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THE RESULTS ANALYSIS OF CYTOLOGICAL EXAMINATION OF VULVAR INTRAEPITHELIAL NEOPLASIA COMPARED TO HISTOLOGY REPORT

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Timely diagnosis and effective treatment of precancerous diseases of the female genital organs prevent the development of oncogynecological diseases. Vulvar intraepithelial neoplasia is a precancerous disease characterized by lesions of the stratified squamous epithelium with impaired maturation and normal keratinization of cells, but without inclusion of the basement membrane in the pathological process. The main methods of diagnosis of vulvar intraepithelial neoplasia are vulvoscopy, cytological and histological examination.

The aim of this study was to assess the clinical significance and effectiveness of different sampling methods for cytological examination in comparison with histological report.

Materials and methods. The study involved 235 women aged 35–79 years, with a mean age of 57±11.3 years with complaints of pain, burning, discomfort and itching in the vulva. All patients underwent a simple vulvoscopy, where atrophy of the mucosa, partial or complete loss of the clitoris and / or labia minora, fissures, ecchymoses (haemorrhages), eroded surfaces, exophytic growths from 1 to 5 cm were detected. Material sampling was performed by various cytological methods.

Results. According to the results of the study, no significant differences between the methods of cytological sampling were observed. The cytological report was compared to the result of histological examination of biopsies. According to the results of cytological examination, squamous cell carcinoma of the vulva was detected in 12 patients, atrophy was identified in 5 women and squamous epithelial scales cytologically detected in the remaining 218 women.

Conclusions. The sensitivity and specificity of cytological examination methods were high in the presence of eroded surfaces and exophytic lesions. It was found that cytological research methods were not informative enough to detect vulvar cancer, which is in the stratum of hyperkeratosis, and was diagnosed in 5.1 % of patients. Therefore, for the reliability of the results and confirmation of the diagnosis it is necessary to conduct histological examination, with the help of which 14.9 % of patients were diagnosed with squamous cell carcinoma

Keywords: vulvar intraepithelial neoplasia, vulvoscopy, squamous cell carcinoma, differentiated type, usual type

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1. Introduction

Malignant lesions of the female reproductive system account for up to 18 % of all types of oncology. Malignancies such as cervical, uterine body (which includes mainly adenocarcinomas originating from the endometrium and some other rare cancers such as sarcomas), ovarian, vulvar, vaginal, fallopian tube and choriocarcinoma are important causes of morbidity and cancer mortality worldwide. Most often, they are detected already in the late stages, when approaches to treatment are significantly limited, and the cancer spreads to neighbouring organs. However, at an early stage of detection, these types of cancer are treatable, and the percentage of recurrence is not high [1, 2].

Cancer of the vulva accounts for only 2–5 % of malignant gynecological tumours. Vulvar squamous cell carcinoma, the most common subtype, has traditionally been considered a disease of postmenopausal women, although the average age of onset has decreased in recent years due to the increase in HPV infections worldwide [3–5]. As a rule, the development of oncogynecological diseases is preceded by background and precancerous processes, which are effectively treatable with timely diagnosis.

In gynecological pathology (ISSVD) since 2015, squamous intraepithelial lesions of the vulva of three degrees of malignancy: low-grade intraepithelial lesion (LSIL) – condylomas, vulvar epithelial neoplasia, usual type, effect of the human papilloma virus; high-grade intraepithelial lesion (HSIL) – vulvar intraepithelial neoplasia, usual type; vulvar intraepithelial neoplasia, differentiated type. The most frequent symptom is itching, mainly at night [6–8].

Vulvar intraepithelial neoplasia (VIN) is a precancerous disease characterized by damage to the multi-layered flat epithelium with a violation of layering, but without inclusion in the pathological process of the basement membrane [9, 10]. The main methods of diagnosing VIN are vulvoscopy, cytological and histological examination [11].

The main purpose of vulvoscopy is to determine the state of the epithelium of the vulva, determine the borders of the lesion, the presence of eroded surfaces, atrophy, or hyperkeratosis, and determine the location of the biopsy [12]. Cytological examination of the vulva allows obtaining additional information about structures that are invisible during examination, such as epithelial

cells of various types, the presence or absence of nuclei in the detected epithelial cells [13]. According to some authors, considering the availability of the cytological method and the rather complicated procedure, the sensitivity and specificity of the method is quite low (from 40 to 70 %) [14–16].

The aim of the work. To evaluate the clinical significance and effectiveness of the application of different sampling methods for cytological research in comparison with histological.

2. Materials and methods of the research

The study involved 235 women, whose average age was 57 ± 4.3 years (from 35 to 79 years), with complaints of pain, burning, discomfort and itching in the vulva. The research was conducted based on the National Cancer Institute during 2019–2021. All patients underwent a simple vulvoscopy, where mucosal atrophy, partial or complete loss of the clitoris and/or labia minora, cracks, ecchymoses (hemorrhages), eroded surfaces, exophytic growths from 1 to 5 cm were noted.

Extract from the protocol of the Bioethics Commission from the State Institution “Institute of Pediatrics, Obstetrics and Gynecology of NAMS of Ukraine” No. 294 dated 12/19/2019. Informed consent was obtained from all patients.

Before extended vulvoscopy, all patients underwent a cytological examination of the vulva using one of four methods of material collection: direct smear-imprint, direct smear-imprint with pre-treatment of the vulva with physiological solution, indirect method of obtaining a smear and liquid cytology.

A cytological preparation – a smear-imprint or a scraping could be performed within a few minutes without using additional special equipment. With the direct method of obtaining a smear-imprint, the slide is intimately adjacent directly to the affected area (ulcers, erosions, crusts, pustules, plaques, etc.). With the indirect method, an Air spatula, a Cytobrush type brush, foam cubes, or a scalpel blade are used to collect the material [17].

The preparation, fixation and staining of the preparation are of practically the main importance for the

correct assessment of the microscopic picture. Staining is carried out according to the method of Papanheim, Leishman, Romanowsky-Giemsa, Papanicolaou [18]. The most common method for detecting dysplastic changes and cancer is Papanicolaou staining [19]. Papanicolaou developed the technique of staining pap smears in accordance with the task of researching sexual function. When staining according to Papanicolaou, hematoxylin, orange dye, and modified eosin are used [20].

Modern technologies ensure the high quality of the cytological preparation, which ensures the accuracy and reliability of the result, due to the arrival of all cells in the laboratory, the enrichment of the cytological material, the automation of the process of applying it to the glass followed by Papanicolaou staining. This is facilitated by liquid cytology analysis (LBC) using BD SurePath technology on the BD PrepMate System analyzer and test system.

Collection of material by the method of liquid cytology [21] allows simultaneous cytological examination, HPV test, immunocytochemical examination (proliferation markers p16/Ki67) [22, 23]. Up to 5–6 “serial” strokes could be made from one collected material. In this work, the 4 above-mentioned methods of taking material for cytological research were used.

Statistical processing of the obtained results was carried out using Microsoft Excel and Statistica 7.0 for Windows. All quantitative indicators were calculated as $M \pm m$, where M is the average value of the indicator, m is the standard error of the average. For indicators characterizing quality features, the absolute number and relative value in percent (%) were indicated. Student's t-test was used to compare data. A value of $p < 0.05$ was considered statistically significant.

3. Research results

235 patients were involved in the study, who were diagnosed with VIN, squamous cell carcinoma and other types of diseases using various methods of cytological examination material collection and comparison with the histological conclusion. Table 1 presents the results of cytological and histological findings.

Table 1

Comparison of results based on cytological and histological research methods

Number of patients	The method of taking cytological material	Diagnosis	The number of cytological findings, n (%)	Number of histological findings, n (%)
98	Smear-imprint	Squamous cell cancer	5 (5.1 ± 0.6)	14 (14.3 ± 1.0)
		Squamous epithelial scales	93 (94.9 ± 1.5)	–
		Keratoses	–	84 (85.7 ± 2.1)
91	Smear-imprint with the application of a physiological solution	Squamous cell cancer	4 (4.4 ± 0.6)	13 (14.3 ± 1.0)
		Squamous epithelial scales	87 (95.5 ± 2.4)	–
		Keratoses	–	78 (85.7 ± 1.5)
41	Liquid cytology	Squamous cell cancer	3 (7.3 ± 0.6)	8 (19.5 ± 1.0)
		Squamous epithelial scales	38 (92.7 ± 2.1)	–
		Keratoses	–	33 (80.5 ± 1.8)
5	Scrape before taking a smear-imprint	Atrophy	5 (100)	–

Note: $p < 0.05$ between characteristics of groups of cytological and histological findings

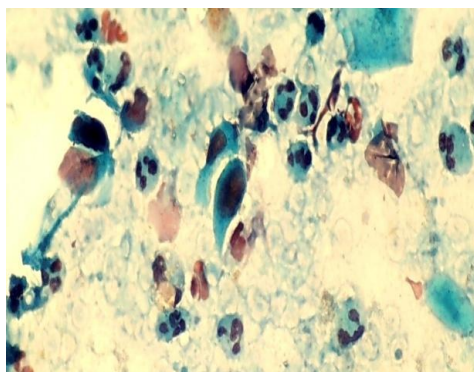


Fig. 1. The cytogram corresponds to an area of squamous cell carcinoma with signs of keratinization. Staining according to Pappenheim, $\times 40$

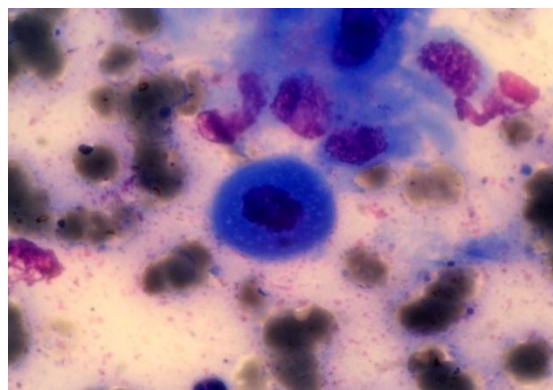


Fig. 2. The cytogram corresponds to keratosis of squamous epithelial cells. Staining according to Pappenheim, $\times 40$

Here are several variants of the microscopic description: cells with atypia of different sizes and shapes, the cytoplasm is dense, the nuclei in part of the cells are hyperchromic; atypical club-shaped cells with hyperchromic large nuclei are present, the cytoplasm is elongated in one of the poles, keratinized; cells with elongated atypia, small cells with hyperchromic nuclei, dense cytoplasm with signs of atypia are present.

The rest of the group, 93 women (94.9 %) out of 98, received the following cytological conclusion: against the background of coccobacillary flora and key cells, squamous epithelial cells and accumulation of squamous epithelial scales are determined, which may correspond to the presence of leukoplakia.

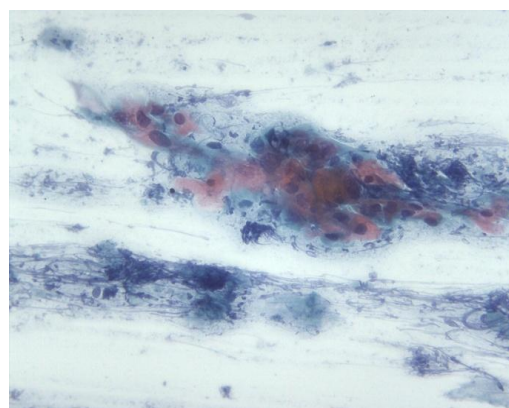
During the histological examination, in 9 (9.2 %) of 93 women, where the vulvoscopic lesion had the appearance of gross leukoplakia and the cytological conclusion - squamous epithelial scales, "squamous cell carcinoma" was established, and in 5 (5.1 %) women this diagnosis was also confirmed histologically

91 women (38.7 %) underwent a smear-imprint with a prior application of saline solution to the vulva. Like the first group, the sensitivity of the research method is high in the presence of eroded surfaces and exophytic lesions. The cytological conclusion "squamous cell carcinoma" was obtained in 4 patients (4.4 %) out of 91.

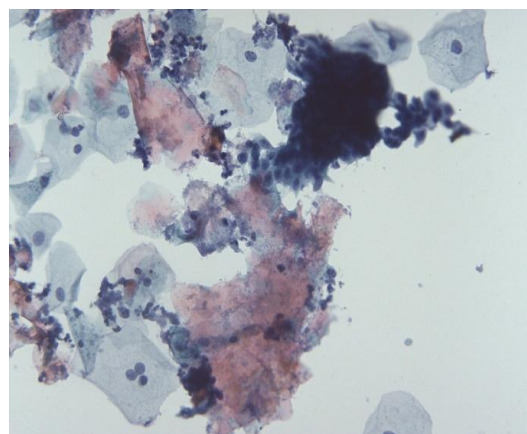
Histological examination revealed "squamous cell carcinoma" in 13 women (14.3 %). Of these, in 5 women, gross leukoplakia of the vulva, accumulation of squamous epithelial scales, parakeratocytes, and keratinization of the cytoplasm were visualized during vulvoscopy (Fig. 2). Cell lysis occurred in 4 patients; the material was lost.

In 32 out of 78 patients of the second group, where vulvar cancer was not histologically verified, the material was destroyed against the background of treatment with physiological solution, which contributed to osmotic cell lysis. Microcellularity was manifested, which was not enough for a cytological conclusion.

Liquid cytology using Cervical-brush type D was performed on 41 women (17.5 %). "Squamous cell carcinoma" was cytologically detected in only 3 patients (7.3 %) out of 41 in the form of single anucleated squamous scales (Figs. 3a, 3b), in contrast to the histological examination, in which 8 women (19.5 %) "squamous cell carcinoma" was verified.



a



b

Fig. 3. Liquid cytology:

a – cytogram corresponds to the area of squamous cell carcinoma with signs of keratinization; *b* – the cytogram corresponds to hyperkeratosis in viral lesions

It is also worth noting that from the obtained data of 3 patients, severe leukoplakia with cracks was noted vulvoscopically in the 1st woman, in the 2nd woman – a mucosal defect in the form of an ulcer, and in the 3rd woman – an exophytic lesion of the clitoris with increased bleeding.

In addition, a scraping from the vulva before taking a smear-imprint was performed in 5 patients (2.1 %) out of 235. In all 5 women of this group, a cytological conclusion was obtained: atrophy, visualization of small

layers of anucleated scales of squamous epithelium, squamous cells epithelium of the surface layer (Fig. 4).

In 3 patients (60 %) out of 5, there was a provocation of dermatoses, such as lichen planus, which manifested as a flat, discretely located purple papule with polygonal edges, which spread to the inner surface of the thighs, abdomen, buttocks, and back during 7–10 days after taking material for research. For this reason, the collection of material by this method was stopped.

Thus, summarizing the obtained results according to the histological conclusion, squamous cell carcinoma of the vulva was detected in 35 patients, and hyperkeratosis in the remaining 200 patients. According to the results of the cytological examination, squamous cell cancer of the vulva was detected in 12 patients, 5 women had atrophy, and in the remaining 218 women, squamous epithelial scales were cytologically detected (Fig. 5).

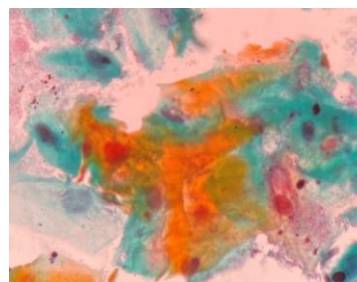
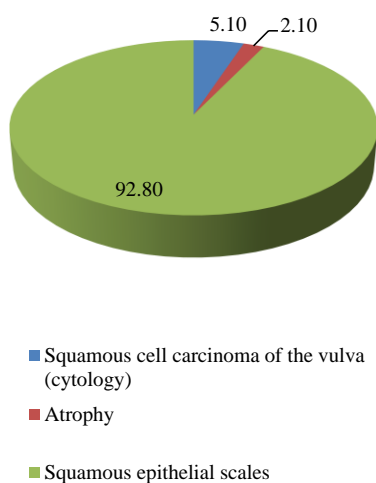


Fig. 4. The cytogram corresponds to layers with anucleate scales of squamous epithelium, cells of the squamous epithelium of the surface layer. Papanicolaou staining, ×40

Negative results of detection of squamous cell cancer of the vulva by the cytological method are, as a rule, associated with the absence of pathological cells in the obtained material for cytological examination.

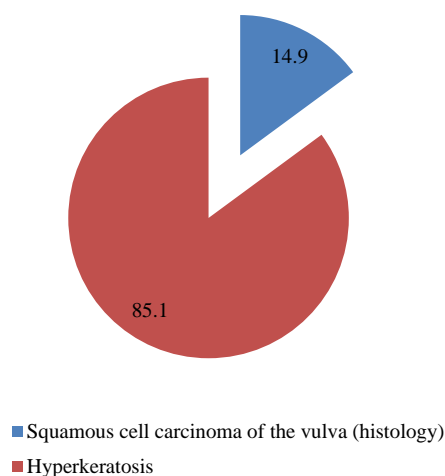


Fig. 5. Comparison of cytological and histological findings

4. Discussion of research results

This study analyzed the use of different collection methods for cytological examination in comparison with histological findings in patients with suspected VIN and leukoplakia. Taking a biopsy is standard procedure for establishing the correct diagnosis in patients with suspected precancerous lesions of the vulva. Using a less invasive diagnostic tool to collect material and determine whether a biopsy is needed could improve patient comfort, particularly in patients with chronic vulvar disease that may require serial biopsies.

There is a significant difference in the diagnosis of VIN and squamous cell carcinoma (SCC) with different methods of taking material for cytological research was not detected. Histological examination revealed a higher percentage of patients with SCC. Obtaining a rapid and accurate diagnosis in women with suspected VIN or vulvar cancer usually results in trial or repeat biopsies. Although histology remains important as it is currently the gold standard, especially for the initial diagnosis of lichen sclerosus and VIN, our results indicate that cytology obtained using the techniques used in the collection of material is also possible. In this study, limitations of diagnosing SCC were that some smears did not have sufficient cells for interpretation and that 36 (15.3 %) patients had material lost due to cell lysis. This

difficulty in obtaining sufficient material was also discussed in the literature [24].

Studies conducted by several authors allowed to evaluate the correlation of cytology results with histological results of VIN or SCC of the vulva. LCG van den Einden with co. indicated that vulvar cytology is the first step in the development of a triage tool to determine which patients with suspected premalignancy or cancer, especially during follow-up, should undergo a follow-up punch biopsy and which patients could avoid that procedure. The study conducted by the authors shows that cytology obtained with the help of a new brush for the vulva is promising as a possible first step in obtaining a diagnosis in patients with suspected (pre)malignant lesions of the vulva [24].

VL Bae-Jump et al. concluded that using a spatula tip for cytology, only 7 of 22 patients (32 %) with biopsy-proven (pre)malignancy had vulvar Pap smears that diagnosed VIN or vulvar carcinoma. They concluded that a negative Pap smear does not necessarily indicate the absence of the disease [17].

M Jimenez-Ayala and B Jimenez-Ayala collected cells for cytology (n=563) by scraping with a scalpel blade. The study reports that cytology could be used to diagnose malignancy with a sensitivity of 98 %, but a high specificity of 95 %. Their better results compared to

ours may be due to a more vigorous scraping method, in which they probably collected more cells from deeper tissue layers. However, the patient's discomfort was not evaluated, and the accuracy of detecting precancerous neoplasms in the work was not investigated [25].

The authors of SA Stabile et al, when comparing conventional and liquid cytology in patients with low risk of cervical cancer, found that liquid cytology had better performance for the diagnosis of atypical cells, and cytohistological concordance was higher than with conventional cytology [26].

Levine et al used a cytobrush to collect cells and analyzed 28 cytological specimens of histologically benign and premalignant lesions. With dyskeratosis as the sole cytologic criterion for VIN or anal intraepithelial neoplasia (AIN), all specimens were histologically consistent except for one (4 %) who was cytologically diagnosed as VIN, but VIN was not identified on biopsy. Presumably, these were all cases of HPV-related VIN or AIN, however, no attempt was made to differentiate between conventional and differentiated VIN [27].

In the work of YT Ouh with co-authors. analyzed the discrepancy between cytology and histology in cervical cancer screening. Almost 4000 patients were included in this multicenter retrospective study. Specified cervical cytology data consisted of 495 normal, 1390 atypical squamous cells of undetermined significance, 380 atypical squamous cells could not exclude a high-grade squamous intraepithelial lesion, 792 low-grade squamous cells, intraepithelial, 593 high-grade squamous cells in the epithelium, 46 squamous cell carcinomas, and 23 adenocarcinomas. HPV-positive data were found in 3008 (79.2 %) patients. The risk of unexpected low-grade histological lesions was higher in patients >45 years of age. In contrast, the risk of 1 unexpected high-grade lesions on colposcopic biopsy was lower in patients ≥45 years of age, and HPV 16/18 infection was higher than other HPVs. The authors concluded that age and HPV genotypes were responsible for the discrepancies between cytology and histology [28].

Study limitations. Inadequate interpretation of results in the diagnosis of SCC in women arose due to obtaining inferior material due to insufficient number of smear cells and loss of samples due to cell lysis. When

studying the anamnesis, special attention should be paid to the presence of concomitant somatic pathology, such as diabetes, diseases of the liver and gall bladder, thyroid gland, as well as to the blood sugar content, bacterioscopy and the presence of a viral infection.

Prospects for further research. Considering the obtained results and analyzing the literature data, it would be important for further studies to consider age categories (i.e., the age when perimenopause usually occurs), body mass index, and HPV genotype when analyzing cytological studies in comparison with histological ones.

5. Conclusions

1. It was established that there is no significant difference between the results of cytological sampling by these methods. The sensitivity and specificity of cytological research methods are high in the presence of eroded surfaces and exophytic lesions.

2. Cytological research methods are uninformative for detecting VIN and cancer of the vulva, which lie in the layer of hyperkeratosis. Physiological solution promotes cell lysis, after which the smear becomes small-celled, and the scraping of the vulva provokes dermatoses.

3. In case of any visible pathological changes of the epithelium of the vulva, and especially those that are not amenable to local treatment, it is necessary to conduct a biopsy with further histological examination.

4. These conclusions also confirm the results of the conducted studies, in which according to the results of histological examination, squamous cell carcinoma of the vulva was detected in 35 patients, while squamous cell cancer of the vulva was detected in 12 patients according to the results of cytological examination.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this research, whether financial, personal, authorship or otherwise, that could affect the research and its results presented in this article.

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