The problems with different management options of women with minor squamous intraepithelial lesions in Pap tests

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Summary

The optimum management of women with minor squamous intraepithelial lesions in Pap tests is controversial. With cytological surveillance after one Pap test showing atypical cells of undetermined significance (ASCUS), a significant proportion of women will have undiagnosed squamous intraepithelial lesions. On the other hand, using immediate colposcopy for ASCUS almost half of the women would not have needed the procedure. This number for referral for colposcopy can be reduced to only those women who test positive for high-risk HPV-DNA, however some women will have undiagnosed squamous intraepithelial lesions. In addition, when surveillance with repeat Pap tests is used for the management of low-grade cervical squamous intraepithelial lesions (LSIL) a significant number of high-grade cervical intraepithelial lesions can be missed. In this article all the problems of each management policy in women with minor squamous intraepithelial lesions in Pap tests are addressed.

Key words: Pap test; Minor squamous intraepithelial lesions; ASCUS; LSIL; CIN.

Introduction

Worldwide, cervical cancer is one of the most frequent malignancies in women and causes considerable morbidity and mortality. The Pap test as a primary screening method for cervical cancer is largely responsible for the decreased incidence of this malignancy. However, the performance of a single conventional cervical smear has been shown to be poor, with sensitivity as low as 47% [1]. The sensitivity of a screening program could be considerably improved by using colposcopy during routine Pap tests but it is costly. In addition, we need to avoid excessive examinations for patients who do not need them, but also to identify the few patients who have clinically significant disease. The association between certain HPV types (types 16, 18, 31, 33, 35, 45, 51, 52, 56, 58, 59, 68) and the development of cervical intraepithelial lesions (CIN) and invasive cervical cancer is well established. An obvious question is whether screening using high-risk HPV-DNA testing could increase the detection of unrecognized cervical lesions in primary cervical cancer screening. Unfortunately, it seems that with the current methods of HPV-DNA testing we do not add sufficient predictive and diagnostic information such as to use it for cervical cancer screening. Consensus guidelines have been developed for the management of women with cervical cytological abnormalities and cervical intraepithelial neoplasia [2]. However, the optimum management of women with minor squamous intraepithelial lesions in Pap tests is controversial. Here, the problems with the different options in the management of women with low-grade squamous intraepithelial lesions will be addressed.

Management options for ASCUS

Atypical cells of undetermined significance (ASCUS) according to the Bethesda system are limited to cases in which the cytological importance is uncertain. However, CIN-2 and CIN-3 can be found in 5% to 9.4% of women with ASCUS [3-5]. Therefore, further attention is needed for women with ASCUS. Three approaches are acceptable for the management: (i) follow-up with Pap tests; (ii) immediate colposcopy; (iii) HPV DNA testing. All of them have their advantages and disadvantages. In the case where follow-up is used with repeat Pap tests the women should undergo Pap tests at four to six-month intervals until two consecutive negative results for intraepithelial lesion or malignancy are obtained; then, the women return to routine cytological screening. Women diagnosed with ASCUS or greater cytological abnormalities on a repeat Pap test should be referred for colposcopy [2]. With this management policy more than two-thirds of lesions will regress to normal, but 39% of patients will have undiagnosed squamous intraepithelial lesions [6]. In the cases where immediate colposcopy was used for management of women with ASCUS, it has been found that 51% of patients would have not needed the procedure. On the other hand, colposcopy has the advantage that it identifies almost 100% of lesions [6]. In this protocol women without CIN are followed-up with a repeat Pap test at 12 months [2]. Some centers prefer to use HPV DNA testing for the management of women with an ASCUS. In this protocol, women who test negative for high-risk HPV DNA are followed-up with repeat Pap test at 12 months [2]. Women who test positive for high-risk HPV DNA are referred for an immediate colposcopy to detect CIN or higher lesions unrecognized by screening cytology. Using this protocol and referring to colposcopy only HPV-DNA positive women, 21% of patients will have undiagnosed squamous intraepithelial lesions (SIL) and 34% would not have needed the procedure [2].

I think there is no controversy on the management of postmenopausal women with ASCUS Pap test. If the women are not taking hormones they should be treated with intravaginal estrogens for two months and have the smear repeated a week after completing the regimen. If persistent ASCUS or greater is found, colposcopy is recommended. If the repeated Pap test is negative for intraepithelial lesions or malignancy then it should be repeated in four to six months. If both repeat Pap tests are negative the patient can return to routine cytological screening [2, 7].

Management options for LSIL

The management of low-grade squamous intraepithelial lesions (LSIL) in Pap tests depends on the clinician or the national guidelines. Approximately, 47% of CIN-1 lesions will spontaneously regress, while 37% will persist as low-grade and 16% will progress to higher-grade preinvasive lesions or invasive cervical cancer [8]. Consequently some authors have advocated surveillance with repeat Pap tests every four to six months for two years. If a repeat Pap test shows persistent abnormality, colposcopy is indicated. After three consecutive Papanicolaou tests have proven negative, patients return to annual follow-up. However, this protocol takes 12 to 18 months from the index smear to obtain a negative result. In addition, approximately 9% to 16% of low-grade squamous intraepithelial lesion (LSIL) Pap tests are associated with CIN-2 and CIN-3 [9, 10]. Therefore, one should remain cautious that repeat Pap tests can miss a significant number of lesions. Excisional modalities (LEEP, laser, cold-knife conization) of the transformation zone are not recommended as an initial method of evaluating LSIL in Pap tests because of the high rate of normal histology [7]. Excisional modalities are preferred for patients with biopsy-confirmed CIN-1 and unsatisfactory colposcopic examination and in patients with a medical history of ablative cervical therapy and recent biopsy-confirmed CIN-1.

Colposcopy with directed biopsies and endocervical curettage is a great option for the management of patients with LSIL Pap tests. I prefer surveillance in women with satisfactory colposcopy and biopsy-confined CIN-1 with repeat Pap tests at four to six month intervals for two years. This management permits regression of important cervical changes, such as those related with human papillomavirus (HPV). According to the 2001 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia the patients should be referred to colposcopy if a repeat Pap test is reported as ASCUS or greater, while after two negative consecutive Pap tests the patients should return to annual cytologic screening [2]. Also, HPV-DNA testing at 12 months is as alternative to two repeat cervical cytology tests in the follow-up of women with CIN-1 [11]. The women should be referred to colposcopy in the case of a positive high-risk HPV DNA result at 12 months. In the case of a negative HPV DNA result at 12 months, the woman should return to annual cytologic screening. Other acceptable management options for women with satisfactory colposcopy, endocervical sampling and biopsy-confirmed CIN-1 include: (i) follow-up with a combination of repeat cytology and colposcopy at 12 months, and (ii) ablative (cryotherapy, electrofulguration, laser ablation) or excisional modalities. Randomized trials have shown no statistically significant differences in cure rates between cryotherapy and laser vaporization. In addition, recurrences after ablative procedures are more likely to be positive for an HPV type other than that detected before treatment, whereas recurrences after excisional procedures tend to be of the same type of HPV as preoperatively. It seems that ablation of CIN promotes a type-specific immune response not available when the lesion and its viral load are excised. Moreover, high recurrence rates in older women and in women previously treated for CIN are consistent with the notion that such women have a decreased ability to clear the virus [12].

In conclusion, the management of minor cytological abnormalities of squamous epithelium in Pap tests is controversial. Using immediate colposcopy for ASCUS about half of the women would not have needed the procedure. In addition, a significant number of high-grade intraepithelial lesions can be missed when surveillance with repeat Pap tests is used for the management of LSIL. Women with biopsy-confirmed CIN-1 should be followed up with repeat pap tests at four to six-month intervals for two years or with HPV-DNA testing at a 12-month interval, while in selected cases ablative or excisional modalities can be used.

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