Original Article

BELGIAN CONSENSUS GUIDELINES FOR FOLLOW-UP OF WOMEN WITH CERVICAL CYTOLOGICAL ABNORMALITIES

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ABSTRACT

In medical care cervical cancer screening is important because it enables the detection of precancer and cancer at an early stage. By adequate treatment after a screening-detected lesion it helps to reduce the mortality related to cervical cancer. Worldwide, many millions of women have smears taken at a more or less regular base and of these, approximately 7% are abnormal, and follow-up is thus required. As this represents an important cost in medical health care and has serious consequences for the affected women, it is important to have uniform and clear guidelines to allow an optimal follow-up and clinical management. A system for the uniform reporting of cervical cytology has been designed by the National Cancer Institute (USA) and resulted in the Bethesda System 1991. The present paper and the terminology used are based on the Bethesda System revised in 2001. It explains the guidelines, based on the 2001 Bethesda System and the 2004 consensus guidelines for the management of women with cervical cytological abnormalities, as developed by the members of the Board of the Belgian Society of Clinical Cytology, and adapted to the Belgian situation.

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INTRODUCTION

Cervical cancer screening by smear taking is a well-established and efficient method that allows the early detection of (pre)cancerous lesions. The treatment of screening-detected lesions has been proven to reduce the incidence of cervical cancer. The first classification of cervical cytology diagnosis was devised in 1954 by George Papanicolaou and consisted of 5 classes (1). It

has since then been used worldwide. A new descriptive system based on morphological criteria was designed in 1968 and embraced by the World Health Organization. Here, class 2 comprised various forms of atypia; class 3 consisted of mild, moderate and severe dysplasia and class 4 included carcinoma in situ. Because there was a need for comprehensive and evidence-based guidelines, the Bethesda System (TBS) was introduced in a workshop at the National Cancer Institute in Bethesda in 1988, and flexible guidelines for reporting cervical and vaginal cytology diagnoses were developed and approved (2). It was revised in 1991 to establish a uniform terminology and standardize diagnostic reports (3). Moreover, a standardized approach for the reporting of adequacy for evaluation of the individual specimens was introduced. In this system the 3 degrees of dysplasia -mild, moderate and severe- and carcinoma in situ were reduced to 2 categories, low-grade squamous intra-epithelial lesion (LSIL) and high-grade squamous intra-epithelial lesion (HSIL). Further changes were made in TBS 2001 including revisions in statements of adequacy, general categorization and interpretation and results of epithelial cell abnormalities, all based on committee review of the literature, input of expert opinions and discussion of the proposed changes on an interactive website (4).

Fundamental differences comprise the qualification of 'atypical squamous cells' (ASC) into 'undetermined significance' (ASC-US) or 'cannot exclude HSIL' (ASC-H). The qualifier 'undetermined significance' was retained to underline that some ASC-US cases are associated with SIL (LSIL or HSIL) and ASC is thus suggestive of SIL. The new term ASC-H includes approximately 5%-10% of all ASC cases, comprising true HSIL and its mimics. In order to avoid confusion with ASC-US, the term 'atypical glandular cells of undetermined significance' (AGUS) has been substituted by 'atypical glandular cells' (AGC) and the glandular abnormalities are then classified as endocervical, endometrial or glandular cells. The management of patients with glandular abnormalities can vary according to the cell type and justifies making the distinction whenever possible. The finding of AGC is important because glandular abnormalities are more associated with high-grade lesions than ASC-US (reference). 'Endocervical adenocarcinoma in situ' (AIS) is a separate category.

Given the better understanding of the role of human papillomavirus (HPV) in the development of (pre)malignant lesions it is recommended to do HPV typing in some smears featuring abnormal results. According to TBS 2001 the results of the HPV typing are recommended to be added to and reported with the cytological report if appropriate and guidelines for its best use are necessary.

The interpretation and result reporting in TBS 2001 is based upon the subdivision 'negative for intra-epithelial lesion or malignancy', 'epithelial cell abnormalities' and 'other'.

As the Belgian Society of Clinical Cytology (Belgische Vereniging voor Klinische Cytologie – Societé Belge de Cytologie Clinique) (BSCC) was one of the Bethesda 2001 Workshop cosponsors and also endorsed TBS 2001, our management guidelines are based on the 2001 Consensus Guidelines for the management of women with cytological abnormalities (5) but, where necessary, adapted according to the Belgian situation of medical practice.

ATYPICAL SQUAMOUS CELLS (ASC)

In TBS 2001, ASC are classified into ASC-US, and ASC-H. The guidelines for the management of ASC are underpinned by considerations such as the fact that even amongst expert cytologists there is a poor reproducibility in interpretation of ASC (6). Next, the chance of having a CIN 2 or 3 confirmed on biopsy is between 5%-17% in ASC-US and 24%-94% in ASC-H (7) but the risk of having invasive cancer in a woman with ASC only is 0.1%-0.2% (8). Given these data, this means that a woman with ASC needs some follow-up work-up but it is to be considered that useless costs, anxiety and inconvenience should be avoided. As postmenopausal women with ASC are less likely to have CIN 2 or 3 than premenopausal women the guidelines are different (9). Similarly, the policy in women younger than 25 years will differ as in this age group there is a high rate of spontaneous regression of ASC lesions (10).

For the management of women with ASC it used to be advised to repeat cervical cytology, to perform immediate colposcopy, to test for high-risk HPV DNA or a combination of repeat smear taking with HPV testing or colposcopy. However, the sensitivity of a single repeat cytological test to detect CIN 2 or 3 is low (0.67-0.85) and to overcome this, guidelines have previously recommended to repeat cytological testing at specific intervals until several consecutive results 'negative for intra-epithelial lesion or malignancy' were obtained (11-13). Moreover, there is little evidence on factors like how often, what interval, and for how long there has to be a repeat cytology follow-up. In addition, repeating cytology can imply a delay in diagnosis of CIN 2 or 3 or even

invasive carcinoma, costs money and time, and causes anxiety amongst the women.

An alternative for the evaluation of women with ASC is the colposcopy. It has the advantage that it promptly alerts the patient and the gynaecologist for the presence of a lesion. The nature of the lesion will appear from the histopathological examination of the biopsy. Expert colposcopists can make a good distinction between normal and abnormal cervical tissues and from a meta-analysis it appeared that the weighted mean sensitivity for discriminating abnormal tissue by colposcopy was 0.96 and the weighted mean specificity 0.48 (14). On the other hand a colposcopy is an expensive and time-consuming procedure.It may lead to overdiagnosis and overtreatment, and referral can cause false concern and fear. By many women the procedure is considered to be uncomfortable.

The ancillary testing for HPV DNA by commercially available highly sensitive molecular methods aims to reduce the number of referrals for colposcopy. In women with ASC the sensitivity of HPV DNA testing for the detection of biopsy-confirmed CIN 2 or 3 is 0.83-1.0 and is higher than the sensitivity of a single conventional or liquid-based repeat smear (11-12,15). For high-risk HPV the negative predictive value of DNA-tests is 0.98 or more. Between 31% and 60% of all women with ASC will have a high-risk HPV but, with increasing age, the majority of high-risk HPV will disappear (15). At present it is not clear what has to be done in women who are high-risk HPV DNA positive but in whom CIN cannot be demonstrated.

Since the introduction of liquid-based cytology, patients do not have to be called back for a HPV test and according to the Belgian guidelines, 'reflex' HPV testing can be done on sample rests of material taken at the initial screening visit if an ASC result is obtained. Women with a negative test for high-risk HPV DNA can be reassured that it is a harmless lesion, that they do not need extra clinical examination and so approximately 50% of women with ASC lesions will be saved from a colposcopy (16).

GUIDELINES FOR THE MANAGEMENT OF WOMEN WITH ASC-US

The preferred option of the BSCC in this group of women is to have a concurrent HPV DNA test for high-risk HPV types (17).

However, depending on the age of the patients different policies are advised given the high rate of spontaneous regression in patients belonging to the younger age group and given the lower risk of developing CIN 2or 3 in postmenopausal women (9-10).

ASC-US in women older than 25 years

In high-risk HPV positive women a colposcopy and biopsy taking within 3 months should be performed.

Low-risk HPV typing is not recommended routinely but if this typing is performed (for example, to differentiate true HR HPV viral load versus cross-reaction with LR HPV), women..... that are low-risk HPV positive should have a repeat cervical cytology test after 6 months and if this is positive a colposcopy and biopsy should be done. In case of a negative smear, a normal screening interval is to be considered.

In HPV-negative patients a repeat smear after 12 months is indicated. If this appears to be positive a colposcopy and biopsy are necessary. In the case of a negative cervical cytology test the woman can have a normal screening interval.

If no concurrent HPV DNA test is performed a repeat smear after 6 months should be taken. If this features abnormalities, a colposcopy and biopsy are advised. In women with a negative cervical cytology test a repeat smear after 12 months is advised and, preferentially, a HPV DNA test should also be performed. If both tests are negative a normal screening interval can be followed. In case one or both, cervical cytology and HPV test, are positive, a colposcopy and biopsy are necessary.

The follow-up of colposcopy and biopsy should include treatment according to the lesion detected if found, and comprise a repeat smear after 12 months and preferentially an HPV test. In case both cervical cytology and the HPV test are negative, a normal screening interval can be followed. If one of the tests is positive, a colposcopy and biopsy are indicated.

ASC-US in women younger than 25 years

In high-risk HPV positive patients a repeat smear should be performed after 6 months. If this repeat smear is positive a colposcopy should be done and a biopsy has to be taken. If the repeat cervical cytology test is negative a concurrent HPV DNA test is indicated. In case of a positive HPV test and a negative repeat smear a colposcopy should be performed and a biopsy has to be taken. If both the HPV typing and cervical cytology test are negative a repeat smear after 12 months combined with HPV testing are advised. If these tests are

both negative the patient should have a normal screening interval whereas if either one is positive, a colposcopy and biopsy taking are advised.

Patients that are low-risk HPV positive should have a repeat smear after 6 months. If this is positive a colposcopy and biopsy are proposed and if it is negative, the patient can have a normal screening interval.

Patients that are HPV negative should have a repeat cervical cytology test after 12 months. If the smear is positive, colposcopy and biopsy taking are needed. In women with negative smears a normal screening interval can be followed.

If a repeat cervical cytology test after 6 months is positive a colposcopy and biopsy taking are advised. In case it is negative, a repeat cervical cytology test after 12 months with or without HPV testing should be taken. If both tests are then negative a normal screening interval is indicated. If one of both tests is positive a colposcopy and biopsy are needed.

If a persistent lesion is present and colposcopy and biopsy reveal a lesion, treatment should be performed according to the detected lesion. If no significant lesion is found at colposcopy and biopsy, a repeat cervical cytology test after 12 months should be taken with or without HPV testing. In case both tests are negative, a normal screening interval can be followed. If one or both tests are positive, the patient has to undergo a colposcopy and biopsy.

ASC-US in postmenopausal women

Postmenopausal women have a lower risk of developing CIN 2 or 3 and have thus to be considered separately (17).

High-risk HPV positive patients should have a colposcopy and biopsy taken within 3 months. Patients positive for low-risk HPV need a repeat cervical cytology test after 6 months. If this is positive, a colposcopy and biopsy should be done and, if negative, a normal screening interval can be followed.

In HPV negative women a repeat smear after 12 months is advised. If the result shows abnormal cytology, a colposcopy and biopsy taking are necessary. In patients with a normal result a normal screening interval can be applied.

In women with clinical or cytological evidence of atrophy and in which there are no contra-indications for the use of intravaginal oestrogens a repeat cervical cytology test can be taken 1-2 weeks after 1 week of oestrogen treatment. If the result of the new smear and a concurrent HPV test are positive a colposcopy and biopsy should be performed. A negative cervical cytology test should be followed by a repeat smear after 6 months and if this appears to be negative as well, a normal screening interval can be followed.

Women with a colposcopy and biopsy result featuring a lesion should be treated according to the detected lesion. In women where the colposcopy and biopsy are negative, a repeat smear with or without HPV test is advised after 12 months. If both cervical cytology and HPV test are negative a normal screening interval will be followed whereas if one or both tests are positive the woman should be referred for a colposcopy and biopsy taking.

Guidelines for the management of women with atypical squamous cells, cannot exclude HSIL (ASC-H)

The recommended follow-up is referral for colposcopy and biopsy taking, preferentially following a HPV test. If the result of the examination is positive, the patient should be treated according to the lesion present. If the colposcopic result is negative and no lesion is detected, a re-evaluation of the cytology, colposcopy and histology is advised. If the revision implies a new interpretation, the management should be in agreement with the re-evaluated interpretation. With a probable HSIL interpretation a diagnostic excision should be performed.

When the interpretation is probably not HSIL, a repeat smear with or without HPV DNA test should be done after 3-6 months. In case both are negative, a normal screening interval has to be considered, and if one or both are positive, the patient has to be referred for colposcopy and biopsy.

If the cytological interpretation of ASC-H is upheld, a cytological follow-up at 6 and 12 months or an HPV DNA testing at 12 months is acceptable. A repeat cervical cytology test featuring ASC or higher or a subsequent positive HPV DNA test justifies a referral for colposcopy and biopsy.

Guidelines for the management of women with low-grade squamous intra-epithelial lesion (LSIL)

The median rate of occurrence of LSIL amounts between 1.6% in the general population up to 7.7% in laboratories serving high-risk populations (18-19). However, cytological LSIL is a relatively poor predictor of the grade of CIN that will be seen on biopsy as e.g. about 15%-30% of women with LSIL on cytology will

feature CIN 2 or 3 in biopsies taken at colposcopy (8, 20). Other aspects are that the cytopathic effects of HPV cannot adequately be distinguished from CIN 1 and that LSIL mostly corresponds with a transient HPV infection. The majority of these lesions will spontaneously regress without treatment or will have disappeared after biopsy taking. In contrast, HSIL results more often from a persistent HPV infection and has a higher progression rate to invasive carcinoma (21). To reduce the risk that women would be lost to follow-up or that invasive cancers would be missed, the ideal attitude should be to refer all these women to colposcopy (22). However, the sensitivity of colposcopy is probably lower in routine clinical practice than published in literature as most studies are published by expert colposcopists. Moreover many women consider it as an uncomfortable procedure, it may raise false concerns about cervical disease, and it is expensive and may lead to overdiagnosis and overtreatment.

LSIL in women older than 25 years

It is the preferred option of the BSCC to have a concurrent HPV DNA test (24).

If high-risk HPV is positive in the testing, the woman should be referred for colposcopy and biopsy taking within 3 months.

When the lesion is low-risk HPV positive a repeat cervical cytology test is advised after 6 months. If this is positive, a colposcopy and biopsy are indicated. In case of negative testing, a normal screening interval can be considered.

With a negative HPV testing result it is advised to repeat the smear taking after 12 months and if then the result is positive the woman should be referred for colposcopy and biopsy. If it is negative, the woman can have a normal screening interval.

In case the repeat cervical cytology test after 6 months is positive, the woman should have a colposcopy with biopsy and if negative, there should be a repeat smear taken after 12 months with or without HPV DNA testing. If both are negative a normal screening interval can be considered and if one or both are positive a colposcopy and biopsy should be done.

In women with a lesion at colposcopy and biopsy the treatment should be in accordance with the lesion. If no lesion is found a repeat cervical cytology test has to be taken after 12 months with or without HPV test and if then both tests appear negative, a normal screening interval has to be followed. When one or both tests are positive, a colposcopy and biopsy have to follow.

LSIL in women younger than 25 years

In this group of women, a different policy is advocated because of the high rate of spontaneous regression of the lesions.

If a concurrent HPV DNA test is high-risk HPV positive a repeat smear should be taken after 6 months and when this repeat is positive, a colposcopy and biopsy should be performed. When the smear is negative a concurrent HPV test should be taken and if this is positive for HPV DNA a colposcopy and biopsy have to follow. In case of a negative testing a repeat smear after 12 months with or without HPV DNA testing should be done. If then both are negative a normal screening interval can be followed. In contrast, when one or both are positive the woman should have a colposcopy and biopsy.

With a low-risk HPV positive result a repeat cervical cytology test should be done after 6 months and if this is positive the woman should be referred for colposcopy and biopsy. When the result is low-risk HPV negative a normal interval can be followed. If the HPV DNA test is negative a repeat smear should be taken after 12 months. In case of a positive result a colposcopy and biopsy should be done and if the result is negative a normal screening interval can follow.

A positive repeat cervical cytology test after 6 months should be followed by a colposcopy and biopsy. A negative repeat smear should be repeated after 12 months with or without HPV DNA testing and if both are negative a normal screening interval is indicated. When one or both tests are positive, the woman should be referred for colposcopy and biopsy.

If, in a persistent lesion, the colposcopy and biopsy findings are positive, treatment should follow in accordance with the lesion present. When the colposcopy and biopsy findings are negative a repeat cervical cytology test after 12 months with or without HPV DNA testing should be done. With both tests negative a normal screening interval may follow, but if one or both are positive the woman should have a colposcopy and biopsy.

LSIL in postmenopausal women

When a concurrent high-risk HPV DNA test is positive a colposcopy and biopsy should be done within 3 months. If the testing is positive for low-risk HPV DNA

a repeat cervical cytology test after 6 months should follow and a positive result should then be followed by a colposcopy and biopsy whereas a negative one should lead to a normal screening interval. A negative HPV DNA test has to be followed by a repeat smear after 12 months. With a positive cytology test, a colposcopy and biopsy are indicated. In case of a negative test a normal interval can be recommended.

If there are no contraindications and if atrophy is clinically or cytologically present a course of intravaginal oestrogen can be applied, followed by a repeat smear 1 or 2 weeks after therapy. At positive result the preferred action will be a concurrent HPV DNA test and a colposcopy with biopsy taking. With a negative cervical cytology test result a repeat cytology after 6 months is indicated and if this result is negative again a normal screening interval can be followed.

With a positive colposcopy or biopsy result the treatment should be in accordance with the lesion. Negative colposcopy or biopsy findings have to be followed by a repeat smear after 12 months with or without HPV DNA test. Negative results will lead to a normal screening interval whereas one or both tests positive, this has to be followed by a colposcopy and biopsy.

Recommendations for the management of women with high-grade squamous intra-epithelial lesion (HSIL)

With a cytological result of HSIL a woman having a significant risk of CIN 2, 3 or invasive carcinoma is identified. Thus a colposcopy with endocervical evaluation and biopsy taking are indicated in this group of patients and in general a high-grade lesion will be detected at colposcopy (25). This group of women will be treated according to the lesion present.

Some women in whom the colposcopy will not confirm the HSIL, however, are at increased risk of having an undiagnosed CIN 2 or 3 (26). Here, first, a re-evaluation of the cervical cytological results and of the histological and colposcopic findings is indicated. Such reappraisal may resolve discrepancies between cytological and histological results (27-28). If the conclusion of the reappraisal is 'probably HSIL', a diagnostic excision is indicated. When it is concluded that the result is 'probably not HSIL', a repeat cytological testing after 3 to 6 months with or without HPV DNA test is advised and if desired an HPV typing can be done in this situation. With a negative cervical cytology result and HPV DNA test, a normal screening interval can be followed. If one or both tests are positive, a colposcopy and biopsy are indicated.

Atypical glandular cells and adenocarcinoma in situ

Three categories of glandular cell abnormalities are distinguished: 1) atypical glandular cells, endocervical, endometrial or glandular cells 'not otherwise specified' (AGC NOS); 2) atypical glandular cells, endocervical or glandular cells 'favour neoplasia' (AGC favour neoplasia); and 3) endocervical adenocarcinoma in situ (AIS).

The risk of finding a high-grade lesion in women with a result AGC favour neoplasia is higher than in women with a result of AGC NOS and the cytological result of AIS indicates women with a high risk of having an AIS or invasive cervical adenocarcinoma (29-30). Cervical cytology is not useful for the detection of endometrial lesions. The presence of endometrial cells in a cervical cytological sample can indicate pathology but is usually benign (31).

Atypical endocervical cells (AGC-ecc), NOS

The BSCC advises to have preferentially a concurrent test for typing of the HPV DNA.

If this test is positive for high-risk HPV, a colposcopy and biopsy are indicated within 3 months.

With a test positive for low-risk HPV a repeat cervical cytology test is indicated after 6 months. If this is positive the woman has to be referred for colposcopy and biopsy and when the HPV test is negative a normal screening interval can be followed.

A negative HPV test should have a repeat cervical cytology test after 12 months. A positive test should be followed by colposcopy and biopsy whereas with a negative test result a normal screening interval may follow.

In case of a repeat cervical cytology test after 3 to 6 months with or without an HPV DNA test and with one or both tests positive a colposcopy and biopsy are necessary. With both tests negative a repeat cervical cytology test after 12 months with or without HPV test are advised. If these are both negative a normal screening interval can be followed. With one or both tests positive a colposcopy and biopsy are indicated.

With positive colposcopy and biopsy results, treatment should be done in accordance with the lesion

present. Negative colposcopy and biopsy results should be followed by a repeat smear after 12 months with or without HPV test. When both tests are negative a normal screening interval can be followed, and one or both tests positive should be followed by a colposcopy and biopsy.

Atypical endocervical cells (AGC-ecc), favour neoplasia

This test result has to be followed by a colposcopy and biopsy with endocervical sampling, preferably following an HPV test. A positive test result has to be followed by treatment according to the lesion.

A negative result at colposcopy and biopsy necessitates a re-evaluation of the cytological, histological and colposcopic findings, as previously described for HSIL. With a revised decision of 'probably AIS' a diagnostic excision is indicated. If the result of the reappraisal is 'probably not AIS', a repeat cervical cytological test after 3 to 6 months with or without HPV test is advised. When both tests are negative the woman can have a normal screening interval. One or both tests positive has to be followed by a colposcopy and biopsy.

Endocervical adenocarcinoma in situ (AIS)

The woman has to be referred for colposcopy and biopsy with endocervical sampling. A positive result should be followed by treatment according to the lesion.

With negative findings at colposcopy and biopsy a re-evaluation of the cytological, histological and colposcopic findings is needed. When the conclusion is 'probably AIS' a diagnostic excision should be performed. With the decision that there is 'probably not AIS' present a repeat cervical cytology test after 3 to 6 months with or without HPV test has to be done. Both results negative may be followed by a normal screening interval. One or both tests positive should be followed by a colposcopy and biopsy.

Normal smear after treatment for HSIL or AIS-ecc

An HPV test and a repeat cervical cytology test should be performed 6 months after treatment in order to avoid false positives. One or both tests positive have to be followed by a colposcopy and biopsy. If both tests are negative it is advised to repeat a cervical cytology and HPV test after 6 months and if these are negative the woman can have a normal screening interval.

CONCLUDING REMARKS

With these guidelines for the management of women with abnormal cervical cytology results the BSCC aims to give recommendations for uniform follow-up based on TBS 2001. This should lead to the best possible treatment and efficient use of health care means to prevent cervical cancer.

REFERENCES

1. Papanicolaou GN. Cytological evaluation of smears prepared by the tampon method for the detection of carcinoma of the uterine cervix. *Cancer* 1954 7: 1185-90.
2. National Cancer Institute Workshop. The 1988 Bethesda System for reporting cervical/vaginal cytological diagnoses. *JAMA* 1989; 262: 931-4.
3. Broder S. From the National Institutes of Health. Rapid communication- The Bethesda System for reporting cervical/vaginal cytologic diagnoses- report of the 1991 Bethesda Workshop. *JAMA* 1992; 267: 1892.
4. Solomon D, Davey D, Kurman R, et al. The 2001 Bethesda System: terminology for reporting results of cervical cytology. *JAMA* 2002; 287: 2114-9.
5. Wright TC, Cox JT, Massad LS, Twiggs LB, Wilkinson EJ. 2001 consensus guidelines for the management of women with cervical cytological abnormalities. *JAMA* 2002; 287: 2120-9.
6. Stoler MH, Schiffman M. Interobserver reproducibility of cervical cytologic and histologic interpretations. *JAMA* 2001; 285: 1500-5.
7. Sherman ME, Solomon D, Schiffman M. Qualification of ASCUS: A Comparison of Equivocal LSIL and Equivocal HSIL Cervical Cytology in the ASCUS LSIL Triage Study. *Am J Clin Pathol* 2001; 116: 386-94.
8. Jones BA, Novis DA. Follow-up of abnormal gynaecologic cytology: a College of American Pathologists Q-probes study of 16.132 cases from 306 laboratories. *Arch Pathol Lab Med* 2000; 124: 665-71.
9. Flynn K, Rimm DL. Diagnosis of 'ASCUS' in women over age 50 is less likely to be associated with dysplasia. *Diagn Cytopathol* 2001; 24: 132-6.
10. Schiffman MH, Brinton LA. The epidemiology of cervical carcinogenesis. *Cancer* 1995; 76: 1888-1901.
11. Solomon D, Schiffman M, Tarone R. Comparison of three management strategies for patients with atypical squamous cells of undertermined significance: baseline results from a randomized trial. *J Natl Cancer Inst* 2001; 93: 293-9.

12. Bergeron C, Jeannel D, Podeva J, Cassonnet P, Orth G. Human papillomavirus testing in women with mild cytologic atypia. *Obstet Gynecol* 2000; 95: 821-7.
13. American College of Obstetricians and Gynecologists. Cervical cytology: evaluation and management of abnormalities. Washington, DC: American College of Obstetricians and Gynecologists; 1993: 1-7. ACOG Technical Bulletin 183.
14. Mitchell MF, Schottenfeld D, Tortolero-Luna G, Cantor SB, Richards-Kortum R. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. *Obstet Gynecol* 1998; 91: 626-31.
15. Sherman ME, Schiffman M, Cox JT. Effects of age and human papilloma viral load on colposcopy triage: data from the randomized atypical squamous cells of undertermined significance/low-grade squamous intraepithelial lesion triage study (ALTS). *J Natl Cancer Inst* 2002; 94: 102-7.
16. Wright TC, Lorincz A, Ferris DG, et al. Reflex human papillomavirus deoxyribonucleic acid testing in women with abnormal Papanicolaou smears. *Am J Obstet Gynecol* 1998; 178: 962-6.
17. ALTS-group. Results of a randomised trial on the management of cytology interpretations of atypical squamous cells of undetermined significance. *Am J Obstet Gynecol* 2003; 188: 1383-92.
18. Keating JT, Wang HH. Significance of a diagnosis of atypical squamous cells of undetermined significance for Papanicolaou smears in perimenopausal and postmenopausal women. *Cancer* 2001; 93: 100-5.
19. Jones BA, Davey DD. Quality management in gynaecologic cytology using interlaboratory comparison. *Arch Pathol Lab Med* 2000; 124: 672-81.
20. Takezawa K, Bennett BB, Wilkinson EJ, Drew PA, Hardt NS. Squamous intraepithelial lesions of the cervix in a high-risk population. *J Lower Gen Tract Dis* 1998; 2: 136-40.
21. Lonky NM, Sadeghi M, Tsadik GW, Petitti D. The clinical significance of the poor correlation of cervical dysplasia and cervical malignancy with referral cytologic results. *Am J Obstet Gynecol* 1999; 181: 560-6.
22. zur Hausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. *J Natl Cancer Inst* 2000; 92: 690-8.
23. Robertson JH, Woudent BE, Elliott H. Cytological changes preceding cervical cancer. *J Clin Pathol* 1994; 47: 278-9.
24. ALTS-Group. Human papillomavirus testing for triage of women with cytologic evidence of low-grade squamous intraepithelial lesions: baseline data from a randomized trial. *J Natl Cancer Inst* 2000; 92: 397-402.
25. Massad LS, Collins YC, Meyer PM. Biopsy correlates of abnormal cervical cytology classified using the Bethesda System. *Gynecol Oncol* 2001; 82: 516-22.
26. Kinney WK, Manos MM, Hurley LB, Ransley JE. Where's the high-grade cervical neoplasia? The importance of minimally abnormal Papanicolaou diagnoses. Obstet *Gynecol* 1998; 91: 973-6.
27. Grenko RT, Abendroth CS, Frauenhoffer EE, Ruggiero FM, Zaino RJ. Variance in the interpretation of cervical biopsy specimens obtained for atypical squamous cells of undetermined significance. *Am J Clin Pathol* 2000; 114: 735-40.
28. Milne DS, Wadehra V, Mennim D, Wagstaff TI. A prospective follow upstudy of women with colposcopically unconfirmed positive cervical smears. *Br J Ostet Gynaecol* 1999; 106: 38-41.
29. Soofer SB, Sidawy MK. Atypical glandular cells of undetermined significance. *Cancer* 2000; 90: 207-14.
30. Lee KR, Manna EA, St. John T. Atypical endocervical glandular cells: accuracy of cytologic diagnosis. *Diagn Cytopathol* 1995; 13: 202-8.
31. Montz FJ. Significance of 'normal' endometrial cells in cervical cytology form asymptomatic postmenopausal women receiving hormone replacement therapy. *Gynecol Oncol* 2001; 81: 33-9.