Management of low-grade squamous intraepithelial lesions of the uterine cervix

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Strategies of management for low-grade squamous intraepithelial lesion (SIL) vary even on a national level. We evaluated the diversity of management algorithms. This should serve as a source to find a common basis for the management of low-grade SIL. A total of 38 representatives and specialists for colposcopy and cervical pathology were contacted to provide national guidelines, recommendations or consensus for the management of patients diagnosed with the cytologic diagnosis of low-grade SIL. In all, 23 addresses (60%) responded. The algorithms provided varied considerably. Three variants of algorithms could be defined. Variant 1 was proposed in 14 countries and recommended colposcopy immediately after cytologic diagnosis of low-grade SIL or at the same time the smear is taken. If available, HPV testing was recommended as a triage option in some countries. Variant 2 is used in three countries and colposcopy is only performed after a repeated abnormal cytologic result within a 6-month interval or after an optional test positive for high-risk HPV. Variant 3, as proposed in six countries, takes into account the socio-economic status of the patient: In patients with poor compliance, ‘see and treat’ management is recommended; in patients where compliance can be assured, follow-up is carried out by cytology and colposcopy. Global policy of management of patients with low-grade SIL can be summarised in three algorithms. Quality standards and outcome parameters must be defined in order to improve the management of women with low-grade SIL.

Keywords: LSIL; management LSIL; cervical lesions

Low-grade squamous intraepithelial lesion (SIL) has been defined as a cytologic diagnosis for patients with smears showing cytologic criteria of permissive HPV infection or CIN I (Anonymous, 1989). This classification (Richart, 1990) is also used for histopathologic diagnosis, and low-grade SIL and low-grade CIN are used synonymously. The gold standard for the definition of cervical disease is histopathologic evaluation. However, it has to be kept in mind that even between expert pathologists inter- and intraobserver variability is high: in a recent study on 194 cervical tissues of different histologic severity, the agreement rate between five expert pathologists was 52% for the diagnosis of CIN I (k value 0.6) (Klaes et al, 2002). Agreement could be improved to 91% (k value 0.9) by immunohistochemical staining for p16INK4a a marker associated with the presence of high-risk HPVs.

In addition to the problem of defining the disease accurately, the natural course of low-grade SIL is variable: The majority of lesions (up to 70%) regress and only 10% of low-grade SIL may progress to high-grade CIN (Nasiell et al, 1986; Östör, 1993; Holowaty et al, 1999). When patients with the cytologic diagnosis of low-grade SIL are stratified in high-risk HPV negative or high-risk HPV positive using a GPS + GP6 + system, all high-risk HPV-negative and 70% of high-risk HPV-positive smears become normal over a period of 4 years (Nobbenhuis et al, 2001). In this series, 62% of smears were high-risk HPV positive. Not a single patient out of 64 patients with the cytologic diagnosis of low-grade SIL progressed to high-grade CIN (Nobbenhuis et al, 1999). However, using the only commercially available HPV test in clinical practice, Hybrid Capture II triaging low-grade SIL in regressors and progressors is not recommended due to the high rate of high-risk HPV positives with this system (i.e. 83%) (Koutsky et al, 1992; Stoler, 2001).

Since conventional histopathologic evaluation and HPV testing do not allow to define the biologic potential of low-grade SIL, there is a wide variety of clinical recommendations for management of disease. It was the purpose of this study to gain an overview of the current clinical practice in various countries in order to see if there is a need for simplification and coordination, for integration of new markers, and a basis for defining common quality and outcome parameters for the management of women with low-grade SIL.

MATERIALS AND METHODS

A letter was sent to 38 different societies and institutions responsible for the definition and coordination of management of patients with cervical abnormalities in the various countries. If published memoranda, recommendations, guidelines or consensus statements or clinical pathways were available, the authors were asked to provide the references or to send copies of the published material. If no such written statements were available, the authors were asked to give their personal interpretation of the national strategies. For each country, an algorithm was produced and
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RESULTS

Colposcopy immediately after the cytologic diagnosis of low-grade SIL is recommended in 11 countries (algorithm 1, Figures 1 and 4). In three European countries (Hungary, Spain and Yugoslavia) – where colposcopy is used as part of routine gynaecologic examination – colposcopy is also considered as an essential tool for managing low-grade SIL, but the colposcopic examination is carried out at the time the smear is taken. In Sweden, there are two different policies for various regions: When a low-grade lesion is detected in a routine cytologic smear, women in the Stockholm area are referred for colposcopy within 4 months. In other parts of Sweden, women with the cytologic diagnosis of low-grade SIL are followed up according to algorithm 2 (Figures 2 and 4).

Following histologic diagnosis of low-grade SIL after 2–6 months repeat examination by cytology and colposcopy is performed in all these countries. Persistent low-grade SIL can be either followed or treated. In health-care systems where HPV testing is available and recommended, high-risk HPV positive patients are followed up closely. In the US, HPV-testing is acceptable not initially, but after 12 months (please see www.asccp.org).

In four countries, cytologic diagnosis of low-grade SIL is followed up by a repeat smear after 6 months and only, when repeatedly abnormal on cytology, colposcopy is performed. When HPV testing is available, high-risk HPV-positive patients undergo colposcopy and, when abnormal findings are confirmed and persist for more than 1 year, treatment is performed (algorithm 2, Figures 2 and 4).

In six countries, management is performed according to the socio-economic status (algorithm 3, Figures 3 and 4). If noncompliance can be expected, ‘see and treat’ with different treatment modalities is recommended. In patients with high compliance, periodic evaluation by cytology and colposcopy is recommended and can be augmented by HPV testing. Lesions persisting for more than 1 year should be treated.

DISCUSSION

Management of women with the cytologic diagnosis of low-grade SIL varies considerably according to the availability of medical resources and socio-economic status of women. Since the histopathologic basis of disease is ill defined and progression markers are not available, there is a need for standardisation of treatment in order to guide the patient and clinician to avoid over- or undertreatment.

Immediate colposcopy after cytologic diagnosis of low-grade SIL (algorithm 1) is costly and may cause unnecessary stress on patients and the health system in countries where colposcopy is not a routine part of the gynaecologic examination. However, delay of histopathologic confirmation by 6 months or longer (algorithm 2) may lead to underdiagnosis and worsening of prognosis. For Germany, it has been shown that in patients with the cytologic diagnosis of low-grade SIL, CIN III is prevalent in 30.2% and invasive cancer in 1% of patients (Petry et al., 1999). In countries...
with excellent quality control of cytology, this rate may be lower and cytologic follow-up may be regarded sufficient.

In health-care systems where high-risk HPV testing is available, triaging in high-risk HPV-positive and high-risk HPV-negative lesions is performed (algorithms 1, 2, and 3). However, for clinical practice, no clear guidelines have been established as to testing of smears or biopsies and choice of HPV test. Tests that include only a certain amount of pooled high-risk HPVs and that show crossreaction between high- and low-risk types are clinically not useful due to low specificity (Arbyn, 2001). Highly sensitive two-tier PCR systems including a panel of 50 HPV types applied to tissue sections and not to smears may be more specific: only 30% of 453 CIN I contained high-risk HPV types and prevalence and distribution of HPV types are significantly different from CIN II or CIN III (Feoli-Fonseca et al, 2001). Thus, HPV systems with improved sensitivity and specificity may become clinically useful. Persistent detection of high-risk HPV, integration of high-risk HPV DNA in the host cell DNA, high viral load, and/or presence of certain HPV variants may be additional markers for future use. ‘See and treat’ as recommended by various countries (algorithm 3, Figure 3) on the basis of low-grade SIL by cytology alone, without biopsy-confirmed CIN I or more severe lesions, is not recommended in the US (please see www.asccp.org) (Figure 4).

There is a need to coordinate the diversing algorithms for the management of patients with low-grade SIL in order to avoid overtreatment: The majority of women with diagnosis of low-grade SIL are young and still desire conception. Standard treatment is still invasive, either using excisional or ablative procedures, which are associated with a peri- and postoperative morbidity rate of up to 10%. The data presented in this enquiry should therefore serve as a basis to start a discussion of a coordinated effort to improve the quality and result of the management of this highly prevalent diagnosis in order to improve women’s health.

ACKNOWLEDGEMENTS

We are grateful to all representatives, and experts for colposcopy and cervical pathology, who were contacted to provide national guidelines, recommendations or consensus opinions for the management of patients diagnosed with the cytologic diagnosis of low-grade SIL.

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