

Management of abnormal Pap smear – consensus guidelines of the National Cervical Cancer Screening Programme in Poland Coordinating Centre, the Polish Gynaecological Society, the Polish Society of Pathologists, and Polish Society of Colposcopy and Uterine Cervix Pathology

A group of experts met December 19, 2008, in Warsaw, to develop **consensus guidelines for the management of women with abnormal cervical cancer screening results.**

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1. Introduction

The main purpose of the guidelines is to increase the effectiveness of precancerous lesions and early stages of cervical cancer detection and to assure proper use of public funds for diagnostic tests done at the follow-up stage of the screening programme results verification. The paramount aim of population-wide screening programme is to detect direct cancer progenitors, namely CIN2, CIN3, AIS (*adenocarcinoma in situ*) and early stages of cervical cancer. Adequate diagnostic methods at the follow-up stage enable early and highly effective histologic diagnosis and the choice of the most suitable treatment.

In screening programme, the abnormal Pap smear results constitute from 1% to 8% of all results. In Poland in 2008 alone there were 19 296 (2,43%) abnormal Pap smear results out of 795 288 tests performed within Cervical Cancer Prevention Screening Programme. (Table I).

The following document has been compiled with the help of medical literature, guidelines from other medical societies in the world and the professional experience of the abovementioned experts. Factors taken into consideration included: cervical pathology epidemiological rates in Poland, accessibility and costs of supplementary tests (cytology, colposcopy, biopsy, histopathologic tests, HPV molecular tests, conization).

2. Normal and abnormal Pap smear results

Recommendations relate to cytologic test results reported using the 2001 Bethesda System which remains the only binding classification. Normal Pap smear result means: lack of cervical intraepithelial neoplasia or malignancy (NILM).

According to the 2001 Bethesda System the following cytologic results are considered abnormal:

ASC – Atypical Squamous Cells; the group is further subdivided into:

ASC-US – Atypical Squamous Cells of Undetermined Significance,

ASC-H – Atypical Squamous Cells in which a high grade squamous intraepithelial lesion (HSIL) cannot be excluded,

LSIL – low-grade squamous intraepithelial lesion,

HSIL – high-grade squamous intraepithelial lesion,

AGC – atypical glandular cells.

TBS cytologic results may also indicate direct proof of **squamous carcinoma cells and adenocarcinoma cells**.

3. Further diagnostic aims

The aim of further diagnosis of women with abnormal Pap smear results is to confirm or exclude cervical intraepithelial neoplasia (CIN) or cancer. Proper diagnostic follow-up methods enable early final histologic diagnosis and immediate therapeutic management, as well as false-positive cytologic result verification.

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Not all abnormal screening results mean that the patient in question has CIN, AIS or squamous carcinoma in the cervix. In each screening programme a certain part of the positive results will prove to be false-positive after further follow-up.

All of the undermentioned diagnostic methods have different sensitivity and specificity, as well as different positive and negative predictive value for intraepithelial neoplasia and cancer. The only method to fully exclude or confirm the presence of CIN or cervical cancer remains to be the histopathologic examination.

When using the method of choice to verify the Pap smear result, one must bear in mind different CIN2+ risk in different abnormal smear result groups. In case of ASCUS and LSIL results, the risk of detecting CIN2+ in the histologic test is the smallest (6-12%). HSIL and ASC-H coexist with the CIN2+ lesions in a large percentage (60-100%). Differences within the group have their source in the quality of the tested populations and the quality of the cytologic tests itself.

The choice of the Pap smear verification method ought to take into account its accessibility for the patients.

The Pap smear result verification methods differ amongst them, also as far as costs are concerned. So far there has been no cost simulation of the different follow-up diagnostic procedures in Poland.

4. Diagnostic methods applied to abnormal cytologic results verification

The following methods are the most frequently used ones:

- repeated Pap smear test,
- HPV test (DNA HR HPV test and mRNA HR HPV test),
- colposcopy with biopsy,
- diagnostic-therapeutic lesion removal (conisation) with histologic evaluation of the sample.

Pap test (cytology) is a procedure during which cells from the cervix and cervical canal are taken with a small cervical brush, spread onto a glass microscope slide and preserved, in the course of no longer than 20 seconds, with alcohol or alcohol based fixative such as Cytofix. Pap test is a screening procedure and should not be treated as final diagnosis of cervical lesions. The cytologic specimens should be examined by authorized personnel and the laboratories should undergo regular quality checks (10% negative results and all positive ones).

HR HPV test is used to detect the presence of DNA or mRNA highly oncogenous human papilloma viruses (HPV). The test does not detect CIN, AIS lesions and cancer. Its diagnostic value lies mainly in the assessment of the risk of precancerous lesions and cervical cancer development. HR HPV tests are of highest prognostic value when selecting women with abnormal cytologic result. DNA HR HPV negative result, evaluating all known, highly oncogenous types of human papilloma virus, excludes the CIN3 presence and cervical cancer. What is more, it indicates that the woman in question will not develop cervical cancer in the course of about six years. However, the negative test result does not exclude the presence of CIN1 and CIN2, due to the fact that some of the lesions may be caused by low-oncogenous viruses. Single positive HPV DNA test result confirms only the presence of these viruses' DNA in the obtained cell samples. It does not allow for the assessment of how long the infection has been going on, thus not differentiating between patients with incidental or persistent infection.

Women with positive DNA HR HPV test result do not need to have the test repeated more often than once every 12 months.

mRNA test allows to distinguish between patients with incidental or persistent infection. The presence of mRNA HPV in the obtained specimen means that E6 and E7 transcripts are present, which in turn proves that the infection is persistent and the process of carcinogenesis had already started. Positive mRNA test result automatically places the woman in the high-risk CIN and cervical cancer development group.

It is advisable to use HPV tests which have the EU certificate for clinical use. Certified DNA HPV tests detect the presence of the DNA of known, highly oncogenous human papilloma virus types. Certified mRNA test detects the transcription process of five highly oncogenous virus types, namely 16, 18, 31, 33 and 45.

Colposcopy is a method of verifying abnormal Pap tests and may be performed with the acetic acid and Schiller's iodine test. Selective biopsy of the cervix is recommended after the colposcopic evaluation. Several samples from the places with the highest lesions intensification ought to be collected. Biopsy specimens, at least a few millimetres in size, should be collected together with stroma fragments. Furthermore, material from the cervical canal should be obtained as well. It is recommended to perform colposcopy and collect material for histologic evaluation also in cases of clinical cervical cancer suspicion when the cervical cancer screening test result was normal.

Colposcopy is a subjective method and its results may depend on the experience of the clinician performing it.

Table I. Abnormal Pap smear results collected between 1 January and 31 December 2008. (Cervical Cancer Screening Prevention Programme).

Pap smear result	Number	% of all results	% abnormal results
ASC-US	9332	1.17	48.36
ASC-H	1032	0.13	5.35
LSIL	5296	0.67	27.45
HSIL	2225	0.28	11.53
squamous carcinoma	237	0.03	1.23
AGC	1174	0.15	6.08
total	19296	2.43	100

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In many cases, especially in women after previous cervical surgical procedures and postmenopausal women, colposcopy may prove to be unsatisfactory (lack of clear vision of the border between the stratified squamous and glandular epithelium). Such colposcopy result does not allow for the exclusion of the pathological lesion existence in the cervical canal.

Colposcopic verification of the abnormal Pap tests must be performed by clinicians with proper training, experience and with the use of highly advanced equipment.

Diagnostic-therapeutic lesion excision – conization of the cervix – is a method of further diagnosis and simultaneous treatment of the CIN-suspected lesion. The procedure should follow colposcopic examination. The entire obtained material is sent for histologic examination. Nevertheless, diagnostic-therapeutic excision may prove to be insufficient for the complete assessment of the cervical cancer lesions. In the event of abnormalities in glandular cells, endocervical curettage should be performed together with diagnostic-therapeutic excision.

In case of abnormal Pap test results, tissue destruction treatment – cryotherapy, chemical coagulation, electrocoagulation and laser vaporisation – is absolutely unacceptable because lack of material for histologic evaluation disqualifies each of these methods.

5. Recommended management in women with abnormal cytologic test results

ASC

In women with ASC, the risk of cervical cancer is small (from 0.1 to 0.2%). CIN2+ occurs considerably more often in the event of ASC-H presence when comparing to ASC-US. Therefore, women with ASC-H diagnosis should undergo further diagnostic treatment, following the HSIL result algorithm.

ASC-US

After ASC-US Pap-test result, the follow-up management should include:

- two Pap smears at six-month intervals,
- or
- HR HPV molecular test.

Two normal Pap tests or one HR HPV negative test result enable the patient to return to standard screening process. Positive HP HPV or abnormal cytologic result is an indication for colposcopic verification.

Negative colposcopic test result in patients with positive HP HPV is an indication for the repetition of the HR HPV test after one year or two cytologic tests, every six months each. Women with ASC-US result should not undergo the conization of the cervix as a primary diagnostic-therapeutic management.

LSIL

LSIL Pap test result follow-up should include:

- two Pap tests at six-month intervals,
- or
- colposcopy with biopsy,
- or
- HR HPV molecular test.

In case of the LSIL result, the risk of CIN2+ and cervical cancer is similar to the case of ASC-US and that is why further follow-up in both these groups remains very similar.

The only exception are post-menopausal women who, due to higher probability of persistent infection, should have the HR HPV test performed as the first line procedure, because that test has higher prognostic value in this group than in case of younger women.

Women with LSIL result should not undergo the cervix lesion excision as diagnostic-therapeutic management.

HSIL and ASC-H

HSIL or ASC-H result should be followed by:

- colposcopy with biopsy of the suspected CIN lesions and cervical canal curettage,
- or
- diagnostic-therapeutic excision with cervical canal curettage

HR HPV testing has no diagnostic and prognostic value in women with HSIL and ASC-H results. If histologic findings after the removal of the lesion or biopsy do not indicate the presence of intraepithelial neoplasia or cervical cancer, the patient ought to have colposcopy and Pap tests every six months. In the event of unsatisfactory colposcopy outcome, the patient ought to always be recommended for the diagnostic-therapeutic lesion removal. Repeated positive HSIL or ASC-H diagnosis after the next cytology test should be verified with colposcopy. Two negative cytology and colposcopy results allow the patient to return to the standard screening tests.

Women with HSIL+ should not undergo any excision procedures as a result of which no material for histologic evaluation is obtained. Diagnostic-therapeutic conization may also be performed in case of patients who intend to bear children. Qualification for such a procedure and the choice of surgical technique must be most careful due to the high infertility or pre-term delivery risk.

Table II. Recommended diagnostic algorithm for women with abnormal Pap smear results.

Result	Repeated cytology	HPV test	Colposcopy (with cervix and cervical canal biopsy)	Diagnostic-therapeutic conization
ASC-US	YES	YES	NO	NO
LSIL	YES	YES	YES	NO
HSIL, ASC-H	NO	NO	YES	YES
AGC	NO	YES	YES	NO
Cancer suspicion	NO	NO	YES	YES

AGC

Atypical glandular cells are rarely found in smears. In most cases they are non-cancerous cells from polyps or tissue altered due to inflammation. Nevertheless, 9% to 38% of women with AGC show signs of CIN2+ lesions or AIS, whereas 3% to 17% have invasive cancer, not only of the cervix but also the *endometrium*, ovary or fallopian tubes.

As the origin of the atypical cells may be different, diagnostic tests such as colposcopy, cervical canal biopsy, *endometrium* biopsy, HR HPV test and transvaginal ultrasound should be performed. First of all, colposcopic examination should be done and material from the endocervical canal should be obtained. Endometrium biopsy is always recommended, regardless of the age of the patient, as AGC lesions may be of the endometrial origin. Repeated Pap test or HR HPV test is insufficient in case of patients with AGC.

HR HPV test should be performed if a satisfactory, negative colposcopy result was obtained and no CIN2+ lesions in the cervical canal were found. Negative result of the test allows for the next Pap smear to be performed after 12 months. Negative results of both tests are an indication that patient may return to the screening programme. In case of women whose biopsy result are negative and the HR HPV test was not performed, a Pap smear should be done four times, every six months. Its normal result enables the patient to return to the standard screening procedure.

Cancerous (epithelial, glandular) cells presence in the Pap smear

The presence of cancerous cells in the Pap smear requires histopathologic confirmation. Colposcopy with selective biopsy and cervical canal curettage are recommended. In case of the pathology of the endometrium, endometrial biopsy ought to be performed as well.

In case of colposcopic suspicion of early invasive cancer, diagnostic conization should be performed instead of the cervical biopsy. Such management allows for the histologic evaluation of the depth of the infiltration and the extent of the lesion. If there is macroscopic tumour on the cervix, biopsy for histopathologic confirmation should be collected instead of conization.

6. The evaluation and management of pregnant women

The abnormal Pap smear result may be as common in pregnant women as in non-pregnant ones. Recommended management in the event of abnormal cervical cancer screening test is similar to that of non-pregnant patients. Each abnormal Pap-smear test result verification should be done in centres which have access to HR HPV testing and highly experienced personnel, especially in colposcopic testing of pregnant women. Colposcopic CIN2+ lesion suspicion determines the necessity of cervical biopsy execution. Endocervical curettage is not recommended for pregnant women.

The only indication to perform the conization procedure during pregnancy is the necessity to confirm or exclude the microinvasion of cancer. The procedure is performed to decide on the optimal delivery time or to determine the indications for surgical delivery. Surgical conization, electroconization or the LEEP procedures carry too much risk of complications for the mother and the foetus.

7. Final comments

Due to rapid development of medical knowledge the present guidelines are hereby deemed binding.