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Importance of Cytological Screening in the Diagnosis of Cervical Diseases

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The purpose of the study was to compare the conventional Pap smear with liquid-based cytology in the early diagnosis of cervical diseases.

Materials and methods. The study included 150 women between the ages of 18 and 73 with cervical diseases. The comparison was held on the basis of the results of histology of liquid-based and conventional Pap smears taken from cervix. Bethesda classification was used to make the diagnosis. Diagnostic performance was calculated in terms of sensitivity, specificity, positive predictive value and negative predictive value.

Results and discussion. During the sensitivity, specificity and prognostic assessment of liquid-based cytology with conventional Pap smears, the sensitivity of liquid-based cytology was higher than the conventional Pap test – 93.1%, and the conventional Pap test was 81.3%. The specificity of liquid-based cytology can be compared with a conventional Pap test (76.2% and 70.6%, respectively). The positive prognostic value was 84.4% in liquid-based cytology and 88.6% in the conventional Pap test. Negative prognostic value was significantly higher in liquid-based cytology than in conventional Pap tests (88.9% and 57.1%, respectively). The total diagnostic value was 86.0% in liquid-based cytology and 78.5% in the conventional Pap test.

As a result of the study it has become clear that liquid-based cytology is an appropriate method for the diagnosis of cervical diseases. There are screening programs for cervical, breast, colorectal and prostate cancer in the country, but due to some psycho-social factors, restrictions and barriers, patients only seek medical attention when there is an urgent need. As a result, more than half of all cancers are diagnosed at a late stage. Thus, the study concluded that liquid-based cytology is more convenient than conventional smear screening for cervical cancer screening. As single-layer smears are easier to examine, cells with atypia are not covered by other cells (inflammation, blood, etc.). In addition, the amount of unsatisfactory smears is minimal. In general, many studies have been conducted comparing liquid-based cytology with conventional Pap smears. The results were different in both the initial studies and the meta-analysis.

Conclusion. Thus, both screening methods predict the likelihood of disease in the same way, but with liquid-based cytology, the number of false-negative results is less, and the sample quality is improved by reducing the number of unsatisfactory smears. Also, women with liquid-based cytology are more likely to get a positive result than those with cervical disease. Liquid-based cytology is superior and more sensitive than conventional Pap tests in the detection of cervical neoplasms.

Keywords: cervical cancer screening, conventional Pap, liquid-based cytology, sensitivity, specificity, predictive value.

Introduction. Cervical cancer (CC) is one of the most common oncological diseases among women in the world. Thus, according to GLOBOCAN, in 2018, 570,000 new cases of the disease and 311,000 deaths due to CC were registered in the world. CC is found in most cases (74%) in developing countries, where it accounts for 15% of all cancers observed in women, and it is the second most common cause of death from cancer. In developed countries, this figure is 4.4% of new cases. In 2018, 4,960 women were diagnosed with cervical cancer for the first time in Azerbaijan, and 6.9% of these women have malignant neoplasms. Among malignant diseases of the female reproductive organs, cervical cancer is in the first place, uterine cancer is in the second, and ovarian cancer is in the third place [1].

The survival rate of CC patients depends on many factors, including the stage at which the disease is detected. Thus, when CC is detected at an early stage, the 5-year survival rate is 92%. The 5-year survival rate is 57% when CC metastasizes to surrounding tissues and regional nodes, and 17% when it infects other organs [2, 3, 4]. In this regard, early detection of the disease and future prognosis can be of great scientific and practical importance in improving the survival of patients, timely treatment and prevention of metastases [5].

Inefficient and irregular screening programs in developed countries are cited as one of the reasons for the increase in the incidence and mortality. Cytological screening is indicated as the main method in the diagnosis of cervical cancer. Following the invention of the Papanicolau (Pap) smear test in the 1950s, there was a significant reduction in the incidence of invasive cervical cancer due to cervical cytological

screening [6]. Pap smears are used to detect precancerous and malignant processes in the cervix. One of the main conditions for increasing the effectiveness of cytological screening is the quality of the material [7]. Therefore, numerous studies are being conducted to improve the screening of cervical diseases and the effectiveness of other alternative diagnostic methods is being studied [8]. According to a number of sources, it is advisable to use a liquid-based cytology method to overcome these problems [9]. This method, first proposed in the United States in 1998, aims to reduce the human factor in the examination and improve the quality of the smear [10]. Liquid-based cytology improves the quality of test specimens and reduces the likelihood of erroneous negative cytological results, thus facilitating the early detection of cervical cancer [11].

The purpose of the study was to compare conventional Pap smear with liquid-based cytology in the early diagnosis of cervical diseases.

Materials and methods. The clinical part of the research was performed in the outpatient department of the Scientific Research Institute of Obstetrics and Gynecology. Laboratory methods of the research were performed in the laboratory of the Scientific Research Institute of Obstetrics and Gynecology. To solve the tasks set in the research work the department included clinical materials of 150 women from 1,369 patients who applied to the Scientific Research Institute of Obstetrics and Gynecology for consultation in 2018-2019. The main group consisted of 130 women with background anamnesis and tumor changes, and the control group included 20 women with normal cytograms. The main group was divided into 3 subgroups. Subgroup I consisted of 50 patients of reproductive age, subgroup II – 39 patients of premenopausal age, subgroup III – postmenopausal women, 41 women. Women diagnosed with cervical cancer were excluded from the study.

The study was carried out in compliance with the basic provisions of the "Rules of ethical principles of scientific medical research with human participation", approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEC Directive No. 609 (dated 24.11.1986), Orders of the Ministry of Health of Ukraine No. 690 (dated 23.09.2009), No. 944 (dated 14.12.2009), No. 616 (dated 03.08.2012). All the participants were informed about the goals, organization, methods of examination and signed an informed consent to participate in the completely anonymous study.

According to the results obtained, the age of women in the main group fluctuated between 18 and 73 years, the average age was 44.8±1.2 years. The average age of women in the reproductive group (n = 50) ranged from 18 to 47 years, the mean was 30.9±0.8, and the average age of women in the premenopausal group (n = 39) ranged from 40 to 53 years, and the mean was 46, 4±0.5; the age of patients in the menopausal group (n = 41) ranged from 47 to 73 years, the mean was 60.1±1.0. The age of patients in the control group (n = 20) ranged from 25 to 39 years, and the mean was 31.6±1.0 years.

Detailed anamnesis was collected from all patients. Objective examination, gynecological examination, ultrasound, liquid-based cytology, conventional Pap smear, colposcopy, biopsy were performed.

All women included in the study underwent cytological examination. Liquid-based cytology was analyzed with a CellScan 100A. An endocervical brush with a removable cap was used on the gynecological table to obtain cytological material. After the mirror is inserted, the cervix is carefully wiped with a clean cotton swab. The examination material was taken from three areas: the ectocervix, the border of the cylindrical epithelium with the multilayered squamous epithelium and the lower 1/3 of the endocervix. The endocervical brush was inserted into the cervical canal through the outer hole of the cervix and rotated 180 degrees once. The brush was cut and thrown into a bottle with liquid inside. Samples were stored at room temperature after collection. The delay between sampling and laboratory processing was no more than 2 hours. The samples were then centrifuged and filtered through a membrane filter, which removed mucus, inflammatory elements and blood cells from the sample and spread the sample on glass.

A glass slide was prepared for each examined patient. The prepared wet smears were fixed in alcohol for 30 minutes and stained according to the Papanicolau staining protocol.

The Bethesda system terminology, created in 1988 and updated in 2001 and 2014, was used to interpret the results of cytological examination of the cervix.

Biopsy materials were taken with FOTEK EA 141M. After a passive electrode was placed under the patient's haunch, the cervix was anesthetized with 10% lidocaine under aseptic conditions, and the material was removed from the area with pathological changes during colposcopy. The iodine negative field was dissected with an electrode petal with a power of 50-70 watts. The depth of dissection and the volume of tissue were selected individually depending on the form and nature of the pathological process.

Statistical analysis was performed by the methods of analysis of variance for quantitative indicators (ANOVA test), discriminant for qualitative indicators (Chi-square Pearson), then statistical accuracy of differences between groups and subgroups was specified with non-parametric U-Mann-Whitney and

H-Kruskal-Wallis methods. The calculations were performed in IBM Statistics SPSS-26.

Research results. The majority of women included in the research group are people living in the Republic of Azerbaijan, mostly in Baku. No significant difference was found in the study of their socio-economic situation. Patients had the status of housewives or workers, and working conditions were not associated with occupational injuries.

When assessing the cytological parameters, it should be noted that the Pap smear was taken from all the examined women by liquid-based cytology (**Table 1**). Dysplasia and malignancy were not reported in 7 (14.0%) women of reproductive age, 10 (25.6%) premenopausal women, and 17 (41.5%) menopausal women. However, 23 (46.0%) women of reproductive age had AS-CUS, 16 (32.0%) women had LSIL, and 4 (8.0%) women had HSIL. AS-CUS was in 13 (33.3%) premenopausal women, LSIL in 13 (33.3%) women, HSIL in 2 (5.1%) women, and AGUS in 1 (2.6%) woman. 11 (26.8%) menopausal women had AS-CUS, 7 (17.1%) women had LSIL, 2 (4.9%) women had HSIL, and 4 (9.8%) women had AGUS (P_H = 0.024).

Also, 20 (100.0%) of the women in the CG had a normal cytogram.

Table 1 – Results of Pap smear with liquid cytology

Pap smear	Control group (n=20)		Reproductive period (n=50)		Premenopausal period (n=39)		Menopausal period (n=41)		P_H =
	number	%	number	%	number	%	number	%	
Normal	20	100%	7	14.0%	10	25.6%	17	41.5%	0.024
AS-CUS	-	-	23	46.0%	13	33.3%	11	26.8%	
LSIL	-	-	16	32.0%	13	33.3%	7	17.1%	
HSIL	-	-	4	8.0%	2	5.1%	2	4.9%	
AGUS	-	-	-	-	1	2.6%	4	9.8%	

Table 2 shows the results of Pap smears taken by conventional, i.e. classical method. In comparison group, 7 women of reproductive age (23.3%) were normal, 12 women were AS-CUS (40.0%), and 6 women were LSIL (20.0%). %), blood elements were in 2 women (6.7%), inflammatory elements in 1 woman (3.3%), insufficient smear – in 2 (6.7%) women. 7 women (30.4%) of premenopausal age were normal, 6 women had AS-CUS (26.1%), 7 women (30.4%) had LSIL, 2 women (8.7%) had inflammatory elements, 1 woman (4.3%) had insufficient smear. 5 women (22.7%) of menopausal age are normal, AS-CUS was in 6 women (27.3%), LSIL – in 2 women (9.1%), HSIL – in 3 women (13.6%), AGUS – in 2 women (9.1%), 3 women (13.6%) had blood elements, 1 woman (4.5%) had inflammatory elements. In CG it was normal in 2 women (100.0%) (P_H = 0.095).

In general, in terms of quality, the traditional cytological analysis was found to be unsatisfactory in 5 cases in subgroup I, 3 women in subgroup II, and 4 women in subgroup III, and no cytological diagnosis was made. The reasons for the unsatisfactory smear were the lack of endocervical cells for analysis in the micropreparation, as the smear was mixed with inflammatory elements and blood cells. The biopsy was taken from acetowhite areas during abnormal colposcopic imaging. On the whole 87 women underwent histological examination. Analysis was taken from 48 women of reproductive age, 6 (12.0%) histological examination results were normal, 37 (74.0%) – CIN1,

Table 2 – Results of Pap smear taken in conventional way

Conventional Pap smear	Control group (n=20)		Reproductive period (n=50)		Premenopausal period (n=39)		Menopausal period (n=41)		P_H =
	number	%	number	%	number	%	number	%	
Normal	2	100%	7	23.3%	7	30.4%	5	22.7%	0.095
AS-CUS	-	-	12	40.0%	6	26.1%	6	27.3%	
LSİL	-	-	6	20.0%	7	30.4%	2	9.1%	
HSİL	-	-	-	-	-	-	3	13.6%	
AGUS	-	-	-	-	-	-	2	9.1%	
Blood			2	6.7%	-	-	3	13.6%	
Inflammatory			1	3.3%	2	8.7%	1	4.5%	
Atrophic cells			2	6.7%	1	4.3%	-	-	

7 (14.0%) – CIN2. Analysis was taken from 35 premenopausal women, 11 (31.4%) histological examination results were normal, 19 (54.3%) – CIN1, 5 (14.3%) – CIN2. Analysis was taken from 37 menopausal women, 16 (43.2%) histological examination results were normal, 16 (43.2%) – CIN1, 2 (5.4%) – CIN2, 1 (2.7%) – CIN3, 2 (5.4%) – condyloma was found (P_H = 0.001) (**Table 3**).

Table 3 – Biopsy results

Biopsy	Control group (n=20)		Reproductive period (n=50)		Premenopausal period (n=39)		Menopausal period (n=41)		P_H =
	number	%	number	%	number	%	number	%	
Normal	20	100%	6	12.0%	11	31.4%	16	43.2%	0.001
CIN 1	-	-	37	74.0%	19	54.3%	16	43.2%	
CIN 2	-	-	7	14.0%	5	14.3%	2	5.4%	
CIN 3	-	-	-	-	-	-	1	2.7%	
Condyloma	-	-	-	-	-	-	2	5.4%	

In the sensitivity, specificity and prognostic assessment of liquid-based cytology with conventional Pap smears, the sensitivity of liquid-based cytology was higher than the conventional Pap test – 93.1%, and the conventional Pap test was 81.3%. The specificity of liquid-based cytology can be compared with a conventional Pap test (76.2% and 70.6%, respectively). The positive prognostic value (pPV) was 84.4% in liquid-based cytology and 88.6% in the conventional Pap test. Negative prognostic value (nPV) was significantly higher in liquid-based cytology than in conventional Pap tests (88.9% and 57.1%, respectively). The total diagnostic value was 86.0% in liquid-based cytology and 78.5% in the conventional Pap test (**Table 4**).

Table 4 – Comparison of liquid-based cytology and conventional Pap smear results with the help of histology

Conventional Pap smear	Pathology			Liquid Based Cytology	Pathology		
	Positive	Negative	Histology		Positive	Negative	Histology
	48	**17**	**65**		87	63	150
+	39	5	44	+	81	15	96
-	9	12	21	-	6	48	54
Se	81.3	±	5.6	Se	93.1	±	2.7
Sp	70.6	±	11.1	Sp	76.2	±	5.4
pPV	88.6	±	4.8	pPV	84.4	±	3.7
nPV	57.1	±	10.8	nPV	88.9	±	4.3
LR+	2.76	Satisfactory		LR+	3.91	Satisfactory	
LR-	0.27	Satisfactory		LR-	0.09	Excellent	
TDV	78.5	±	5.1	TDV	86.0	±	2.8

Discussion. This article presents the results of a screening research for cervical cancer. In this research, the analysis of 150 women was analyzed. It has become clear that liquid-based cytology is an appropriate method for the diagnosis of cervical diseases. There are screening programs for cervical, breast, colorectal and prostate cancer in the country, but due to some psycho-social factors, restrictions and barriers, patients only seek medical attention when there is an urgent need. As a result, more than half of all cancers are diagnosed at a late stage. Thus, the study concluded that liquid-based cytology is more convenient than traditional smear screening for cervical cancer screening. As single-layer smears are easier to examine, cells with atypia are not covered by other cells (inflammation, blood, etc.). In addition, the amount of unsatisfactory smears is minimal. In general, many studies have been conducted comparing liquid-based cytology with conventional Pap smears. The results were different in both the initial studies and the meta-analysis.

FDA has conducted a number of large, independent meta-analyzes comparing the clinical performance of liquid-based cytology and conventional Pap smears. These analyses showed that liquid-based cytology increased the detection rate of LSIL and HSIL cytology by 47% (P <.0011) and 116% (P <.0002), respectively, compared to the Pap test [12].

In a study with colleagues Bernstein and Abulafia in order to evaluate the performance of the ThinPrep Pap test alone demonstrated a significant improvement in sample adequacy and detection rates of LSIL and HSIL cytologies in liquid-based cytology compared to conventional Pap tests [13]. Also using 1,000 split samples with co-authors in Singh V.B. evaluating the diagnostic accuracy of liquid-based cytology compared to conventional Pap smears, an unsatisfactory result of 1.7% was observed. The main reason for the unsatisfactory result was the lack of epithelial cells in the conventional Pap smear, i.e. its insufficiency and blood in the smear. Inflammatory organisms were detected almost equally in both methods, but were better seen in LBC samples. Liquid-based cytology may be equivalent to conventional Pap smears because of the significant reduction in unsatisfactory results, the correct distribution of the smear, less time for screening, and better management of hemorrhagic, inflammatory specimens and, finally, greater sensitivity and specificity of liquid-based cytology [14].

Nishio H. and co-authors studied 312 women in Japan between 2013 and 2014. Diagnostic performance was calculated in terms of sensitivity, specificity, positive prognostic value (pPV) and negative prognostic value (nPV) to detect CIN2. Liquid-based cytology and conventional Pap smear sensitivities were 100.0% and 98.8%, specificity – 17.2% and 23.8%, positive prognostic value – 56.1% and 57.9%, and negative prognostic value – 100.0% and 94.7%, respectively. Although liquid-based cytology is more sensitive to the detection of CIN2, they did not see a significant difference between the two methods, and therefore concluded that liquid-based cytology could be an alternative to Pap smears for cervical cancer screening [15].

Conclusion. Thus, both screening methods predict the likelihood of disease in the same way, but with liquid-based cytology, the number of false-negative and unsatisfactory results is small. Also, women with cervical disease are more likely to get a positive result with liquid-based cytology. As liquid-based cytology is more sensitive and specific, it is superior to conventional Pap tests in the detection of cervical neoplasms.

Perspectives of further research. Further development of tests in the detection of cervical neoplasms is planned. Liquid material with cervical samples can be used for molecular biological studies, including HPV typing.

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РОЛЬ ЦИТОЛОГІЧНОГО СКРИНІНГУ В ДІАГНОСТИЦІ ЗАХВОРЮВАНЬ ШИЙКИ МАТКИ

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Резюме. Мета. Порівняння традиційного мазка Папаніколау з рідинною цитологією у ранній діагностиці захворювань шийки матки.

Методи. У дослідженні взяли участь 150 жінок віком від 18 до 73 років із захворюваннями шийки матки. Порівняння проводилося на підставі результатів гістології мазків на рідкій основі та традиційних мазків Папаніколау, взятих із шийки матки. Для встановлення діагнозу використовувалася класифікація Bethesda. Діагностичні показники розраховувалися з погляду чутливості, специфічності, позитивної прогностичної цінності (PPV) та негативної прогностичної цінності (NPV).

Результати. Під час оцінки чутливості, специфічності та прогностичної оцінки рідинної цитології з використанням традиційних мазків Папаніколау чутливість рідинної цитології була вищою, ніж у традиційного Папаніколау-тесту, 93,1%, а традиційний Папаніколау-тест склав 81,3%. Специфічність рідинної цитології можна порівняти з традиційним Папаніколау-тестом (76,2% та 70,6% відповідно). Позитивне прогностичне значення (pPV) склало 84,4% при рідинній цитології та 88,6% при традиційному Папаніколау-тесті. Негативна прогностична цінність (nPV) була значно вищою за рідинної цитології, ніж при традиційних Папаніколау-тестах (88.9% та 57,1% відповідно). Загальна діагностична цінність склала 86,0% при рідинній цитології та 78,5% при традиційному Папаніколау-тесті.

Висновки. Обидва методи скринінгу передбачають ймовірність захворювання однаково, але при цитології на основі рідини кількість помилково-негативних результатів менша, а якість зразка покращується за рахунок зменшення кількості незадовільних мазків. Жінки, яким робили рідинну цитологію, з більшою ймовірністю отримають позитивний результат, ніж жінки із захворюванням шийки матки. Рідина цитологія більш якісна і чутлива, ніж традиційні Папаніколау-тести, у виявленні новоутворень шийки матки.

Ключові слова: скринінг раку шийки матки, традиційний Папаніколау тест, рідинна цитологія, чутливість, специфічність, прогностична цінність.

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