STRUČNI ČLANAK
PROFESSIONAL PAPER

Gynaecol Perinatol 2016;25(4):147–158

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# ZAGREB 2016 CLASSIFICATION OF CERVICAL CYTOLOGY FINDINGS – MODIFICATION OF ZAGREB 2002 AND NCI BETHESDA SYSTEM 2014 CLASSIFICATIONS

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*Professional paper*

*Key words:* classification of cervical cytologic findings, Pap test

**Summary.** The objective of the Zagreb 2016 classification as the third modification of the unique classification of cervical cytology findings based on the previous Zagreb 2002 and the latest Bethesda 2014 classifications is standardization of cervical cytology findings for the whole Croatia, according to the latest concepts on the biologic behavior of cervical cancer and its precursors. Besides cytomorphological lesions, Zagreb 2016 includes recommendations for diagnostic-therapeutic procedures in line with the international recommendations and the experience of Croatian cytologists and gynecologists. It was presented and accepted by Croatian clinical cytologists at the Croatian Society of Clinical Cytology Convention held on December 12, 2016 in Zagreb. The main modifications relative to the Zagreb 2002 classification refer to the following: classification of 'koilocytosis', i.e. cytomorphological lesions associated with human papillomavirus, into the category of low-grade squamous intraepithelial lesions (LSIL); classification of 'atypical glandular cells – probably reactive lesions' into the category of non-neoplastic lesions; and the introduction of 'atypical glandular cells – not othervise specified' (AGC-NOS) into the category of abnormal glandular cells. In addition, the finding of endometrial cells in women aged ≥45 and absence of the transformation zone elements is highlighted.

## Introduction

The Bethesda System (TBS) classification of cervical cytology findings was introduced nearly three decades ago, in 1988, first in the USA, and then in most countries worldwide (1). TBS was developed in response to the requirement for a uniform and reproducible terminology to derive clear recommendations for clinical procedures. Based on the then novel concepts on cervical neoplasia, modifications of this classification were adopted in 1991 and 2001, aiming at reducing variations in cytologist interpretation and improving the choice of further diagnostic-therapeutic procedures (2,3). Upon recognizing the concepts that resulted in TBS terminology and based on our own experiences, a unique classification of cervical cytology findings known as Zagreb 1990 (4) and Zagreb 2002 (5) was also introduced in Croatia, as modifications of the original TBS classification and its amendments and/or changes.

Currently, instead of the conventional Pap test for detection of cervical lesions, liquid-based cytology (LBC), as well as simultaneous testing (co-testing) for high-risk human papillomavirus (HR HPV) and Pap test have been increasingly applied, giving preference to the HR HPV test for primary screening. The approval and ever wider use of prophylactic HPV vaccine have entailed changes in the strategy of both screening for cervical cancer and its prevention and treatment (6,7). TBS principles and terminology have also greatly influenced standardization of cytologic findings in other localizations such as thyroid gland (8) and pancreas (9), urine cytology (10), as well as of histologic terminology for squamous lesions of the lower anogenital tract associated with HPV infection (11). In addition, guidelines for the treatment and follow up of cervical lesions have recently been based on the principles involving the same procedures for the same risk (12). Guidelines for the procedures for abnormal cytology with triage, using HR HPV test, HPV testing in primary screening with the use of cervicovaginal cytology as a 'reflex' triage test for positive HPV screening, and introduction of HPV vaccine have led to TBS updating in 2014 in order to upgrade morphological criteria and add new information on cervical cytology (13). In the future policies of cervical cancer screening that include primary HPV screening, cytology has assumed the role of diagnostic test of high accuracy required for correct choice of further workup or patient follow up.

Modification of the Zagreb 2002 unique classification of cervical cytology findings (5) and the latest TBS 2014 classification (13) has resulted in a new modification for Croatia named Zagreb 2016, presented and adopted by the Croatian clinical cytologists at Convention of the Croatian Society of Clinical Cytology, Croatian Medical Association, held on December 12, 2016 in Zagreb *(Fig. 1)*.

**PAP TEST - ZAGREB 2016 UNIQUE FORM OF CYTOLOGIC FINDING OF UTERINE CERVIX**

**Last name and first name:** **Date of birth:**

**Address:** **City:** **Phone:** **e-mail:**

**OIB:** **MBOO:**

**Institution/unit:** **Sampling date:**

| **Partus** | **Cyclus** | **LMP** | ☐ **Postmenopause** |
|---|---|---|---|

**Contraception:** ☐Hormones ☐IUD ☐Other ☐Without

**Previous diagnostic-therapeutic procedures** (cytology / histology / therapy / other)

| **Specimen** | **Identification no.** | **Lab logbook no.** |
|---|---|---|
| ☐V | | |
| ☐C | | |
| ☐E | | |
| ☐Vulva | | |
| ☐Other | | |

**HPV test** (result / method / institution/date)

**Colposcopy** (result /date)

**Clinical diagnosis:** ☐w.n.l. ☐Other

**Pap test indication** ☐Screening ☐Workup/diagnostic ☐Follow-up

**Pap test specimen type** ☐Conventional ☐Liquid-based cytology

Signature of supervising physician

**Specimen adequacy**

☐ **Satisfactory for interpretation/evaluation**

☐ **Unsatisfactory for interpretation/evaluation**

☐ Specimen rejected /not processed

☐ Specimen examined, but evaluation of epithelial abnormality is not possible

Comments for the specimen adeuacy:

☐ Incorrect label
☐ Broken slide
☐ Poor fixation or preservation
☐ Scant celluarity
☐ No endocervical cylindrical cells
☐ No transformation zone cells
☐ Obscuring with leukocytes/inflammation
☐ Blood obscuring
☐ Smeared in few levels
☐ Forein material presence
☐ Other:

**General categorization**

☐ Negative for intraepithelial lesion or maligancy
☐ Abnormal cells

**Descriptive diagnosis**

**Microorganisms – cytomorphologically consistent with**

☐ Bacillus vaginalis ☐ Gardnerella vaginalis
☐ Mixed flora ☐ Actinomyces
☐ Fungi ☐ Cellular changes associated with HSV
☐ Trichomonas ☐ Other:

**Other non-neoplastic findings:**

☐ Reactive cellular changes associated with:
☐ Inflammation ☐ IUD
☐ Radiation ☐ Other:
☐ Repair ☐ Reserve cells
☐ Parakeratosis ☐ Dyskeratoses ☐ Hyperkeratosis
☐ Endocervical cylindrical epithelium - reactive and stimulated
☐ Squamous metaplastic epithelium – reactive and stimulated
☐ Glandular cells post hysterectomy
☐ Endometrial cells
☐ of menstrual period ☐ in postmenopause
☐ ≥ 45 years of age
☐ Atrophy
☐ Cytohormonal status incompatibile with age and anamnesis
☐ Other:

**Abnormal cells**

**Squamous cells**

☐ Atypical squamous cells (ASC)
- ☐ Of undetermined significance (ASC-US)
- ☐ Cannot exlude HSIL (ASC-H)
- ☐ Cannot exlude invasion

→ V

☐ Squamous intraepithelial lesion (SIL)

| | | | |
|---|---|---|---|
| ☐ Low grade SIL (LSIL) | ☐ Changes associated with HPV / Koilocytosis | | C |
| | ☐ CIN 1 / Mild dysplasia | | |
| ☐ High grade SIL (HSIL) | ☐ CIN 2 / Moderate dysplasia | | E |
| | ☐ CIN 3 | ☐ severe dysplasia | |
| | | ☐ carcinoma in situ | |
| | ☐ Cannot exclude early invasion | | |
| | ☐ Plus: cellular changes associated with HPV | | |

☐ Squamous cell carcinoma

**Glandular cells**

☐ Atypical glandular cells (AGC)
- ☐ Not otherwise specified (AGC-NOS)
- ☐ Favor neoplastic lesion (AGC-neoplastic)
  - ☐ Favor intraepithelial lesion
  - ☐ Favor invasive lesion

☐ Adenocarcinoma in situ (AIS)

☐ Adenocarcinoma

**Origin**

☐ Endocervical
☐ Endometrial
☐ Extrauterine
☐ Not otherwise specified

→ V, C, E

☐ **Atypical cells of undetermined significance**

☐ **Other malignant neoplasms**

**Recommendation:**

☐ Repeat smear ☐ HPV test
☐ Repeat after therapy ☐ Colpscopy
☐ Repeat in 6 months ☐ Histology
☐ Repeat in 12 months ☐ Further examination
☐ Regular follow-up ☐ Other:

**Remarks:**

**Received:** **Replied:** **Cytogechnologist (signature):** **Cytologist (signature):**

*Figure 1.* Unique classification of cervical cytological findings „Zagreb 2016“

## Referral Form Data Entered by the Gynecologist/Medical Doctor

Entering woman's respective data is one of the preconditions for appropriate cytologic analysis of the vaginal-cervical-endocervical (VCE) smear and Pap test. The referral form is filled out by the gynecologist/medical doctor and should include the following: woman's last and first name, smear ID number, date of birth, and personal identification number (OIB) and/or identification number of the insured person (MBOO) by which the cytologic finding is computer linked to other woman's findings irrespective of the possible last name change. Besides clinical diagnosis, clinical data of interest are parity, date of last menstruation, and contraception or hormone therapy. In addition, previous diagnostic-therapeutic procedures (cytology, histology, therapy, etc.), their timing and results, and the last colposcopy finding are relevant for the cytologist. The section in the Zagreb 2016 referral form that is filled out by the gynecologist also contains data on previous HPV test including the finding, method, institution, and date of HPV testing. New sections where indication for Pap test (screening, workup/diagnosis, or follow up) is entered and type of Pap test (conventional or LBC) can be filled out by gynecologist or cytologist.

## Sample Adequacy

Assessment of sample adequacy remains one of the most important components of Bethesda system to ensure quality (14). As in previous modifications, specimens are classified into two groups according to sample adequacy, 'satisfactory' and 'unsatisfactory' (3,5,13).

***Satisfactory cytology sample*** means that the smears are thin-layered, cells are not overlapping, and all transformation zone elements including squamous epithelium cells, metaplastic and endocervical cells are present. Cells are well preserved and the specimen contains at least 8,000–12,000 squamous cells in conventional smear and at least 5,000 cells in LBC sample. A simple method of fast determination of sample cellularity by use of "reference images" is proposed for conventional specimens and of representative fields of cell count for LBC specimens. Notes on specimen inadequacy, specimen obscured with leukocytes, blood or necrosis, lack of endocervical columnar cells and transformation zone elements, presence of foreign material, poor cell fixation or preservation can be listed in cytologic finding. Based on this information, the physicians taking samples can decide on the need of repeating the test. In case of atrophy following chemo-irradiation therapy, hysterectomy or trachelectomy, minimal cellularity of 5000 and 2000 cells, respectively, is considered satisfactory (6,15).

***Unsatisfactory cytology sample*** mostly results from too low celularity, poor cell fixation or preservation, sample obscured with blood, leukocytes or bacteria (>75% of squamous epithelium cells obscured), or strong cytolysis (>75% of squamous epithelium cells undergoing cytolysis). Assessment of specimen adequacy is subjective and the cytologist should describe the reason for this finding evaluation (13).

## General Categorization

Although 'general categorization' is an optional part of the classification, it serves clinician for fast triage of cytologic findings. Similar to previous classification modifications (4,5), while aiming at rapid orientation in terms of negative/positive finding, only the following two groups have been retained: 'negative for intraepithelial or invasive lesion' and 'abnormal cells', although Bethesda 2014 optionally suggests the group 'others' as well, referring to the finding of endometrial cells in women aged ≥45 (6,13).

## Descriptive Diagnosis

Descriptive diagnosis includes 'microorganisms' and 'other non-neoplastic findings' that may be found along with the two above mentioned groups in 'general categorization', and 'abnormal cells', i.e. squamous, glandular, atypical cells of undetermined significance and other malignant neoplasms. A cytologic finding of 'microorganisms' refers to the microorganisms that are identified directly or according to their cytopathic effect on the cells; *Bacillus vaginalis* prevails in normal vaginal flora in women of generative age; mixed vaginal flora is a frequent finding but need not be associated with inflammation; fungi are found in the form of spores and/or pseudomycelium, and mostly refer to *Candida albicans*; *Trichomonas*, a protozoan, usually causes severe inflammation; *Actinomyces* is usually found in intrauterine device (IUD) or pessary carriers, with or without cellular inflammation; *Gardnerella vaginalis* is generally associated with the bacterial vaginosis syndrome, i.e. 'shift in vaginal flora suggestive of bacterial vaginosis' (13), causing unpleasant discharge and inflammation; lesions associated with the cytopathic effect caused by herpes simplex virus (HSV); 'others' refer to cocci, diplococci and amebae. The CMV cytopathic effect may also be detected in cervicovaginal smears and is highlighted in Bethesda 2014 (13).

***Other non-neoplastic findings*** include inflammatory and reactive (irritating) lesions on the cells of squamous, endocervical columnar and metaplastic epithelium, alterations associated with radiotherapy and IUD, reparatory epithelium as a sign of cervicovaginal epithelium lesion and inflammation; reserve cells usually in atrophic smear or as a sign of damage and inflammation in generative age. Benign proliferative keratinization alterations on squamous epithelial cells (parakeratosis, dyskeratosis, hyperkeratosis) and columnar cells found after hysterectomy are also listed among non-neoplastic lesions. A finding of endometrial cells beyond menstrual cycle and in postmenopause, i.e. in women aged ≥45 (6,13) is considered pathologic and requires additional workup due to possible lesions in the endometrium or uterine body.

## Abnormal Cells

### Squamous cells

Cytomorphological lesions of the stratified squamous epithelium are categorized as in the previous modification (5).

***Atypical squamous cells*** (ASC) include various lesions which, according to definition, indicate that cytologic changes of squamous epithelial cells are not distinct enough in quality or quantity to point to squamous intraepithelial lesion (SIL), and in rare cases to carcinoma (16,17). This category is most common in the interpretation of abnormal cervical cytology findings since a number of non-neoplastic conditions can also induce cytologic changes that are interpreted as ASC, e.g., inflammation, poor fixation, atrophy with degeneration, hormonal effect, and other cellular artifacts.

In Zagreb 2016, ASC continues to be subcategorized, just as in Zagreb 2002 modification (5), as follows: atypical squamous cells of undetermined significance (ASC-US); atypical squamous cells – high-grade squamous intraepithelial lesion (HSIL) cannot be excluded (ASC-H); and atypical squamous cells – invasion cannot be excluded (ASC – invasion cannot be excluded). By definition, ASC-US denote cellular cytologic changes that suggest low-grade squamous intraepithelial lesion at the most (LSIL) but the criteria for this interpretation are not met completely (16,17). It is considered that no more than 2%–5% of cervicovaginal samples should be classified in this category in a low-risk population, whereas its prevalence in high-risk population may be two- to threefold greater (16,18,19). In this category, SIL was detected in 29,1%–43% and invasive carcinoma in 1,7% of biopsy specimens (18,19). Cytologic findings of atypical parakeratosis, atypical repair, atypia in post menopause or atrophy, decidual cells, trophoblast cells, and bare cell nuclei without cytoplasm have been frequently interpreted as ASC-US (13).

Atypical squamous epithelial cells suggesting high-grade squamous intraepithelial lesion (ASC-H) are a subgroup of atypical/borderline lesions suspect of HSIL, and according to Bethesda classification also of carcinoma in some cases (3,6). This category is used when the number of abnormal cells is so low that the diagnosis is uncertain and implies a finding of no more than 5%–10% of abnormal squamous cells. Cytologic interpretation of the ASC-H finding is related to atypical immature metaplasia, dense cell clusters, pronounced atypical repair, severe atrophy, and post-irradiation lesions associated with residual or recurrent carcinoma (13). In order to differentiate cytologic pictures of ASC-H and potential invasion, the ASC – invasion cannot be excluded category related to the previous 'suspect' finding (20) and 'abnormal' finding in previous classifications (4) employed in Croatia, have now been retained in the Zagreb 2016 classification. In the SIL group, the only modification relative to the Zagreb 2002 classification (5) refers to cytologic interpretation of low-grade SIL; besides the above mentioned cellular changes suggesting cervical intraepithelial neoplasia grade 1 (CIN 1), i.e. mild dysplasia, it also includes lesions associated with HPV infection, mostly in the form of cytopathic effect, koilocytosis, as stated in Bethesda classifications (1,3,6,13).

Subdivision of the HSIL category remains the same as in the previous classification (5). It should be noted that besides inclusion of particular SIL categories, a category of cervical intraepithelial lesion (CIN), i.e. dysplasia/carcinoma *in situ*, has been included as in previous modifications employed in Croatia (4,5), providing the clinician with an option to choose the length of patient follow up or additional workup.

The category of 'planocellular carcinoma/squamous carcinoma' remains the same as in previous classifications (4,5).

### Glandular (columnar) cells

Cytomorphological lesions of the columnar epithelial cells are relatively rare as compared with squamous epithelium. Similar to the previous modification (5), these are divided into three groups: atypical glandular cells (AGC), adenocarcinoma *in situ* (AIS), and adenocarcinoma. Considering the great variety of cellular lesions, the origin of the columnar epithelium (endocervical, endometrial, extrauterine, or undetermined) should be specified in each group and subgroup of abnormal columnar cells.

Although AGC is a rare finding in cervicovaginal cytology (0,19%–0,27%) (21–23), histopathologic examination reveals a wide spectrum of abnormalities in both squamous and columnar epithelium (24,25). This category differs from the previous modification (5) by introducing, besides the existing subgroups of AGC – intraepithelial lesion probable and AGC – invasive lesion probable, a new subgroup of atypical glandular cells not otherwise specified (AGC-NOS) identical to the one found in the TBS classification (3,6,13). Namely, according to the recommendation of Croatian gynecologists (26) and re-evaluation based on cytologic analysis from three Croatian centers (Osijek, Rijeka and Zagreb) presented at the Sixty Years of Gynecologic Cytology in Petrova Hospital Symposium held on March 7, 2014, the AGC – reactive lesion probable has been reclassified into the group of 'non-neoplastic lesions', thus having reduced the rate of findings categorized as AGC and consequently the number of unnecessary workup procedures.

The category of 'adenocarcinoma *in situ*' (AIS) has been recognized as a unique entity, as in the previous classifications (3,5), with a characteristic cytologic picture, just as the group of 'adenocarcinoma'. It should be noted that endometrial or extrauterine adenocarcinoma can be differentiated from endocervical adenocarcinoma according to cytologic lesions, which should be clearly described in the finding form. Therefore, it is emphasized that the origin of columnar epithelium should be specified in case of any AGC group or sub-

group whenever possible, thus directing further diagnostic and therapeutic procedures (26,27).

### Atypical cells of undetermined significance

Cytomorphological lesions that do not correspond to any of the mentioned categories, while the cells do not show distinct characteristics of malignancy, should be interpreted as 'atypical cells of undetermined significance'. Atypical cells with pronounced degenerative changes or cells of mesenchymal origin, where differential cytologic diagnosis cannot be made, are most frequently described in this category (5,6,13).

### Other malignant neoplasms

The category of 'other malignant neoplasms' is a rare cytologic finding. Malignant cells do not originate from cervical squamous and/or columnar epithelium but suggest other malignant lesions that may occur in the cervix, either as variants of cervical carcinoma or as rare primary tumors occurring in the uterine body or adnexa (mesenchymal origin, lymphoma or melanoma origin). They can be recognized in cytologic specimens but differential diagnosis is usually hampered by the very nature of cytologic specimen and morphological overlap with other entities (5,6,13).

## Instructions

At the end of the referral form, the cytologist provides instructions to the clinician, sometimes to improve the quality of samples, and guidelines for diagnostic workup (26,27). These instructions should be precise and clear, based on relevant literature, representing cytologist's recommendations based on the cytologic finding and patient clinical data, as well as previous findings and therapeutic procedures. The instructions should be phrased as suggestions, in line with the national and international clinical practice and guidelines (26,27).

Pap test, i.e. diagnostic cytology of the cervix, can be performed beyond the recommended screening intervals within the workup in symptomatic patients, e.g., increased and abnormal discharge, abnormal bleeding in clinical picture or history, cervix of suspect appearance, genital tumor growth, presence of condyloma, etc. (26). Repeat Pap test is required in case of unsatisfactory samples. Post-therapeutic re-testing is required in case of detecting cells with very severe inflammatory lesions and abundant leukocytes. In other non-neoplastic findings, earlier re-testing should not be ordered (6,13). If Pap test reveals pronounced disorders of keratinization (parakeratosis, dyskeratosis and/or hyperkeratosis), re-testing within 12 months can be suggested; if the cytologist considers cytologic follow up or HPV testing necessary within 6 months, such a finding should be re-classified as ASC-US. Although representing negative Pap test finding, very pronounced reactive lesions of metaplastic squamous and endocervical columnar epithelium may occasionally also be the reason for the cytologist to recommend earlier re-testing. In the screening population, recommending earlier repeat Pap testing for non-neoplastic findings should be used only exceptionally. In case of endometrial cells beyond menstruation, in postmenopause, and in women aged ≥45 (if the date of last menstruation is not stated), examination of the endometrium (ultrasound, direct cytology or histopathology of the endometrium) should be recommended. In case of atrophic epithelium with severe degenerative changes, cytologic examination after local estrogen application can be ordered due to difficulties in cell interpretation.

In case of abnormal cytologic finding, repeat examination in at least 6 months, HPV test, colposcopy and histology can be recommended, depending on the grade of epithelial abnormality and in line with guidelines for the diagnosis and treatment of cervical lesions (26,27).

## Conclusion

The Zagreb 2016 classification is a unique classification of cervical cytology findings for Croatia. In comparison with the previous classification (5), some modifications have been done in line with the international recommendations (6,13) and based on the experiences acquired by the Croatian cytologists and gynecologists (26).

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*Paper received:* October 2nd 2016

*Paper accepted:* November 16th 2016