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ABSTRACT

of the dissertation for the degree of Doctor of Philosophy

ASSESSMENT OF CLINICAL AND PATHOMORPHOLOGICAL CRITERIA FOR CERVICAL PRECANCER DISEASES

Speciality: 3242.01– Pathological anatomy

Field of science: Medicine

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GENERAL DESCRIPTION OF THE WORK

Relevance of the theme: After cardiovascular diseases, oncology diseases rank second in the world in terms of mortality rates. For this reason, the early diagnosis of neoplastic processes remains one of the most pressing issues in modern medicine. Among neoplastic processes, cervical cancer occupies one of the leading positions. According to the American Cancer Society, cervical cancer is diagnosed in an average of 1.3 million women each year, with 4,500 of these cases resulting in lethal outcomes[1].

The annual cytological examination using the Pap smear method has significantly reduced the incidence of cervical cancer in the U.S[2].

In 1988, the Bethesda System was established to classify pre-invasive and invasive cervical lesions based on histopathological and cytopathological changes. This system includes categories for low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL)[3].

In K.D. Hateh's research, the risk levels associated with HPV types in the development of cervical cancer and CIN have been determined. Specifically, HPV types 16, 18, 45, and 46 are classified as high-risk, while types 31, 33, 35, 51, and 52 are considered moderate-risk. Conversely, HPV types 6, 11, and 43 pose a low risk for CIN development.[4].It has been established that the false negative rate of Pap smears in women with CIN ranges from 8% to 50%. Proper technical collection of the Pap smear and its interpretation by

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[1]APGO Objectives. Cervical neoplasia and carcinoma. In Beckman CRB et al. editors. Obstetrics and Gynecology. // 4th ed. Philadelphia: Lippincott Williams and Wilkins, 2002. p. 547-565.

[2]Hartman K.E, Hall S.A [et al.] Screening for Cervical Cancer. Systematic Evidence review.No.25. (Prepared by the Research Triangle Institute, University of North Carolina Evidence-based Practice Center under contract No.290-97-0011). Rockville, MD: Agency for Healthcare Research and Quality. January 2002. p. 10-13.

[3]The 1988 Bethesta System for reporting cervical/ vaginal cytological diagnoses. National Cancer Institute Workshop. JAMA. 1989 Aug 18; 262(7): 931-4.

[4]Nubia M. Xavier F.N et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. Engl J Med. 03 Feb 6; 348 (6): 518-27.

a qualified cytopathologist can reduce the frequency of false negatives to about 5%.

The determination of tumor markers CA 125, CEA, and SCC is diagnostically significant in women's reproductive system cancers and is used to ensure the effectiveness of treatment.

The study of complex diagnostic methods and pathomorphological criteria for precancerous cervical conditions facilitates early diagnosis of these diseases and allows for appropriate corrections by specialized physicians, ultimately reducing the frequency of neoplastic processes, disease rates, and mortality rates. All of this significantly impacts women's health.

Research dedicated to the complex diagnostic methods for cervical precancerous conditions and the risk factors contributing to these diseases is limited and often contradictory. Overall, early detection of cervical cancer and precancerous conditions, which occupies a unique position among gynecological cancers, can provide valuable insights and advancements in the field, potentially serving as a new step in protecting human health. Considering the relevance of the issue, the objectives of the study have been established.

The aim of the study. The aim of the study is to investigate complex diagnostic methods and pathomorphological criteria for cervical precancerous diseases and pre-invasive cancer in women of reproductive age who belong to high-risk groups.

Objectives of the study:

1. To study the risk factors for cervical intraepithelial neoplasia (CIN).
2. To investigate the prevalence of human papillomavirus (HPV) infection (genotype) in comparative groups.
3. To assess the diagnostic significance of tumor markers (CA 125, CEA, SCC) in women with CIN.
4. To examine the characteristics of colposcopic and cytological examinations in women with CIN.
5. To study the features of histopathological examination in women with CIN.

Materials and methods of study.

The study included 100 women of reproductive age (18-45 years) from 2015 to 2019. Among them, 20 were healthy women

forming the control group (Group I), while 80 were in the high-risk group for cervical cancer (Group II - main group). The women in Group II were further divided into two subgroups: IIA – those with identified cervical pathology (n=41), and IIB – those without identified cervical pathology (n=39).

The menstrual function characteristics and any irregularities among the examined women were analyzed, along with their reproductive function. Body weight, height, body mass index (BMI), waist circumference (WC), and hip circumference (HC) were measured for all participants in the study. Additionally, the waist-to-hip ratio (WHR) was calculated.

In accordance with the study's objectives, the following procedures were performed on women in both the control and main groups: colposcopy (Schiller test), collection of Pap smear samples, and laboratory analyses. These included the determination of human papillomavirus (HPV) genotypes through polymerase chain reaction (PCR) on samples taken from the vagina, as well as the assessment of tumor markers in the blood: CA 125, CEA (carcinoembryonic antigen), and SCC (squamous cell carcinoma). Additionally, ultra-sound examinations and excisional biopsies were conducted, followed by histological analysis of the biopsy specimens.

Laboratory analyses: Before food intake, venous blood samples were collected from the patient in a resting state to assess the tumor markers SCC, CEA, and CA 125. These tumor markers were measured using the Abbott Architect Cobas e411 system in fully automated mode, with reagents from Roche Diagnostics.

In the ultrasound examination of the genital organs, a vaginal transducer was utilized. During the study, the length, anteroposterior diameter, and width of the uterus, as well as the length, width, and thickness of the ovaries, were assessed in women from both the control and main groups during their reproductive years. The ultrasound examination was conducted using a modern 4D device, the Voluson E6.

After each colposcopic examination, descriptions of the cervix and vagina were recorded. The Schiller test was used to detect neoplastic processes.

The Pap smears were coded with specific requisition forms and numbers, prepared for histopathological examination. Each requisition form for the Pap smear was filled out individually for every patient.

The Pap smears were included in the study based on the following criteria: there were sufficient flat epithelial cells, maintaining their integrity. Endocervical cells were observed in all Pap smears. Each smear contained at least five intact cells, along with a minimum of two endocervical glandular or squamous metaplastic cell clusters. Flat epithelial cells comprised at least 10% of the preparation. For moderate to severe dysplasia, biopsies were taken from the pathological area for histological examination to confirm the diagnosis.

The results obtained from the study were subjected to statistical analysis. In the processing of quantitative indicators within the groups and subgroups, a non-parametricmethod, the U test (Wilcoxon-Mann-Whitney), was applied.

Key theses to be defended:

– In the group of 80 women with a risk of cervical intraepithelial neoplasia (Group II), several factors were found to occur with higher frequency, including: excess body weight and obesity (16.95%), polycystic ovarian syndrome without insulin resistance (11.3%), HPV infection (13.56%), early initiation of sexual activity (7.91%), a family history of cervical cancer (7.91%), low socioeconomic status (6.78%), thyroid gland pathologies (6.78%), having more than three pregnancies (6.22%), and prolonged use of combined oral contraceptives (6.22%). Relatively fewer instances were noted for factors such as Chlamydia trachomatis (4.52%), HSV II (2.26%), CMV (2.26%), having multiple sexual partners (2.83%), and premature ovarian failure (2.83%).

– The high prevalence of cervical pathologies in women with excess body weight and visceral obesity is attributed to neuroendocrine and metabolic changes present in these individuals. Among 30 women with excess body weight and obesity, polycystic ovarian syndrome was found in 15 (50%), and Type 2DM was identified in 6 (20%).

- In women at risk for cervical intraepithelial neoplasia, the HPV 16 and 18 serotypes are detected in 13.56% of cases. HPV increases the incidence of precancerous cervical diseasesin patients with metabolic-endocrine pathologies (62.7%). Among women with CIN I, the HPV 16 serotype is found in 7.3%, and the HPV 18 serotype is also present in 7.3%. In women with CIN II, the HPV 16 serotype is detected in 9.8%, while the HPV 18 serotype is found in 12.2%. In all women with CIN III, the HPV 16 serotype is present in 17.1% of cases.
- In women with detected cervical pathologies, the levels of CA125, CEA, and SCC oncological markers are significantly higher compared to women in the risk group for cervical pathologies without any detectable issues. This allows for the use of these oncological markers in monitoring diagnosis and treatment progress.

  In women identified as being in the risk group for cervical cancer with diagnosed cervical pathologies—CIN I, CIN II, and CIN III—the levels of CA125, CEA, and SCC were statistically significantly higher than those in the control group. In the IIA subgroup, these markers were 20.9±1.8 (0.7-38.2) IU/ml for CA125, 4.2±0.3 (0.7-7.0) ng/ml for CEA, and 3.0±0.2 (1.1-5.0) ng/ml for SCC, while in the control group, the corresponding values were 13.0±1.1 (5.4-21.0) IU/ml, 1.9±0.1 (1.1-3.4) ng/ml, and 1.5±0.1 (0.8-2.4) ng/ml.
- In women of reproductive age, during colposcopy, cervicalpathologies such as leukoplakia, punctation, mosaic, atypical vascularization, and metaplasia are observed. After the acetic acid test, a whitish-gray appearance is noted, while iodine-negative areas are observed after the iodine test.

  During the pathologic examination of cervical pathologies, in ASCUS (Atypical Squamous Cells of Undetermined Significance), hyperchromasia of the nuclei in surface epithelial cells, irregularity of nuclear membrane contours, nuclear duplication, cellular anisocytosis, and dystrophy in the cell cytoplasm are present. In LSIL (Low-Grade Squamous Intraepithelial Lesion), parakeratosis, nuclear dyskeratosis, and

slight cytolysis are seen in the nuclei of squamous and intermediate cells. The nuclear-cytoplasmic ratio changes to approximately 1:2, with some nuclear growth indices exceeding three times. In HSIL, more severe cellular damage, noticeable cellular atypia, nuclear dyskeratosis, pathological mitoses, and in some areas, naked nuclei are present. In carcinoma in situ, deeper changes in cell nuclei, irregular nuclear contours, and the presence of two or more nuclei within rough, even "bare cytoplasm" are observed, along with disrupted cell boundaries and cell disintegration.

– In the histological examination of biopsy materials from cervical pathologies, in CIN I, an increase in cell proliferation is observed, with cells in the basal and parabasal layers being round and oval in shape, their nuclei appearing enlarged and having irregular membrane surfaces, and the cytoplasm showing basophilic staining. In CIN II, more than half of the epithelial layer is involved in the pathological process, with disruption of vertical anisomorphism and the presence of basal cell hyperplasia, as well as an increase in the number of nuclei. In CIN III, significant damage to the flat epithelial layer is noted, with only a few individual cells preserved in the upper layer of the epithelium. There is uneven distribution of epithelial cells, an increase in large dark-nucleated cells in the superficial layer, and the cytoplasm remains narrow around the nucleus. In carcinoma in situ, neoplastic changes are observed in a focal, multicentric form, with thickening of the epithelial covering and disruption of anisomorphism. The presence of cellular and nuclear polymorphism, disturbance of cellular polarity, and the presence of giant cells with irregular membranes and large nuclei are also noted.

Scientific novelty of the study.

Based on the conducted scientific research, the risk factors for cervical intraepithelial neoplasia in reproductive-age women have been identified. The study utilized new terminology for precancerous cervical diseases. It has allowed for the assessment of the significance of cytological, morphological, and functional examinations in the early diagnosis of precancerous and invasive processes of the cervix. The

findings revealed the dynamics of cytological and morphological changes depending on the severity of precancerous processes.

The development of pathological criteria for precancerous and invasive diseases will enable clinicians to select appropriate treatment strategies and significantly reduce the incidence of cancer.

Theoretical and practical significance of the study.

In the conducted scientific research, the complex diagnostics of risk factors for cervical preinvasive diseases in women were studied through clinical, cytological, morphological, and colposcopic examination methods for the early diagnosis of cervical intraepithelial neoplasias. Additionally, the pathomorphological criteria for preinvasive and invasive cervical diseases were developed.

As a result of this research, the importance of screening examinations-specifically cytological testing and colposcopy-for the early diagnosis of preinvasive diseases has been scientifically substantiated. The implementation of these examinations has guided specialized physicians in selecting appropriate treatment methods. Based on this, recommendations for pathologists and clinician specialists have been developed, aimed at reducing the incidence of cervical preinvasive and invasive diseases through the proposed comprehensive measures.

Approbation of dissertation.

The results of the research were discussed on January 28, 2022, at a joint meeting of the Department of Pathological Anatomy, Human Anatomy and Terminology, and the Department of Obstetrics and Gynecology II at Azerbaijan Medical University. Additionally, individual findings from the work were presented at various conferences dedicated to current issues in pathological anatomy and histology, including:The V Congress of the Russian Society of Pathologists (Chelyabinsk, June 1-4, 2017);The VI International Symposium and Training Course on "Molecular Medicine and Pharmacy" (Karachi, Pakistan, November 6-9, 2017);A conference dedicated to the 120th anniversary of Aziz Aliyev (Azerbaijan, February 9, 2017); A conference on "Modern Achievements in Healthcare" dedicated to the 95th anniversary of academician Zarifa Aliyeva (Azerbaijan, April 27, 2018);An international scientific-

practical conference on "The Role of Innovative Technologies in Medical Education and Clinical Practice" (Samarkand, Uzbekistan, May 6, 2021);Presentations at the IV International Turkish Forensic Expert Congress (October 26-29, 2023).

Organization where the Dissertation was conducted.

The dissertation work was carried out at the Department of Pathological Anatomy of Azerbaijan Medical University.

Scientific publications.

13 works have been published based on different fragments of the dissertation. Among these, there are 7 theses and 6 journal articles. Notably, 4 theses and 3 articles have been published in foreign journals.

Volume and structure of the dissertation. The dissertation is written in 152 computer pages (characters) of text. It consists of the structural sections: “Introduction”, “Main Content of the Dissertation”, “Conclusion”, “Results,” “Practical Recommendations”, and “References”.

A total of 201 sources of literature were used in the writing of the dissertation. The dissertation includes 38 figures, 14 tables, and 3 graphs.

The dissertation has a total of 171037 characters, including: introduction – 17047, Chapter I – 450 10, Chapter II – 28 470, Chapter III – 25784, Chapter IV – 13 508, Chapter V – 12666, conclusion – 25977, results – 2148, practical recommendations – 760 characters.

RESULTS OF INDIVIDUAL RESEARCH

The research was conducted at the Department of Pathological Anatomy of the Azerbaijan Medical University (AMU), in the Departments of Forensic-Histological and Pathological Anatomy of “The Association of Forensic Medicine and Pathological Anatomy” Public Legal Entity of The Ministry of Health, at the Educational and Surgical Clinic of the AMU, and the Republic Family Planning Consultation Center of the Azerbaijan Republic.

Women in the reproductive age group were classified into the risk category based on the following factors:

- Visceral obesity
- Polycystic ovary syndrome
- Hormone-active ovarian tumors
- Alcohol consumption
- Smoking
- Presence of sexually transmitted infections, as well as other infections (chlamydia, cytomegalovirus, herpes simplex virus type II, human papillomavirus infection)
- Having multiple sexual partners
- Long-term use of combined oral contraceptives (COCs)
- Low socioeconomic status, including inadequate nutrition
- Early initiation of sexual activity (before age 16)
- Early pregnancies
- Three or more completed pregnancies
- Family history of cervical cancer
- Immunosuppression

The study investigated the frequency of risk factors contributing to the development of cervical cancer in reproductive-age women.

Higher incidences of cervical pathologies were observed in women with excess body weight and visceral obesity. This can be attributed to the neuroendocrine and metabolic changes occurring in these women. Visceral adipose tissue is not insulin-sensitive; rather, it serves as a depot for steroid hormones. Consequently, these women are at increased risk not only for cervical pathologies but also for hyperplastic diseases and cancers of the endometrium, colorectal cancer, and breast cancer.Among the women with obesity, 10 (33.33%) were found to have endometrial glandular-cystic hyperplasia, further supporting the proliferative effect of estrogens on the endometrial lining associated with visceral obesity. Among the 30 women with excess body weight and obesity, 15 (50%) were diagnosed with polycystic ovary syndrome, and 6 (20%) had type II diabetes mellitus. The average weight of women with visceral obesity was 80.6 ± 2.1 kg (range: 54-104 kg), with a Body Mass

Index (BMI) of 28.9 ± 0.6 kg/m², indicating that they fall within the overweight category according to WHO guidelines (considered as overweight with a BMI of 25-29.9 kg/m²).

The risk group included five women diagnosed with premature ovarian insufficiency (POI), characterized by early menopause occurring between the ages of 38 and 41. The cervical issues observed in these patients were linked to sexually transmitted infections and comorbid conditions. Among the subjects, one had toxic goiter, while four were diagnosed with type I hypothyroidism (chronic autoimmune thyroiditis, also known as Hashimoto's disease). Atypical Squamous Cells of Undetermined Significance (ASCUS) were detected in these women; however, follow-up PAP smears revealed no pathological findings.

Metabolic and endocrine disorders, including ovarian hormonal-active tumors and thyroid pathologies, alongside sexually transmitted and other infections, contribute to an increased risk of cervical pathologies. Notably, the prevalence of HPVinfections within this cohort was 13.56%. This heightened prevalence is associated with the proliferative and destructive cellular changes induced by the virus, which can facilitate the development of neoplastic processes. Additionally, the presence of neuroendocrine and metabolic alterations appears to further exacerbate the risk of HPV-related cervical neoplasms.

In a study involving 100 women in their reproductive years, the average age was found to be 35.5 ± 0.8 years, ranging from 19 to 47 years. When analyzed by individual groups, the age ranges were as follows: the control group had an average age of 34.9 ± 2.0 years (19-47), the IIA subgroup averaged 35.1 ± 1.2 years (20-45), and the IIB subgroup averaged 36.3 ± 1.2 years (20-47).

Analysis of menstrual function revealed that 15 women (15%) experienced regular menstrual cycles, while 85 women (85%) had irregular cycles. The average weight of the women studied was 77.6 ± 1.4 kg (50-108), with an average height of 1.67 ± 0.01 m (1.54-1.78) and a body mass index (BMI) of 27.9 ± 0.4 kg/m². When examining the individual groups, the control group (n=20) had a mean weight of 76.6 ± 3.7 kg (50-98), a height of 1.68 ± 0.01 m (1.61-1.78), and a BMI of 26.9 ± 1.2 kg/m². In the IIA subgroup

(n=41), the average weight was 80.6 ± 2.1 kg (54-108), height was 1.67 ± 0.01 m, while the IIB subgroup (n=39) showed an average weight of 75.3 ± 2.1 kg (52-99) and height of 1.66 ± 0.01 m, with a BMI of 27.4 ± 0.7 kg/m². No statistically significant differences were found between the parameters of women with cervical pathology and those without, compared to the control group ($p > 0.05$).

When analyzing anthropometric indicators, it was determined that the average waist circumference (WC) among the participants was 84.0 ± 1.4 cm (62-113), the thigh circumference (TC) was 90.6 ± 0.9 cm (74-115), and the WC/TC ratio was 0.92 ± 0.01 (0.78-1.12). For the individual groups, the results were as follows: the control group had a WC of 82.3 ± 3.1 cm (66-102), TC of 90.5 ± 2.01 cm (78-104), and a WC/TC ratio of 0.90 ± 0.02 (0.78-1.01). The IIA subgroup showed a WC of 87.9 ± 2.1 cm (66-113), TC of 92.4 ± 1.5 cm (74-115), and a WC/TC ratio of 0.95 ± 0.01 (0.78-1.12). In the IIB subgroup, the measurements were 80.7 ± 2.0 cm (62-105) for WC, 88.7 ± 1.3 cm (76-105) for TC, and a WC/TC ratio of 0.91 ± 0.01 (0.78-1.03).

Increased body weight and adipose tissue accumulation, particularly in the abdominal region, were more pronounced among women in the risk group, especially in the IIA subgroup.

The medical history of the women involved in the study revealed a high prevalence of childhood infectious diseases (26.87%), respiratory illnesses (26.08%), and obesity (11.86%).

The mean age of first sexual intercourse among the women examined was 21.9 ± 0.7 years (ranging from 18 to 29 years). There were no statistically significant differences in the age of first sexual intercourse between the IIA and IIB subgroups compared to the control group ($p > 0.05$). Additionally, when comparing the IIA and IIB subgroups to each other, no significant statistical differences were observed ($p > 0.05$).

It was determined that among the 100 women studied, 8 (8%) had no history of childbirth, 65 (65%) had 1-2 births, and 27 (27%) had 3-4 births. The indicators for women with and without cervical pathology did not differ significantly from those in the control group ($p > 0.05$).

When analyzing the number of abortions, it was found that 17 women (17%) had a history of abortion, with 62 women (62%)

having experienced 1-2 abortions, and 21 women (21%) having had 3 or more abortions. The breakdown in individual groups was as follows: in the control group, there were 6 (30%) with no abortions, 11 (55%) with 1-2 abortions, and 3 (15%) with 3 or more; in the IIA subgroup, there were 5 (12.2%) with no abortions, 23 (56.1%) with 1-2 abortions, and 13 (31.7%) with 3 or more; while in the IIB subgroup, there were 6 (15.4%) with no abortions, 28 (71.8%) with 1-2 abortions, and 5 (12.8%) with 3 or more.

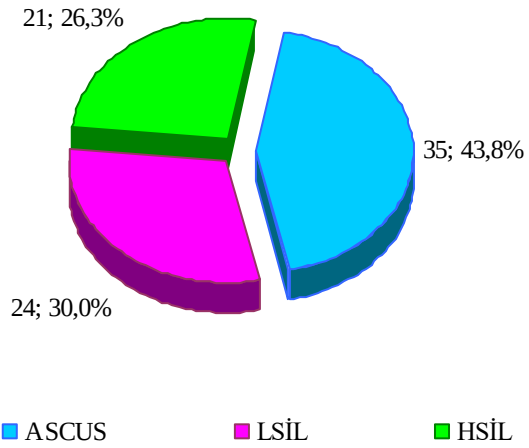
As observed, there were no statistically significant differences in the number of births or abortions both within the subgroups and when compared to the control group.

Investigation of the Impact of Human Papillomavirus on the Severity of Cervical Intraepithelial Neoplasias

Among 80 women included in the risk group (main group), the results of the PAP smears revealed 35 (43.75%) cases of ASCUS, 24 (30%) cases of LSIL, and 21 (26.25%) cases of HSIL (Graph1). Among the 35 women with ASCUS, after receiving treatment for contamination and inflammation, 5 (14.29%) were diagnosed with CIN I (IIA subgroup) upon re-evaluation with a PAP smear three months later. The remaining 30 women (85.71%, IIB subgroup) showed no pathological findings. Therefore, the study found that 14.29% of the 35 women with ASCUS were diagnosed with CIN I.

Twenty-four women with LSIL underwent a repeat cytological examination after 3 months. Among them, CIN I was found in 13 (54.17%) and CIN II in 2 (8.33%) in the IIA subgroup, while no pathology was identified in the remaining 9 (37.5%) in the IIB subgroup. Thus, CIN II was detected in 8.33% of the women with LSIL.

Twenty-one women with HSIL were referred for biopsy. CIN I was identified in 4 (19.05%), CIN II in 10 (47.62%), and CIN III in 7 (33.33%) of these women. In those with CIN III, cervical excision was performed, and the obtained materials were subjected to further histological examination. Among these 7 women, CIN III was confirmed in 4 (19.05%) and carcinoma in situ (CIS) in 3 (14.29%), who subsequently underwent total abdominal hysterectomy.



Graph 1. Frequency of pathological changes in women (n=80) belonging to the high-risk group for cervical cancer.Twenty-four women with LSIL underwent a repeat cytological examination after 3 months

Thus, among the 80 women in the high-risk group for cervical cancer, 43.75% were found to have ASCUS, 30% had LSIL, and 26.25% had HSIL. Specifically, CIN I was identified in 14.29% of those with ASCUS, 54.17% of those with LSIL had CIN I, while 8.33% had CIN II. For women with HSIL, 19.05% had CIN I, 47.62% had CIN II, and 33.33% had CIN III. The interpretation of the study results indicates that more severe cervical changes are observed, particularly among women with LSIL and HSIL, necessitating greater vigilance from clinicians. When HSIL is detected, histological examination is essential, as it aids in selecting appropriate treatment strategies.

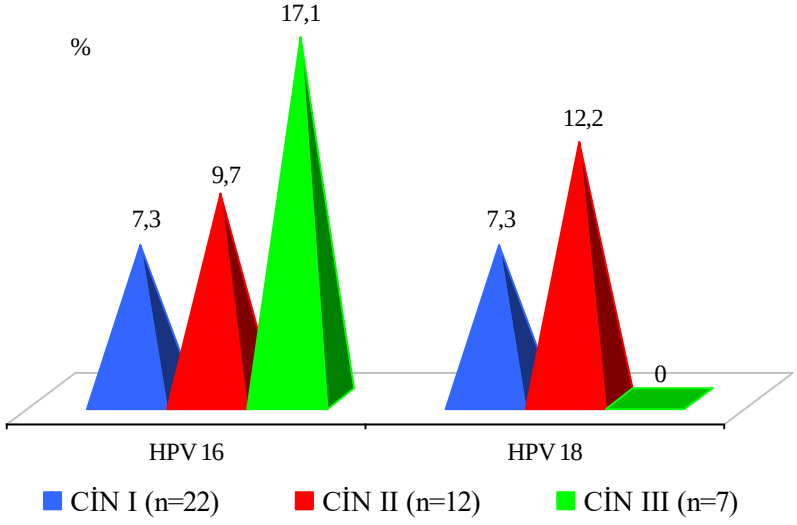
The study also examined sexually transmitted and other infections among the women, revealing that risk factors for cervical cancer included Chlamydia trachomatis in 4.52% (n=8), HSV II in 2.26% (n=4), and CMV in 2.26% (n=4), while HPV serotypes 16 and 18 were observed in 13.56% (n=24) of cases (calculations based on the total number of risk factors).

Considering the significant role of HPV in the development of cervical pathologies, the study investigated the impact of high-risk oncogenic HPV serotypes on the severity of cervical intraepithelial neoplasia. Among the 24 women with identified cervical changes,

HPV positivity was confirmed. Specifically, 14 women tested positive for HPV serotype 16, and 10 for serotype 18. Of these, 22 belonged to the IIA subgroup, while 2 were in the IIB subgroup. The two women in the IIB subgroup, both with HPV serotype 18, initially presented with ASCUS in their PAP smears. After addressing contamination and receiving anti-inflammatory treatment, follow-up PAP smears revealed no cervical pathology. These women were monitored over time, and no progression was noted.

In total, within the IIB subgroup (n=39), 5 cases of ASCUS were identified, of which only 2 were associated with HPV serotype 18. Given that ASCUS was observed against a backdrop of inflammatory changes, no pathology was found after anti-inflammatory treatment. Among the remaining 3 women with ASCUS in the IIB subgroup, SMV was detected.

In the IIA subgroup (n=41) with identified cervical pathologies, the distribution of lesions was as follows: CIN I accounted for 53.66% (n=22), CIN II for 29.27% (n=12), and CIN III for 17.07% (n=7). Among the women with CIN I (n=22), the prevalence of HPV serotypes was as follows: type 16 was detected in 7.3% (n=3) and type 18 in 7.3% (n=3). In the cases of CIN II (n=12), HPV type 16 was found in 9.7% (n=4) and type 18 in 12.2% (n=5) (Graph 2).



Graph 2. Frequency of HPV serotypes 16 and 18 in different degrees of CIN severity (%)

Among the women with CIN III, HPV type 16 was detected in all 7 cases (17.1%) (Graph 2). Therefore, HPV types 16 and 18 were identified in 6 women (14.6%) with CIN I, 9 women (22%) with CIN II, and 7 women (17.1%) with CIN III in the IIA subgroup. In total, HPV types 16 and 18 were present in 22 out of 41 women in the IIA subgroup. Although HPV types 16 and 18 were also found in the IIB subgroup, they did not lead to any morphological changes in the cervix.

Investigation of the impact of metabolic-endocrine changes on the severity of CIN

Analysis of risk factors for the development of cervical cancer revealed that metabolic-endocrine pathologies accounted for 62.73% (n=81) of cases. These pathologies included: overweight and obesity at 16.95% (n=30), polycystic ovary syndrome without insulin resistance at 11.3% (n=20), hormonal-active ovarian tumors at 1.7% (n=3), long-term use of combined oral contraceptives at 6.22% (n=11), thyroid pathologies at 6.78% (n=12), and ovarian insufficiency syndrome at 2.83% (n=5). Thyroid pathologies included diffuse toxic goiter at 1.7% (n=3), primary hypothyroidism at 2.26% (n=4), and secondary hypothyroidism at 2.83% (n=5). As observed, women with overweight and obesity exhibited a higher frequency of cervical pathologies.

In women with polycystic ovary syndrome (PCOS) related to overweight and obesity, insulin resistance and compensatory hyperinsulinemia were identified. Among these women, HPV types 16 and 18, along with various degrees of cervical intraepithelial neoplasia (CIN), were found in 12 cases (40%). Specifically, among HPV-positive women with obesity, CIN I was identified in 6 cases (20%), CIN II in 4 cases (13.33%), and CIN III in 2 cases (6.67%).

Furthermore, various degrees of CIN were also identified against the backdrop of other infections in overweight and obese women. For instance, CIN I was observed in 4 women (13.33%) with Chlamydia trachomatis, and CIN II in 1 woman (3.33%). Additionally, in a woman with CMV, CIN I was found (3.33%), while 2 women with HSV II presented with CIN II (6.67%) (see Table 1)

Table 1

Frequency of CIN among Women with Overweight and Obesity

№	Excess body weight and obesity n=30	CIN I		CIN II		CIN III	
		n	%	n	%	n	%
1	Obesity + HPV 16, 18 + insulin resistance with PCOS	3	10				
2	Obesity + HPV 16, 18	3	10	4	13,33	2	6,67
3	Obesity + Chlamydia trachomatis	4	13,33	1	3,33		
4	Obesity + HSV II			2	6,67		
5	Obesity + CMV	1	3,33				
6	Obesity + T2DM	6	20				
7	Obesity only	2	6,67				
	Total	19	63,33	7	23,33	2	6,67

CIN I was also observed in the context of metabolic-endocrine changes without any accompanying infections. Specifically, CIN I was identified in 2 women (6.67%) with isolated obesity and in 6 women with type II diabetes and obesity. During the study, CIN I was detected in 22 women (53.65%), CIN II in 12 women (29.27%), and CIN III in 7 women (17.07%), with corresponding findings of obesity and overweight in 19, 7, and 2 cases, respectively (totally 28 cases).

Thus, among the 30 women with obesity and overweight, 28 (93.33%) were found to have varying degrees of cervical intraepithelial neoplasia, with 12 (40%) testing positive for HPV types 16 and 18. Out of these women, 28 (93.33%) were classified into the IIA subgroup, while the remaining 2 (6.67%) were placed in the IIB subgroup, as no cervical pathology was identified in them.

Insulin resistance (IR) was absent in 20 women (25%) diagnosed with polycystic ovarian syndrome (PCOS). Among these women, neoplastic changes in the cervix were identified in 5 (25%). Specifically, in women with PCOS without insulin resistance, CIN II was found in 3 (15%) and CIN III in 2 (10%). All women with CIN were positive for HPV types 16 and 18. The endocrine changes associated with PCOS create an entry point for HPV infection, facilitating the development of significant cervical alterations.

Hormonal Active Tumors of the Ovaries (HATO**)**-granulosa cell tumors were found among the risk factors for cervical cancer at a rate of 1.7% (n=3). CIN II was diagnosed in 2 of these women, and CIN III in 1. All three cases were accompanied by positive HPV types 16 and 18.

Pathologies of the thyroid gland accounted for 6.78% (n=12) of the risk factors, with CIN III detected in only 1 woman (8.33%) who was positive for HPV 16 and 18. Long-term use of combined oral contraceptives (more than 5 years) made up 6.22% (n=11) of the risk factors. In these women, CIN I was identified in 3 (27.28%), and CIN III in 1 (9.1%) who was positive for HPV 16 and 18.

Thus, the analysis of the research results indicates that metabolic-endocrine changes, particularly excess body weight, obesity, and PCOS, increase the frequency of cervical pathologies. HPV infection further elevates the incidence of precancerous conditions of the cervix against the backdrop of metabolic-endocrine changes. Among women with metabolic-endocrine pathologies, 62.73% (n=81) tested positive for HPV 16 and 18, with CIN I identified in 7.4% (n=6), CIN II in 11.1% (n=9), and CIN III in 8.6% (n=7).

Results of colposcopic examination of cervical pathologies in women of reproductive age

During the colposcopic examination, the classification system ratified at the 7th World Congress was applied for the evaluation of cervical pathologies.

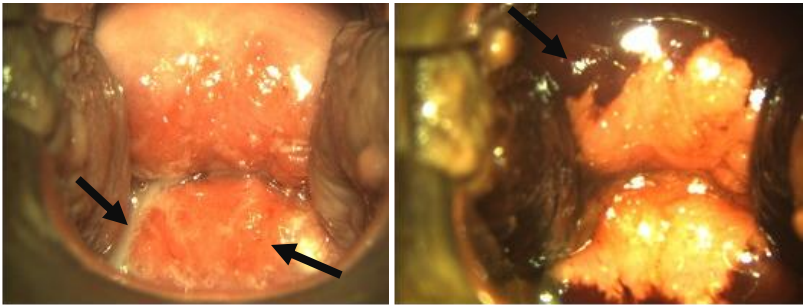
In healthy women of reproductive age, the boundary between the endocervix and ectocervix is located at the external os of the cervical canal. Cervical pathologies are primarily detected in healthy, mature women around the area of the external os, while in women of reproductive age, the transformation zone is visible in the region of the external os.

In cervical pathologies observed in women of reproductive age, such as leukoplakia, punctation, mosaic patterns, and atypical vascularization, white-gray areas were noted after the acetic acid test, and iodine-negative areas were observed following the iodine test.

In cases of atypical metaplasia, the weakly acetowhite layer differed from the white layers formed in other cervical pathologies. It was also noted that the formation of acetowhite layers occurred in cases of injury and infectious pathologies involving inflammatory cells. A definitive diagnosis was established through biopsy.

Unlike the normal vascular structure of the cervix, punctation revealed fine branches of afferent arterial and efferent venous vessels extending toward the surface.

In the atypical transformation zone, areas of hyperkeratosis, bleeding, and mucosal-purulent regions with a bluish-white appearance were observed (Figure 1).



a b

Figure 1. Main Group. Transformation Zone. Colposcopic Images of the Cervix. Acetic Acid Test (a), Iodine Test (b).

Weak iodine-negative areas are observed in certain epithelial cells of the cervix due to the loss of glycogen, which characterizes a mosaic appearance.

In women of reproductive age, leukoplakia can also be found on suspicious surfaces of the cervix. The colposcopic appearance of leukoplakia is characterized by the development of the keratin layer of the epithelium, resulting in smooth or irregular surfaces with a whitish, glossy membrane and the presence of iodine-negative zones. In leukoplakic areas, there are no intermediate cells accumulating glycogen, which creates the appearance of iodine-negative areas during the Schiller test.

The formation of these areas has been observed in both HPV-positive and HPV-negative women.

Study of the changes in tumor markers in cervical intraepithelial neoplasia

In the study, the levels of CA 125, CEA, and SCC in the serum of all women of reproductive age were investigated. The results obtained in individual subgroups were comparatively analyzed with those of the control group, as well as among the IIA and IIB subgroups.

In women included in the risk group for cervical cancer, with cervical pathologies such as CIN I, CIN II, and CIN III (IIA, n=41), the levels of CA125, CEA, and SCC were statistically significantly higher than those of the control group ($p<0.01$, $p<0.001$, $p<0.001$). Specifically, in the IIA subgroup, these markers were 20.9±1.8 (0.7-38.2) IU/ml, 4.2±0.3 (0.7-7.0) ng/ml, and 3.0±0.2 (1.1-5.0) ng/ml, whereas in the control group, the values were 13.0±1.1 (5.4-21.0) IU/ml, 1.9±0.1 (1.1-3.4) ng/ml, and 1.5±0.1 (0.8-2.4) ng/ml.

When comparing the results of the IIB group (n=39) with those of the control group, no statistically significant difference was found ($p>0.05$). The levels of CA125, CEA, and SCC in the serum of women from the IIA and IIB subgroups were compared, revealing that the IIB subgroup had higher and statistically significant values compared to the IIA subgroup ($p<0.05$, $p<0.001$, $p<0.001$).

Thus, in women from the IIA subgroup with cervical pathologies, the levels of the tumor markers CA125, CEA, and SCC were reliably higher than those in the control group and in the analogous indicators of the IIB group without cervical pathologies. The determination of these tumor markers is recommended for the diagnosis of cervical pathologies and for monitoring treatment progress.

Pathological features of ASCUS in cervical pathologies in women of reproductive age

In the cytological examination of PAP smears from women in the main group (Group II) of reproductive age, changes in the nuclear-cytoplasmic ratio of ectocervical cells were observed, along with notable irregularities in the nuclear membrane. This cytological picture has been described as indicative of internal cell damage in ASCUS—cells of uncertain significance.

During ASCUS, the nuclei of flat cells appear relatively hyperchromatic, and the cytoplasm of these cells shows weak and pale staining due to a decrease in glycogen content. It is important to differentiate the cytological picture of ASCUS from reactive changes that occur in flat cells. While reactive changes involve a relative enlargement of the nucleus, hyperchromatic nuclei and the absence of a clear area around the nucleus have been observed (see Figure 2).

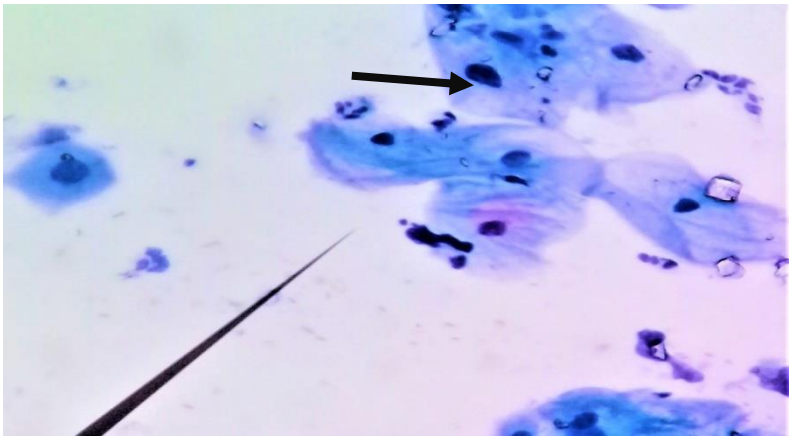


Figure 2. Main Group: ASCUS. Cervix. PAP Smear. Magnification x 200. Description provided in the text.

In ASCUS, surface cells are large and light pink in color, while intermediate cells are polygonal with diffuse chromatin. Parabasal cells are characterized by central nuclei, oval in shape, and are observed singly. Endocervical cells, or glandular cells, are noted for having clear, normal cytoplasm and round nuclei located near the apical surface. In ASCUS, hyperchromasia is observed in the nuclei of surface epithelial cells, along with indistinct nuclear membrane contours, nuclear duplication, and dystrophic changes in the cell cytoplasm.

Pathological features of LSIL in cervical pathologies in women of reproductive age

Among precancerous pathologies in reproductive-age women, LSIL occurs after ASCUS. LSIL represents low-grade intraepithelial

lesions and exhibits more pronounced changes compared to ASCUS. Specifically, parakeratosis, hyperkeratosis, nuclear dyskaryosis, and mild cytolysis are observed in the nuclei of flat and intermediate epithelial cells.

The nuclear-cytoplasmic ratio of these cells is altered, approaching approximately 2:1. Some cells have lost their original histological structure and size, with the growth rate in the nuclei of certain cells exceeding three times. The nuclei of surface and transitional epithelial cells are notably enlarged, with rough membrane surfaces. Hyperchromasia is evident in the nuclear material, indicating an excess of chromosomes.

Pathological features of HSIL in cervical pathologies in women of reproductive age

In women of reproductive age, HSIL, or high-grade intraepithelial lesions, presents with more pronounced cell damage compared to ASCUS and LSIL. In PAP smears, the nuclei of flat epithelial cells are oval or round in shape. Parabasal cells exhibit light pink cytoplasm and large dark nuclei. These nuclei are often duplicated, and their membranes appear rough.

Surrounding HSIL cells, small cells with dense cytoplasm can be observed, while areas of cytolysis may also be present. It is evident from the PAP smears that cellular atypism is significantly pronounced in HSIL. Dyskaryosis is noted in the nuclei, along with mitoses and, in some areas, even naked nuclei.

Pathological features of cervical Carcinoma in situ in women of reproductive age

In PAP smears from the cervix of women of reproductive age, atypical cells characteristic of cervical canal columnar and cuboidal cells are aggregated during carcinoma in situ. However, changes in the nuclei of atypical cells are more profound and differ somewhat from HSIL. The cells in the PAP smears vary in shape and size, as well as in nuclear diversity. Nuclear contours are irregular and

jagged, and the presence of two or more nuclei within the cytoplasm is identified.

Disruption of cell boundaries, cell disintegration, and even the presence of "naked nuclei" in some areas are noted.Cytological examination does not allow for differentiation of dysplasia resulting from metaplasia. Sometimes, cells obtained from the upper surface of the epithelial layer do not reflect the processes occurring in the basal layers. In such cases, biopsy is considered essential for the histological examination of the cervix.

Results of histological examinations

In cases of mild dysplasia (CIN I) in the cervix during the reproductive period, low-grade dysplastic changes are observed, characterized by preserved vertical anisomorphism. Proliferation of basal layer cells is noted in the lower third of the epithelial layer. The cells in the basal and parabasal layers exhibit rounded and oval shapes, with basophilic staining in the cytoplasm.

The nuclei of the basal and parabasal cells are enlarged and display irregular membrane surfaces. Staining variations are evident, including hypochromic, normochromic, and hyperchromic nuclei. The chromatin structure is distinctly observable in the nucleoli. The number of cells undergoing mitosis is relatively increased among hyperplastic cells; however, atypical mitoses are infrequently observed.

CIN II, indicative of moderate dysplasia, is characterized by the involvement of half or more of the epithelial layer in the pathological process. Pathohistological examination reveals disruption of vertical anisomorphism and hyperplasia of basal cells within the epithelial layer. An increase in the number of mitotically active nuclei is noted upon examination of the basal membrane.

In severe dysplasia (CIN III), a substantial portion of the cervical squamous epithelial layer is affected. Evidence of maturation and differentiation is only seen in isolated cells within the uppermost layer of the epithelium. No vertical anisomorphism or stratification disruption is observed in the cells located at the lower surface of the epithelial layers. Epithelial cells appear unevenly distributed, with an increased frequency of larger cells exhibiting darkly staining nuclei in the surface layer. Additionally, the increased

number of nuclei in epithelial cells and their hyperchromicity are significant findings.

Histological features of cervical carcinoma in situ in reproductive-age women

Microscopic examination of biopsy samples from reproductive-age women with cervical carcinoma in situ (Cr in situ) reveals thickening of the epithelial lining, loss of architectural differentiation, cellular and nuclear polymorphism, decreased basophilia in the cytoplasm, disruption of cellular polarity, increased nuclear size, irregularities in cell membranes, the presence of large atypical cells, and an increase in the number of pathological mitoses.

As the degree of cellular polymorphism in the cervix increases during the reproductive period, the histological architecture and prognosis are adversely affected, accelerating the progression toward cancer. Changes in cell morphology, variations in nuclear shape and density, and alterations in the nuclear-cytoplasmic ratio are indicators of pathological processes occurring in the cervix. A significant feature during this period is the increased chromatin content in dysplastic cells, with some nuclei exhibiting euchromatic areas. Changes within the nuclei of tumor cells are associated with variations in their chromosome numbers.

While colposcopic examination and PAP smear results can assess the degree of dysplastic changes associated with precancerous pathologies, they do not conclusively rule out Cr in situ or microinvasive cancer. Thus, histological examinations are considered the definitive and essential diagnostic method.In conclusion, clinical, laboratory, histological, and cytological assessments are crucial for the early diagnosis of precancerous conditions of the cervix in reproductive-age women. A comprehensive interpretation of the obtained results plays a vital role in selecting treatment options and determining clinical strategies. Collaboration between pathologists and clinicians is essential, enabling timely evaluation and prognosis of pathological conditions and facilitating appropriate treatment planning.

CONCLUSIONS

1. Among the risk factors for cervical cancer, metabolic-endocrine disorders represent a significant 45.78%, while sexually transmitted and other infections account for 12.6%, with HPV types 16 and 18 being the most common contributors (13.56%). Additional risk factors include having multiple sexual partners (2.83%), low socioeconomic status (6.78%), early initiation of sexual activity (7.91%), experiencing more than three pregnancies (6.22%), and having a family history of cervical cancer (7.91%), which were less frequently observed [1,5,9].
2. HPV types 16 and 18 were associated with pathological changes in the cervix in 22 women (27.5%). Specifically, HPV type 16 was identified in 17.5% of women with cervical pathology, while type 18 was found in 10%. Notably, in 2 women (2.5%) who tested positive for HPV type 18, no pathological changes were observed. Among women diagnosed with CIN I, HPV type 16 was present in 7.3% and type 18 in 7.3%. For those with CIN II, HPV type 16 was found in 9.8% and type 18 in 12.2%. Additionally, HPV type 16 was detected in 17.1% of women with CIN III [3,4,7,8].
3. Cervical cancer risk groups, including women with cervical pathologies such as CIN I, CIN II, and CIN III, exhibited significantly higher levels of CA125, CEA, and SCC compared to the control group ($p<0.01$, $p<0.001$, $p<0.001$). In the IIA subgroup, the levels were 20.9±1.8 (0.7-38.2) IU/ml for CA125, 4.2±0.3 (0.7-7.0) ng/ml for CEA, and 3.0±0.2 (1.1-5.0) ng/ml for SCC, whereas the control group showed values of 13.0±1.1 (5.4-21.0) IU/ml, 1.9±0.1 (1.1-3.4) ng/ml, and 1.5±0.1 (0.8-2.4) ng/ml, respectively[2,10].
4. Among 80 women in the risk group, PAP smears revealed 43.75% with ASCUS, 30% with LSIL, and 26.25% with HSIL. Women with ASCUS underwent repeat PAP smears 3 month after receiving treatment for contamination and inflammation, with CIN I identified in 14.29% of cases, while 85.71% showed no pathology. During colposcopy, targeted biopsies

were performed in women with pathological changes, particularly in cases of recurrent LSIL and HSIL[4,6,13].

5. Based on colposcopic examination, biopsies from 21 women with HSIL revealed 19.05% with CIN I, 47.62% with CIN II, and 33.33% with CIN III. Additionally, CIS was identified in 14.29% of women with CIN III. In cases of recurrent LSIL, histological analysis showed CIN I in 54.17% and CIN II in 8.33% of cases[11,12,13].

PRACTICAL RECOMMENDATIONS

1. The data obtained can be utilized as foundational material for the study of precancerous cervical pathologies during gynecological examinations and surgeries, as well as in the selection of new treatment methods.
2. Additionally, the gathered data can be utilized as valuable supplementary material in the creation of methodological guidelines, educational resources, and monographs focused on the early diagnosis of precancerous cervical pathologies.
3. The materials acquired during the research can be used as educational resources in the teaching process of pathology, specifically for gynecological diseases. This includes macroscopic images of precancerous cervical pathologies, microscopic images reflecting cellular and tissue changes, and colposcopic images.

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LIST OF ABBREVIATIONS

AGC	– Atypical glandular cells
ASC	– Atypical squamous cells
ASC-US	– Atypical squamous cells of undertermined significance
ASC-H	– Atypical squamous cells cannot exclude HSIL
HPV	– Human papillomavirus
CIN	– Cervical intraepithelial neoplasia grade
CIS	– Carsinoma *in situ*
LSIL	– Low grade squamous intraepithelial lesion
HSIL	– High grade squamous intraepithelial lesion
NOS	– Not otherwise specified
SIL	– Squamous intraepithelial lesion
TBS	– Terminology Bethesda System
PAP smear	– Papanicolaou smear
CEA	– Carcinoembryonic antigen
SSCA	– Squamous cell carcinoma antigen
SSC	– Squamous cell carcinoma
CMV	– Cytomegalovirus
CA 125	– Cancer antigen 125
CD	– Cervical diseases
C	– Cervix
CL	– Cervical lesions
USG	– Ultrasounography
ECC	– Endocervical curettage
WHO	– World Health Organization

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