for several months to minimize the risk of bleeding [5].

A colposcopically-directed radiosurgical loop electrode with a diameter of 100 μm is used for cervical biopsy in pregnant women. This diameter of the working surface has the advantage of minimizing radiofrequency contact with cervical tissue, thereby reducing the likelihood of coagulation changes [6, 7]. In recent publications, there is little description of the technique of cervical biopsy during pregnancy using scalpel, conchotome, or other mechanical methods.

The authors identified few publications addressing cervical biopsy during pregnancy and the differences observed in nonpregnant women. The procedural steps remain similar. The process is conducted in the outpatient setting, employing standard antiseptics. The biopsy is performed after an extended colposcopy and is guided by a video colposcope throughout the intervention. The tissue specimen intended for histopathology must contain both pathologic and healthy tissue. For the surgery, loop electrodes of a radiofrequency device are recommended to reduce blood loss. In most cases, the incision and coagulation mode of different power is used. Following the collection of a specimen, hemostasis is achieved with a balloon electrode. Subsequently, the wound surface of the cervix is treated with a potassium permanganate solution. There are no fundamental differences in the procedural characteristics of cervical biopsy between pregnant and nonpregnant women [6].

In view of the described events, the question arises why it is the cervical biopsy in nonpregnant patients that is not a matter of concern for physicians and is performed frequently, whereas cervical biopsy during pregnancy is performed only in exceptional cases and requires a specialist with great experience and readiness to assist in case of complications. There are several reasons why the technique of cervical biopsy during pregnancy is not currently standardized. Clinicians try to avoid invasive procedures during pregnancy because of the risk of miscarriage and the development of complications during surgery. Cervical biopsy during pregnancy is performed only when CC is suspected. In the late stages of pregnancy, the visual identification of pathological areas (tissue swelling, deciduosis, and contact bleeding with ectopia of the columnar epithelium) poses a significant challenge during cervical biopsy. Overall, cervical biopsy during pregnancy is rarely performed and is indicated only under strict clinical criteria, typically carried out by an experienced specialist, often in the hospital setting. The authors' objective was to identify differences in cervical biopsy performed in pregnant and nonpregnant women.

The study aimed to evaluate the procedural characteristics of cervical biopsy and the histopathological findings in biopsy specimens obtained during pregnancy.

METHODS

Study Design

The authors conducted an observational, single-center, retrospective, randomized, controlled study comparing cervical biopsy techniques in pregnant and nonpregnant patients.

Eligibility Criteria

Inclusion criteria: reproductive age (18–45 years), indications for cervical biopsy (morphologically unconfirmed diagnosis of CIN I, CIN II, CIN III, or CIS, abnormal cytology, and combination with highly oncogenic HPV).

Exclusion criteria: age over 45 years, no indication for cervical biopsy.

Study Setting

All patients were followed up at the Women's Clinic of the Yekaterinburg Clinical Perinatal Center.

Study Duration

The retrospective study was planned for the autumn of 2023, and the material collection (examination of patient

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outpatient records) was conducted from December 2023 to March 2024. The data analysis was performed in March and April 2024. No deviations from the schedule were observed.

Intervention

The outpatient records of pregnant and nonpregnant patients who underwent cervical biopsy were analyzed. In addition, medical history, cytological reports, polymerase chain reaction (PCR) results, video colposcopy protocols, cervical biopsy technique, and histopathological findings were evaluated.

The identification of HPV 16, 31, 33, 35, 52, 58, 67, 18, 39, 45, and 59 in endocervical specimens was performed by PCR according to the generally accepted method.

Colposcopy was performed with an MK-200 Scanner colposcope using the standard method. The interpretation of colposcopic findings was based on the International Classification of Colposcopic Terminology adopted at the 2011 World Congress in Rio de Janeiro.

During colposcopy, the scope of biopsy was determined based on the type of transformation zone, its area, the type of glandular lesions, the degree of lesion severity, and polymorphism of colposcopic features. The material was collected using special tungsten loops attached to the Fotek device (Fotek LLC, Yekaterinburg). After biopsy, the excision site was examined with a colposcope and additional material was collected, if necessary. After diagnostic loop biopsy, cervical material was collected for morphology in all patients; endocervical curettage after biopsy was performed only in nonpregnant patients.

The morphological examination of cervical biopsy specimens and cervical scrapings was performed using standard methods. Cervical tissue samples were fixed in 10% neutral buffered formalin and paraffin-embedded, with subsequent microtomy of paraffin blocks.

Main Study Outcome

The indications for cervical biopsy were evaluated, along with the consistency between cytological and morphological diagnoses.

Additional Study Outcomes

The differences in cervical biopsy techniques between pregnant and nonpregnant women were analyzed.

Subgroup Analysis

Twenty-eight female patients participated in the study. In order to attain the stud goal, the participants were divided into two groups: group 1 consisted of pregnant women who underwent cervical biopsy during the above period (n = 13); group 2 consisted of nonpregnant women who underwent cervical biopsy on the same or subsequent day as in group 1 (n = 15).

Outcomes Registration

Descriptive, analytical, and statistical methods were used to record main and additional outcomes.

Ethics Approval

The study was conducted in accordance with the ethical standards set forth in the Declaration of Helsinki. The study was approved by the Local Ethics Committee of the Ural State Medical University (Extract of Minutes No. 9 dated December 22, 2023).

Statistical Analysis

The sample size of patients in group 1 was determined by the number of procedures in pregnant women in the current period.

A comparative statistical analysis was performed on the obtained data using the Microsoft Excel software package. Pearson chi-squared test was used to assess statistical significance. Data were considered statistically significant at $p < 0.05$.

RESULTS

General Characteristics of the Study Groups and Histopathological Findings of Cervical Biopsies

The group of pregnant women included 13 participants, a mean age of 35.15 years and a gestational age of 18.83 weeks. Cervical biopsy was performed during pregnancy to exclude invasion in all cases. The diagnosis of CIN was confirmed in 76.5% of cases and excluded in 23.5% of cases.

Group 2 consisted of 15 women, a mean age of 37.2 years. The diagnosis of CIN was confirmed by histopathology of the biopsy specimens in all cases.

Comparative analysis of histopathological findings revealed no statistically significant differences in the detection rates of CIN I, CIN II, or CIN III between the groups. However, cervical leukoplakia was significantly more common in group 2 (14 cases, 93.3%), whereas no cases were recorded in group 1 (p = 0.003). Nabothian cysts were identified in four cases (30.8%) in group 1 but were absent in group 2 (p = 0.045). Dyskeratosis was diagnosed by morphological examination only in group 1 patients (5 cases, 38.5%; p = 0.027). The other results of morphological examination of the cervical tissue in pregnant and nonpregnant patients did not show statistically significant differences (Table 1).

Procedural Characteristics of Cervical Biopsy in Pregnant and Nonpregnant Women

For comparative evaluation of the cervical biopsy technique during pregnancy, a detailed description of the procedure was performed in two patients from different groups.

The first patient in group 1 underwent cervical biopsy during pregnancy due to suspected invasion (cytologically confirmed high-grade squamous intraepithelial lesion (HSIL), the presence of coarse acetowhite epithelium, and mosaicism and punctation on extended colposcopy). The biopsy

Table 1. Key morphological findings in cervical biopsy specimens from pregnant and nonpregnant patients (n = 28)

Morphological parameter	Group 1 (Pregnant, n = 13), abs. (%)	Group 2 (Nonpregnant, n = 15), abs. (%)	Statistical Significance (p)
CIN I	0 (0,0)	4 (26,7)	0,077
CIN II	2 (15,0)	7 (46,7)	0,199
CIN III (including transformation into CIS)	8 (61.5)	4 (26.7)	0.241
CIN not diagnosed based on morphology	3 (23.1)	0 (0.0)	0.078
Leukoplakia	0 (0.0)	14 (93.3)	0.003*
Cervicitis	9 (69.2)	14 (93.3)	0.601
Nabothian cyst	4 (30.8)	0 (0.0)	0.045*
Condyloma	0 (0.0)	1 (6.7)	0.359
Ectopia	1 (7.7)	0 (0.0)	0.293
Dyskeratosis	5 (38.5)	0 (0.0)	0.027*
Fibrovascular tissue without covering epithelium	1 (7.7)	0 (0.0)	0.293
Fragments of intact mucosa	0 (0.0)	2 (13.3)	0.201
No morphological results available	1 (7.7)	0 (0.0)	0.293

* Statistically significant differences, $p < 0.05$.

was conducted between 16 and 17 weeks of gestation, resulting in the initial diagnosis. After insertion of a vaginal speculum (a condom was placed on the speculum so that the vaginal walls would not interfere with the procedure), the cervix and vagina were irrigated with a saline solution and cavitated with low-frequency ultrasound. An extended colposcopy was then performed to locate the biopsy site. The biopsy was performed in the absence of anesthesia using a small loop on the Fotek device in a single pass in the cutting mode with a power of 60 W (Fig. 1).

Subsequently, additional hemostasis was achieved through the application of an electrode and a power of 60 W, operating in the soft mode on the Fotek device. The hemostasis was further augmented by the use of an argon plasma torch on the same device. The obtained specimen of cervical tissue was subsequently sent for histopathology. A tampon soaked in antiseptic was inserted into the vagina for several hours.

The second nonpregnant patient from group 2 underwent cervical biopsy indicated by abnormal cytology (HSIL according to Bethesda classification), presence of HPV of high oncogenic type and abnormal colposcopic findings (extensive iodine-negative area). The procedure was performed during the first menstrual period after extended colposcopy. As with the technique employed in group 1, the genital tract was initially irrigated with saline and subsequently cavitated using low-frequency ultrasound. An extended colposcopy was then performed to locate the biopsy site. The infiltrative anesthesia with 1 mL of bupivacaine hydrochloride was administered; no contraindications were identified. A multifocal biopsy was performed at several points using a video colposcope with subsequent endocervical curettage. The Fotek device was set to cutting mode, with a power of 60 W. Hemostasis was performed with an argon plasma torch and a ball-type electrode, in the soft mode, with a power of 60 W (Fig. 2).

After hemostasis, an antiseptic tampon was inserted into the vagina for several hours. The material obtained by broadband radiosurgery was sent for histopathology.

DISCUSSION

This study showed a high incidence of CIN III (morphologically confirmed) in pregnant women, supporting the hypothesis that cervical biopsy in pregnancy is performed only when CC is suspected. Conversely, in nonpregnant cases, the indication for biopsy may be suspicion of CIN I, CIN II, CIN III, and CC. Consequently, data on mild dysplasia in pregnant women after biopsy is less prevalent [2].

Mild to moderate cervical dysplasia (morphologically confirmed CIN I or CIN II) after cervical biopsy is more prevalent in nonpregnant women.

The authors found no significant differences in the incidence of benign cervical lesions in the two groups, including condyloma, glandular ectopia, cervicitis, and tissue fibrosis ($p > 0.05$).

In nonpregnant women, leukoplakia and cervicitis are morphologically more common among benign conditions. In pregnant patients, nabothian cysts and dyskeratosis are more frequent.

The technique of cervical biopsy during pregnancy differs in the absence of anesthesia, which is to be avoided to prevent complications associated with anesthesia, including

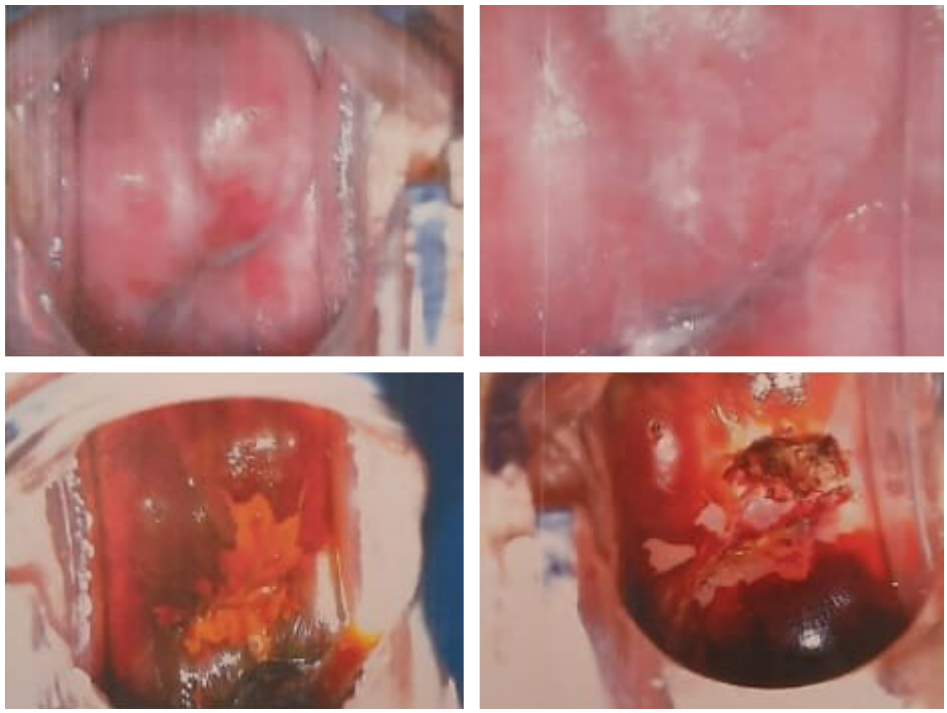

Fig. 1. Cervical biopsy in a pregnant patient under videocolposcopic guidance (author's photo).

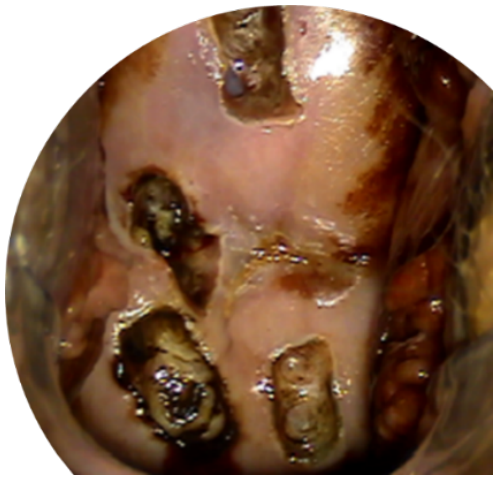

Fig. 2. Multifocal cervical biopsy in a nonpregnant patient (author's photo).

tachycardia and allergic reactions. More often, a targeted biopsy is performed rather than a multifocal biopsy due to the risk of bleeding and other complications. The procedure requires longer hemostasis with the use of different types of energy (argon or diathermal electrocoagulation) and tamponade.

Study Limitations

The study is limited by the small sample size. During pregnancy, this procedure is performed in exceptional cases.

CONCLUSION

Cervical biopsy performed during pregnancy is more frequently associated with CIN III histopathological findings (61.5%). Indications for biopsy are mainly cytologic findings of HSIL and suspected invasion. According to cervical biopsy data, the incidence of CC in pregnancy is not higher than in nonpregnant patients. Cervical biopsy during pregnancy is distinguished by the absence of anesthesia, the frequent use of targeted rather than multifocal biopsy, the omission of cervical canal curettage, and the need for prolonged hemostasis.

ADDITIONAL INFORMATION

Authors' contribution. E.A. Rosyuk: conception and study design, manuscript writing and editing, statistical data analysis; T.A. Oboskalova: manuscript editing; A.A. Shtanova: literature review, collection and analysis of literature sources, manuscript preparation and writing; A.S. Sarapulova: manuscript writing, data analysis; A.E. Filatov: manuscript writing, statistical data analysis; E.I. Neff: surgical treatment of patients, material collection; T.E. Verba: surgical treatment of patients, material collection. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work).

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Ethics approval. The study was conducted in accordance with the ethical standards set out in the Helsinki Declaration. The study

was approved by the Local Ethics Committee of Ural State Medical University (Protocol No. 9, dated December 22, 2023).

Consent for publication. The patients who participated in the study signed an informed consent to participate in the study and publish medical data.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Е.А. Росюк — идея и дизайн исследования, написание и редактирование статьи, статистический анализ данных; Т.А. Обоскалова — редактирование статьи; А.А. Штанова — обзор литературы, сбор и анализ литературных источников, подготовка и написание текста статьи; А.С. Сарапулова — написание текста статьи, анализ данных; А.Е. Филатов — написание текста статьи, анализ статистических данных; Е.И. Нефф — хирургическое лечение пациентов, набор материала; Т.Е. Верба — хирургическое лечение пациентов, набор материала. Все авторы подтверждают соответствие своего авторства международным критериям ICMJE (все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией).

Благодарность. Авторы выражают признательность руководству ЕКПЦ: главному врачу, канд. мед. наук О.Л. Ксенофонтовой, заведующей поликлиникой ЕКПЦ И.В. Салимовой, заведующей гинекологическим отделением А.В. Туреевой за возможность проведения исследования на базе центра.

Этическая экспертиза. Исследование проведено в соответствии с этическими стандартами, изложенными в Хельсинкской декларации. Исследование одобрено локальным этическим комитетом ФГБОУ ВО «УГМУ» МЗ РФ, выписка из протокола № 9 от 22.12.2023 г.

Согласие на публикацию. Участники исследования подписали информированное согласие на участие в исследовании и публикацию медицинских данных.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Раскрытие интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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