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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.

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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

Class III: Moderate to Severe

Class IV: Severe/CIS

CIN I

CIN II

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 un-

changed, 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 mor-

bidity 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

Motrin®

(ibuprofen) tablets

Product Information

Action: Ibuprofen has demonstrated anti-inflammatory, analgesic and antipyretic activity in animal studies designed to specifically demonstrate these effects. Ibuprofen has no demonstrable glucocorticoid effect.

Following a single 200 mg dose of ibuprofen in humans, useful blood levels were demonstrable in 45 minutes and still present in six hours but at barely detectable levels. Peak levels occurred at approximately one hour after ingestion. Levels were lower when taken in conjunction with food.

Ibuprofen is rapidly metabolized and eliminated in the urine. The excretion of ibuprofen is virtually complete 24 hours after the last dose. The serum half-life of ibuprofen is 1.8 to 2 hours. There is no evidence of drug accumulation or enzyme induction.

Ibuprofen has been found to be less likely to cause gastro-intestinal bleeding in doses usually used than is acetylsalicylic acid.

Clinical trials in man have shown activity of a dose of 1200-1800 mg of ibuprofen daily to be similar to that of 3.6 grams of acetylsalicylic acid daily.

Indications and Clinical Uses: Motrin (ibuprofen) is indicated for the treatment of rheumatoid arthritis and osteoarthritis. Motrin is also indicated for the relief of mild to moderate pain accompanied by inflammation in conditions such as musculo-skeletal trauma and post-dental extraction. Motrin is also indicated for the relief of pain associated with dysmenorrhea.

Contraindications: Motrin (ibuprofen) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to acetylsalicylic acid or other nonsteroidal anti-inflammatory agents. (see WARNINGS).

Motrin should not be used during pregnancy, in nursing mothers or in pediatric patients because its safety under these conditions has not been established.

Warnings: Anaphylactoid reactions have occurred in patients with known A. S. A. hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported in patients receiving Motrin (ibuprofen). Peptic ulceration, perforation, or severe gastrointestinal bleeding can have a fatal outcome, and although few such reports have been received with Motrin, a cause and effect relationship has not been established. Motrin should be given under close supervision to patients with a history of upper gastro-intestinal tract disease.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in colour vision have been reported. If a patient develops such complaints while receiving Motrin (ibuprofen), the drug should be discontinued and the patient should have an ophthalmological examination. Fluid retention and edema have been reported in association with Motrin therefore, the drug should be used with caution in patients with a history of cardiac decompensation or renal disease.

Motrin, like other nonsteroidal anti-inflammatory agents, can inhibit platelet aggregation but the effect is quantitatively less and of shorter duration than that seen with acetylsalicylic acid. Motrin has been shown to prolong bleeding time (but within the normal range) in normal subjects. Because this prolonged bleeding effect may be exaggerated in patients with underlying hemostatic defects, Motrin should be used with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients on Motrin should be cautioned to report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

When Motrin is added to the treatment program of patients who have been on prolonged corticosteroid therapy, and it is decided to discontinue this therapy, the corticosteroid should be tapered slowly to avoid exacerbation of disease or adrenal insufficiency.

Aseptic meningitis has been reported in connection with Motrin therapy in patients with systemic lupus erythematosus. Such patients may also develop hypersensitivity reactions to Motrin such as fever, rash or abnormal liver function more often than those with other disorders. Caution should therefore be exercised when considering Motrin therapy for patients with systemic lupus erythematosus.

Drug Interactions

Coumarin-type anticoagulants: Several short-term controlled studies failed to show that Motrin significantly affected prothrombin times or a variety of other clotting factors when administered to individuals on coumarin-type anticoagulants. However, because bleeding has been reported when Motrin and other nonsteroidal anti-inflammatory agents have been administered to patients on coumarin-type anticoagulants, the physician should be cautious when administering Motrin to patients on anticoagulants.

A. S. A.: Animal studies show that A. S. A. given with nonsteroidal anti-inflammatory agents including Motrin yields a net decrease in anti-inflammatory activity with lowered blood levels of the non-A. S. A. drug. Single dose bioavailability studies in normal volunteers have failed to show an effect of A. S. A. on Motrin blood levels. Correlative clinical studies have not been done.

Adverse Reactions: The following adverse reactions have been noted in patients treated with Motrin (ibuprofen):

Note: Reactions listed below under Causal Relationship Unknown are those which occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, the possibility of a relationship to Motrin cannot be excluded.

Gastrointestinal: The adverse reactions most frequently seen with Motrin therapy involve the gastrointestinal system.

Incidence 3 to 9%: nausea, epigastric pain, heartburn.

Incidence 1 to 3%: diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the gastrointestinal tract (bloating or flatulence).

Incidence less than 1%: gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, hepatitis, jaundice, abnormal liver function (SGOT, serum bilirubin and alkaline phosphatase).

Central Nervous System:

Incidence 3 to 9%: dizziness

Incidence 1 to 3%: headache, nervousness

Incidence less than 1%: depression, insomnia

Causal relationship unknown: paresthesias, hallucinations, dream abnormalities.

Dermatologic:

Incidence 3 to 9%: rash (including maculopapular type)

Incidence 1 to 3%: pruritus

Incidence less than 1%: vesiculobullous eruptions, urticaria, erythema multiforme

Causal relationship unknown: alopecia, Stevens-Johnson syndrome.

Special Senses:

Incidence 1 to 3%: tinnitus

Incidence less than 1%: amblyopia (blurred and/or diminished vision, scotomata and/or changes in colour vision). Any patient with eye complaints during Motrin therapy should have an ophthalmological examination (see PRECAUTIONS).

Causal relationship unknown: conjunctivitis, diplopia, optic neuritis.

Metabolic:

Incidence 1 to 3%: decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Hematologic:

Incidence less than 1%: leukopenia and decreases in hemoglobin and hematocrit

Causal relationship unknown: hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes (e.g. purpura, epistaxis, hematuria, menorrhagia).

Cardiovascular:

Incidence less than 1%: congestive heart failure in patients with marginal cardiac function, elevated blood pressure

Causal relationship unknown: arrhythmias (sinus tachycardia, sinus bradycardia, palpitations).

Allergic:

Incidence less than 1%: anaphylaxis (see CONTRAINDICATIONS).

Causal relationship unknown: fever, serum sickness, lupus erythematosus syndrome.

Endocrine:

Causal relationship unknown: gynecomastia, hypoglycemic reaction.

Renal:

Causal relationship unknown: decreased creatinine clearance, polyuria, azotemia.

Symptoms and Treatment of Overdosage: A nineteen month old child weighing 12 kg ingested from 2800 to 4000 mg of Motrin (ibuprofen) and presented with apnea, cyanosis and responded only to painful stimuli. Oxygen and parenteral fluids were given and at 12 hours she appeared completely recovered. Two other children (10 kg each) ingested 1200 mg of Motrin each and there were no signs of acute intoxication or late sequelae. A 19 year old male who had ingested 8000 mg of Motrin reported dizziness, and nystagmus was noted. He recovered with no reported sequelae after parenteral hydration and three days' bed rest.

In cases of acute overdosage, the stomach should be emptied by vomiting or lavage, though little drug will likely be recovered if more than an hour has elapsed since ingestion. Because the drug is acidic and is excreted in the urine, it is theoretically beneficial to administer alkali and induce diuresis.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis:

The initial daily dosage in adults is 1200 mg divided into 3 or 4 equal doses. Depending on the therapeutic response, the dose may be adjusted downward or upward. The daily dosage should not exceed 2400 mg.

Maintenance therapy, once maximum response is obtained, will range from 800 to 1200 mg per day.

Mild to moderate pain accompanied with inflammation, dysmenorrhea: 400 mg repeated as required every 4 to 6 hours. The daily dosage should not exceed 2400 mg.

Children: Due to the lack of clinical experience, ibuprofen is not indicated for use in children under 12 years of age.

Supplied: 200 mg (yellow), 300 mg (white), 400 mg (orange) sugar-coated tablets and 600 mg (peach) film-coated tablets in bottles of 100 and 1000.

Product monograph available on request. CE 1542 1C

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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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