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Title: The Usefulness of Papanicolaou test in cytomorphological evaluation of squamous cell abnormalities of the cervix.

Running Title: The usefulness of of Papanicolaou test

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ABSTRACT

Objective: Papanicolaou test as a screening method is suitable method in prevention of cervical cancer. The aims of study was to detecting the prevalence of various cervical cytology results in the squamous epithelial tissue of endocervix and endometrium in women, aged 18-70 years, according to Bethesda system (2014).

Methods: This was a hospital based cross-sectional study conducted on 16790 Pap smears prepared from women aged 18-70 years between January and December, 2017.

Results: The evaluation of the results is hospital based not the whole country. Diagnosis of atypical squamous cells of undetermined significance (ASC-US) was made in 72 (12%) cases. Atypical squamous cells as a HSIL (ASC-H) was seen in 36 cases (6%) , HPV infection was in 26 cases (4%), Low-grade squamous intraepithelial lesion (LGSIL or LSIL) as a CIN 1, 27 cases (5%) and as a CIN 2 13 cases or 2%. High- grade squamous intraepithelial lesion (HGSIL or HSIL) or CIN 3 in 5 cases (1%). The prevalence of various epithelial abnormalities as a AGC (glandular epithelial cell abnormalities) was determined in 20% of women (119 cases) and other abnormalities even to 50% (298 cases).

Conclusions: According to these results (high prevalence of epithelial cell abnormalities in cervical smears due to I-XII) Pap test as a screening methods should begin at 18 years. This screening test can detect abnormal cervical cells before they turn into malignant neoplasm or can be used as a good screening method to detect the earliest signs of carcinogenesis.

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INTRODUCTION

According to the increase of incidence of malignant diseases, the early diagnosis, therapy and treatment are the most important. Analyzing the cells and their ratio is particular important for determining and approving the physiological or pathophysiological mechanisms. Cytodiagnostics as a method is based on the analysis of the cells size, diameter, cytoplasm content, nuclear size, cell membrane construction, fixation of the material staining and their ratio (1).

The aim of cytology and their used principles and methods is to observe the normal or modified processes that occur at cell level (1). The use of these principles and methods makes it possible to accurately determine all the changes of the cells. By using suitable high quality appliances and reagents, proper staining and advanced microscopy the cell analysis can be carried out. For this purpose, it is necessary to prepare the slides to be monitored correctly and efficiently. The microscopic preparation itself is prepared in an appropriate manner according to certain confirmed protocols. The cytology can be exfoliative and aspirational (2, 3). Aspiration cytology uses aspirate, cells for analysis are taken with puncture using a fine needle and based on the negative pressure generated during the procedure, the cells are injected from the tissue in which they are located (2). Exfoliative cytology as a part of clinical cytology use the cells which are desquamated from body surfaces especially the cells from different layers of epithelial tissues. For that purpose the cells are microscopic examined (their morphology, structure, dimensions, staining) and are detect different changes or malignancy in the cells or confirmed the presence of abnormal or atypical cells as a result of some infection, inflammation or parasitic infestations. Exfoliative cytology used simple, quick and non-invasive techniques and collect the material from mouth, urine, sputum, abdominal, pleural or peritoneal fluid and vaginal secretion (3). Unlike the cells in exfoliative cytology, cells in aspiration cytology have preserved morphology and structure, and in this context, changes are more easily visualized and confirmed (2).

The cytological techniques are fast, simple and cheap and they are acceptable from the patients. Papanicolaou or Pap smears as a material are prepared in the procedure as a mechanical exfoliation, when the cells are scraped from the cervix with a spatula (4). Papanicolaou test (abbreviated as Pap test) as a method is very useful for early detection of cervical cancer. This test was named according to George Papanicolaou (1883-1962) American scientist and academic teacher with Greek origin. Pap-test examines the possible changes in cervical cells. The Pap-test may indicate whether there is infection abnormal cervical cells, or to detect the earliest signs of carcinogenesis. Also with Pap smear can be detect infections and evaluate a visible lesion or abnormal cervical cells that can later alter into malignant cells (4, 5). Treatment of infections and precancerous conditions of the cervix can prevent the development of cancer. According to the 2018 data, current estimates indicate that every year 151 women are diagnosed with cervical cancer and 59 die from the disease. Cervical cancer ranks as the 6th most frequent cancer among women in Macedonia and the 3rd most frequent cancer among women between 15 and 44 years of age (6). The visit of gynecologist should be about 10 to 20 days after the first day of the menstrual cycle. At least 2 days before visiting the gynecologist or before doing the test, do not use vaginal creams, medications, tampons, powders or deodorants, have a sex

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or douche. The examination is painless, but for some women it's an unpleasant moment. The gynecologist, with a brush or spatula, collects the cells from the cervix and as a sample of material (smear) spread thinly on a microscope slide and sent to a cytological laboratory for testing. PAP-test as a technique is a part of liquid-based cytology (4). The stain in this technique, pass through various modifications, from conventional Pap-methods to rapid and modern technique with only intention to reduce the the time taken for staining (7, 8). In R.Macedonia Pap-test as a screening method is performed on women around 18 years of age until the age of 70. The aim of the test is to detect pre-cancerous or cancerous cells or other abnormal, atypical cells in the squamous epithelial tissue of endocervix and endometrium, caused by human papillomavirus (HPV) (which is sexually transmitted), bacterial infection or parasitic infestations. According to Bethesda system, 2014 (9) interpretations of results can be:

- negative for intraepithelial lesion or malignancy or positive for:
- epithelial cell abnormalities (squamous cell or glandular) or
- other malignant neoplasms

The aims of study was to detecting the prevalence of various pre-cancerous or cancerous cells or other abnormal, atypical cells in the squamous epithelial tissue of endocervix and endometrium in women in Macedonia, aged 18-70 years, according to Bethesda system (2014).

MATERIAL and METHODS

All participants were informed of the nature and purpose of the research. Only those participants who give consent are included in the study. The study was approved by the Ethics Committee of Faculty of medical sciences/ 20.12.2017/Case number: 2002-288/27 and tests were conducted in accordance with the Declaration of Helsinki and with the principles of good clinical practice.

This was a hospital based cross-sectional study conducted on 16790 Pap smears, prepared from women of Macedonia aged 18-70 years, at the Clinic for Gynecology and Obstetrics in Skopje , between January and December (I-XII), 2017 (Table 1). The most common infections of the patients are infections with *Trichomonos vaginalis*, *Gardnerella vaginalis* and followed by infection with *Candida albicans*. Abnormal results are reported according to the Bethesda system, 2014 (8, 9) and they include negative results for intraepithelial lesion and positive result for:

- squamous cell abnormalities (SIL), evaluated as: atypical squamous cells of undetermined significance (ASC-US), atypical squamous cells – cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LGSIL or LSIL), high-grade squamous intraepithelial lesion (HGSIL or HSIL) and squamous cell carcinoma
- glandular epithelial cell abnormalities (AGC).

The basic morphological criteria which the degree of lesion is diagnosed are: differentiation of the cells, the degree of maturation and stratification of the epithelium, nuclear morphology and

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mythotic activity (7, 8, 9). According to Bethesda system, 2014 (9) we detect atypical epithelial cells dissimilar with other cells, but without dyskaryosis. These cells we (8, 9) contained within group in atypical squamous cells of undeterminate significance and they are the most important because can be followed by the development of a malignant tumor cells.

RESULTS

The evaluation of the results is hospital based not the whole country. In the present study 16790 PAP smears were examined in our cytology lab. 96% of smears were negative. The age range of the patients was 18 to 70 years. The mean age was 26.5 ± 10.73 . Majority of cases were in the age group of 30-39 years (35.25%). Mean age of patients with low grade intraepithelial lesions (LSIL) was 25.8 ± 15.2 . The youngest patient was at the age of 18. The cervical cancer have been diagnosed in women under the age of 35 years. Categorization of cases according to the results of cervical cytology using a Pap-test are confirmed in Table 1. Diagnosis of atypical squamous cells of undetermined significance (ASC-US) was made in 72 (12%) cases. Atypical squamous cells as a HSIL (ASC-H) was seen in 36 cases (6%), HPV infection was in 26 cases (4%), Low-grade squamous intraepithelial lesion (LGSIL or LSIL) as a CIN 1, 27 cases (5%) and as a CIN 2 13 cases or 2%. High-grade squamous intraepithelial lesion (HGSIL or HSIL) or CIN 3 in 5 cases (1%). The prevalence of various epithelial abnormalities as a AGC (glandular epithelial cell abnormalities) was determined in 20% of women (119 cases) and other abnormalities even to 50% (298 cases).

CONCLUSIONS

This study observed a high prevalence of epithelial cell abnormalities in cervical smears in our set up. Pap smear examination is widely accepted screening method in countries like Macedonia, where the population is predominantly rural with low socio-economic status and poor health outcomes, where marriage at an early age. According to these results (high prevalence of epithelial cell abnormalities in cervical smears due to I-XII) PAP-test as a screening methods should begin at 18 years and with this screening test can be detect abnormal cervical cells before they turn into malignant neoplasm or can be used as a good screening method to detect the earliest signs of carcinogenesis. Treating these atypical or abnormal cells in endocervix and endometrium can be prevent carcinogenesis and most cases of cervical cancer. By implementing and introducing PAP-test as a cytological screening methods in women between 18-70 years, can be significantly reduces the risk and reduces the incidence of cervical cancer.

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Table. 1 Categorization of cases according to the results of cervical cytology using a PAP-test from January (I) to December (XII)

	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	SUM
Negativ	520	1155	1150	1138	1213	1087	1208	1255	1660	2054	2255	1499	16194 (96%)
Positive													596 (4%)
ASC-US	11	4	4	5	8	8	6	5	5	9	5	2	72 (12%)
ASC-H	1	1	1	1	9	5	2	5	1	3	5	2	36 (6%)
HPV	1	4	0	3	3	1	2	3	2	0	1	6	26 (4%)
CIN 1 (LGSIL)	1	3	1	5	4	1	0	1	2	4	4	1	27 (5%)
CIN 2 (LGSIL)	1	1	2	0	0	0	1	2	0	0	3	3	13 (2%)
CIN 3 (HGSIL)	0	3	0	0	0	0	0	0	1	1	0	0	5 (1%)
AGC	11	8	3	9	22	25	6	24	8	2	0	1	119 (20%)
Abnormalities	26	24	11	23	46	40	17	40	19	19	18	15	298 (50%)
SUM													16790

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