H. A. Toews

The Abnormal Pap Smear: A Rationale for Follow Up

SUMMARY

Cervical intraepithelial neoplasia (CIN) is readily identifiable by cytology, so theoretically, most cases of invasive carcinoma should be preventable. Risk factors for carcinoma of the cervix are related to sexual activity, therefore screening should be similarly related. All women should have routine annual cytology as soon as they are sexually active. The high risk male partner should also be considered when taking a history. Those with moderately atypical smears or higher should be referred for further colposcopic evaluation. Good quality cytology will reduce the incidence of false negative smears. Some cases of CIN progress, some remain static, some regress. Colposcopy is valuable in assessing cervical changes; cone biopsy should be required only when colposcopy is inconclusive, or invasion is suspected. Sampling errors in cytology account for the majority of false negative results. (Can Fam Physician 1983; 29:759-762).

SOMMAIRE

La néoplasie cervicale intra-épithéliale (NCI) est facilement identifiable par cytologie. Théoriquement, on devrait donc pouvoir prévenir la plupart des cas de cancers invasifs. Les facteurs de risque pour le carcinome du col sont reliés à l'activité sexuelle: on devrait donc faire en sorte que le dépistage y soit associé de la même façon. Toutes les femmes devraient subir une cytologie annuelle de routine dès qu'elles deviennent actives sexuellement. Le partenaire mâle à haut risque devrait aussi être pris en considération au moment de l'histoire du cas. Celles dont les frottis sont modérément ou plus fortement atypiques devraient être référées pour une évaluation colposcopique plus poussée. Une cytologie de bonne qualité réduira l'incidence de frottis faux-négatifs. Certains cas de NCI progressent, d'autres demeurent stationnaires, d'autres régressent. La colposcopie est valable pour évaluer les changements au niveau du col; la biopsie en cône n'est pas indiquée à moins que la colposcopie ne soit pas concluante, ou qu'on suspecte une invasion. Les erreurs de prélèvement d'échantillons cytologiques sont la cause de la majorité des résultats faux-négatifs.

Dr. Toews is assistant professor of obstetrics and gynecology in the Faculty of Medicine at the University of Manitoba. Reprint requests to: Women's Hospital, Health Sciences Centre, 735 Notre Dame Avenue, Winnipeg, MB. R3E 0L8.

INVASIVE SQUAMOUS cell carcinoma of the cervix is preceded by recognizable states of cervical dysplasia and carcinoma in situ, now also collectively referred to as cervical intraepithelial neoplasia (CIN). Both cytology and colposcopy were developed in the 1920s as screening methods to identify such pre-invasive lesions. Cytology has long since been recognized as the more feasible screening tool, while colposcopy is most useful in further identification and management of the lesion. When cytology and colposcopy are combined, a diagnostic accuracy of 99.5% has been achieved,[1] thereby obviating the need for cone biopsy in the majority of cases. This is especially important in young women who wish to have children and in pregnant women where the complications of cone biopsy have been most significant.

Since CIN is identifiable by cytologic screening methods, most cases of invasive cancer should be ideally preventable. Cervical screening programs have reduced the incidence of invasive carcinoma of the cervix, but there is room for further improvement. Some of this can be achieved by good quality smears and by appropriate follow up and treatment of patients with abnormal smears.

Terminology

Various terminologies for the reporting of cytology smears are cur-

rently being employed. Some laboratories use the categories Class I to Class IV, describing cells from normal to carcinoma. Others prefer to diagnose their smears as mild, moderate and severe dysplasia and carcinoma in situ to describe abnormal squamous cells. CIN is a recent introduction; the various categories correspond as follows:

Class I: Normal	
Class II: Mild	CIN I
Class III: Moderate to Severe	CIN II
Class IV: Severe/CIS	CIN III

Etiology of Cervical Neoplasia

Epidemiological evidence suggests that herpes simplex virus type II (HSV II) is associated with and may lead to the development of premalignant changes in the cervical epithelium.[2] HSVII RNA has been detected in a high percentage of patients with in situ and invasive cancer.[3] However, it has not yet been established which portion of the virus is responsible for the malignant transformation.

Other factors besides herpes simplex virus are likely involved in the development of cervical neoplasia. There is little doubt that they are related to intercourse, increased parity and sexual activity. Early age at first intercourse, increased parity, and multiple sexual partners are generally regarded as important risk factors in the development of carcinoma of the cervix. However, not all women who have developed in situ or invasive carcinoma have had multiple sexual partners, and some studies have suggested the existence of the high-risk male.[2] Risk factors to be considered should obviously also include a history of multiple sexual partners in the patient's sexual partner.

Natural History of CIN

An important problem in dealing with follow up and diagnosis of abnormal cervical smears is the extent and rate at which CIN may change. The natural history of CIN encompasses three types of cases: those which progress, those which remain static, and those which regress. A recent study in British Columbia indicates that regression does occur, especially in young women.[4] If some cases regress and others persist unchanged, then our estimates of the mean duration of CIN must include some cases which progress to invasive cancer after a very short interval.

Patients who convert from cytological negativity to significant dysplasia or invasive cancer during a given period of time represent the incidence of CIN. From such information, direct determination of conversion rates and patterns of cytologic change during the transformation can be made. The rate of CIN may be increasing, especially in women aged 20-30. One study found the incidence rate to be highest at age 25-29.[5] The same authors calculated the conversion rate in patients with negative or slightly dysplastic entry smears to be 2.1-2.3 years. These are significantly shorter than the previously estimated rate of six years. Such findings must influence our attitude about the frequency of routine cervical smears and the follow up of abnormal smears.

Screening Schedules

Theoretically, patients at increased risk of developing carcinoma of the cervix should be screened more frequently than those patients who are at low risk. On the basis of epidemiological and sociological evidence, the female population can be classified into different groups in terms of risk. Women at low risk are those who have never had sexual intercourse and those who have had a previous hysterectomy and continuously negative cytology. The group at risk comprises all other women, but within this group there is a subgroup who are at increased risk by reason of parity and early and diverse sexual contacts. The relative risk of each of these factors is not entirely clear. There is no evidence that high risk patients progress more rapidly from minimal changes to invasive cancer and no correlation has been demonstrated between conversion interval and age of patient.[5] It may be difficult for the physician in clinical practice to identify high risk patients. Furthermore, it is becoming increasingly common for both men and women to have more than one sexual partner, and consequently selective screening based on high risk has very little application.

One of the most controversial issues in recent years has been the recommended frequency of cytologic screening. The 1976 Walton Report recommended that a woman should enter a screening program when she became sexually active, or at age 18 and have a repeat smear in one year.[6] If these were normal, then three-yearly smears to age 35 and five-yearly smears to age 60 were recommended. This produced a great deal of debate and the 1982 revised report recommends an annual Pap smear in all women between ages 18 and 35 and five-yearly smears thereafter until age 60.[7] These recommendations are valid, of course, only with smears of good quality without significant atypia.

The Abnormal Cervical Smear

Cytology has proven to be an excellent tool in detecting preclinical cervical dysplasia and occult invasive carcinoma. Apart from detection of abnormality, cytology can predict the degree of dysplasia and suggest the possibility of invasion. However, it has no preventive value in itself; and there must be appropriate follow up and treatment of the abnormal smear. Patients with invasive cancer, despite one or more smears during the previous five years, have often had at least one abnormal smear, implying that follow up may not have been adequate.[8]

Colposcopy is particularly valuable in assessing cervical abnormalities in young women. It can define the extent and location of the lesion, predict the severity of dysplasia and identify vascular patterns consistent with invasion. A colposcopist will also usually take a direct punch biopsy from the area of most significant change for further histologic evaluation. Under ideal circumstances, cytologic, colposcopic and histologic findings should agree within one degree of dysplastic severity. Diagnostic cone biopsy is required only in those cases where colposcopy is inconclusive or invasion is suspected. Inconclusive findings usually involve lesions which extend into, or are located entirely in, the endocervical canal and are thus out of reach of colposcopic vision. Severe acute cervicitis can also render colposcopy inconclusive. Such patients will require re-examination following appropriate treatment but will not usually require cone biopsy.

There is no evidence that oral contraceptives or intrauterine contraceptive devices increase the risk of developing cervical cancer. Patients who wear intrauterine contraceptive devices have an increased incidence of certain types of cervical infection and on this basis may show minimal atypia more frequently. The common recommendation that oral contraceptives be discontinued and contraceptive devices be removed in patients with abnormal cytology is probably not valid and certainly not wise. Patients who have abnormal smears should not be allowed to become pregnant until a colposcopic and tissue diagnosis has been made.

Women whose cervical cytology suggests moderate dysplasia, severe dysplasia, carcinoma in situ or invasive disease should be assessed colposcopically.

Minimally atypical smears (CIN I) are generally considered to be benign. Especially in young women, such changes are frequently related to cervicitis and vaginitis. Treatment of the infection in these cases will cause the smear to revert to normal. Repeat cytology should be carried out six to eight weeks following treatment. If the cytology becomes negative, then the smear should be repeated in six months and then annually. If repeat cytology is again atypical, then the patient should be referred to colposcopy for further evaluation.

Colposcopy has been especially valuable in managing the pregnant patient with abnormal cytology. All patients should have a cytology smear in the first trimester if they have not been screened in the six months before the onset of the pregnancy. Those with abnormal cytology should be referred for colposcopy. Colposcopic examination is possible throughout pregnancy but is much more difficult with an extremely vascular and often posterior cervix of late pregnancy.

The squamocolumnar junction is usually visible in the pregnant patient and colposcopic assessment with directed punch biopsy is highly accurate and carries no morbidity. Cone biopsy is only necessary in those patients with microinvasion and those in whom invasion is suspected at colposcopy and not confirmed on biopsy. Cone biopsy on pregnant patients has been associated with significant morbidity and pregnancy loss.[10] The patient with an abnormal smear in pregnancy should not be subjected to cone biopsy without prior evaluation of the cervix by an experienced colposcopist.

False Negative Smears

In some patients, patterns of cytologic conversion may show continuously increasing atypia up to carcinoma.[5] Some cases, however, never progress beyond minimal to moderate dysplasia or even show retrogressive cytologic changes before histologic confirmation of severe dysplasia or carcinoma in situ (CIN III). These represent apparent false negative cytology, probably due to sampling errors. The discovery of invasive disease or significant dysplasia in patients with previous negative smears must also lead to suspicion of false negative smears, especially in patients with squamous carcinoma. Lesions other than squamous cell carcinoma, such as adenocarcinoma and carcinosarcoma, do not shed cells that are easily identified in screening cytology. They may be cytologically negative or present with atypical smears.

A significant number of patients with atypical smears have lesions much more severe than suggested by the cytology. Sandmeier et al. reported that 27% of patients with atypical smears had significant lesions, including 3.4% with invasive cancer.[9] Some of these patients showed a higher level of abnormality on repeat smear, but some never progressed beyond atypical. It is therefore evident that although minimal dysplasia per se is a benign lesion, persistent atypical smears require further colposcopic and histologic evaluation.

Sampling Techniques

Papanicolaou first thought of using vaginal pool aspirate for collecting cellular samples from the uterus and cervix. This method, however, yields very high false negative rates (63%).[11] Ayre developed the concept of scraping the squamocolumnar junction and devised a spatula which is still widely used. Richart and Vaillant demonstrated that samples derived from both cervical scrapings and endocervical mucous yield the most abundant numbers of well-preserved cells for diagnosis.[11]

Lesions may be located on different areas of the transformation zone, the area between the original location of the squamocolumnar junction and the present location of the squamocolumnar junction. Some lesions are located within the transformation zone adjacent to the original squamocolumnar junction, while others are more commonly located near the endocervix. In order to sample the cervix appropriately, one must obtain material from the whole area. Sampling of the transformation zone to the original squamocolumnar junction is best done by the circumferential scraping technique, while sampling of the endocervical junction is best obtained with a moistened Q-tip.[11] Good visualization of the cervix and recognition of the transformation zone area is essential to obtain good smears.

Sampling Errors

There are a number of possible reasons for false negative cervical smears. The necessity for careful documentation of material in both the physician's office and the laboratory is obvious. Proper techniques in collecting and fixing cellular material is very important and failure to observe them probably leads to the majority of inadequate smears. Failure to visualize the cervix properly will prevent the collection of material from the transformation zone and produce sampling errors. In very small lesions and in lesions located in the vaginal vault or high in the canal, sampling errors cannot be entirely prevented. Lesions with a keratinizing tendency do not have representative cells at the surface. In sampling such lesions, cells from beneath the keratinized layer must be obtained in order to reflect the true nature of the lesion. Infection and bleeding can obscure pertinent cells and collection of material during menstruation should be avoided. Where severe infection is present, the cytology smear should be postponed whenever possible until the cervicitis is resolved.

Conclusions

Further reduction in the incidence of invasive cancer of the cervix is essential. This can be achieved by screening all women at risk, using

cervical cytology. All significantly abnormal smears and persistent atypical smears should be referred for colposcopic evaluation and treatment. The incidence of false negative errors can be reduced by good sampling techniques. ◉

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