Procedures in Family Practice

Cervical Cytology: Use and Follow-Up

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The Pap smear was introduced to clinical medicine 35 years ago. It is the most practical means of screening for precancerous lesions of the cervix. Endocervical and ectocervical samples improve detection. Colposcopy and colposcopically directed biopsy will document the most advanced lesion in almost all cases. The need for conization has been greatly reduced. Treatment of intraepithelial neoplasia will prevent the development of invasive cancer of the cervix.

Exfoliative cytology (Pap smears) became clinically useful in 1943 when Doctors George Papanicolaou and Herbert Traut of Cornell University published their monograph, "Diagnosis of Uterine Cancer by the Vaginal Smear." Although one still hears of the Pap smear being referred to as a "cancer test," subsequent refinements in diagnostic cytology and its use in mass screening programs have identified a spectrum of asymptomatic precancerous lesions. The greatest contribution made by the Pap smear is in the detection of such lesions, thus permitting early treatment and dramatically reducing the incidence of invasive carcinoma of the cervix and the number of deaths attributable to it. As a result of the success of cytologic screening, cancer of the cervix should be considered a preventable disease.

A 1976 survey for the American Cancer Society estimates that 79.0 percent of females 18 years of age and older in the United States have had at least one Pap smear in their lifetime; 50.3 percent have had a smear within the past year.[1] Thus, a significant segment of the population is not having cervical cytologic examinations in a day when invasive cancer of the cervix still ranks as the fifth most common cancer among women. The American Cancer Society has devoted considerable effort toward making the public aware of the need for annual Pap smears and in conducting mass screening programs. At least three states (New York, Illinois, and Hawaii) have health codes requiring cervical cytology during the hospitalization of adult females who have not had a recent Pap smear. Many hospitals outside of those states are taking the initiative in writing regulations requiring cervical cytology reports on all of their female admissions 20 years of age and older.

Ultimately, however, it is the primary care physician who must be relied upon to initiate and perform annual Pap smears on the individual patient. Suggestions for cytologic screening are given in Table 1.[3] When such a procedure becomes part of the routine practice of medicine, it is appropriate to review periodically opinion concerning the reason for the test, its accuracy, how it should be performed, and its interpretation and follow-up.

Cervical Intraepithelial Neoplasia

As a result of the acceptance of cytologic screening by asymptomatic women and the accessibility of the cervix to visual examination and sampling, a great deal has been learned about the pathogenesis of cervical cancer. The neoplastic process is usually confined to the squamocolumnar junction and a small area on either side of it referred to as the transformation zone. It is in this

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biologically active area that the columnar epithelium and its associated reserve cells, which characteristically cover the cervix of a child, are transformed through a process of squamous metaplasia into the mature squamous epithelium of the adult cervix.

On occasion, a series of atypical intraepithelial changes may take place within this transformation zone which represent a disturbance in the process of squamous metaplasia and are precancerous in nature. These transformations are referred to collectively as cervical intraepithelial neoplasia (CIN). The two major components of CIN are the dysplasias and carcinoma in situ. The dysplasias, depending upon their degree of atypicality, may be subclassified as mild, moderate, and severe. The most advanced form of CIN is carcinoma in situ. The use of this subclassification of CIN is important because the biological potential for the development of invasive cancer varies according to the degree of neoplasia that is present.

The highest incidence of cervical dysplasia occurs in the third decade of life. The mean age of carcinoma in situ of the cervix is 34 years; that of invasive carcinoma is 48 years. Prospective studies have shown an annual progression rate from dysplasia to invasive cancer of 5 to 6.4 percent. Reports documenting the number of cases of carcinoma in situ which become invasive cancer range between 25 and 70 percent.[4]

As most CIN is asymptomatic and invisible, cervical cytology has proven to be the most practical means for detecting it. Fortunately, the spectrum of CIN is present long enough to permit its detection, documentation, and eradication before invasive cancer supervenes. Herein lies the value of routine cervical cytology screening.

Accuracy of Cervical Cytology

For several reasons the accuracy of cervical cytology cannot be expressed with certainty in terms of the usual false-positive and false-negative percentages used for other laboratory tests. Identification of specific precursor lesions and early cancer is subject to individual interpretation. Some precursor lesions regress spontaneously, trauma (scraping and biopsy) may remove the lesion or induce regression, and the determination of such rates requires delayed repeat examinations and long-term follow-up.

A recent study using colposcopy in the evaluation of 352 consecutive abnormal smears reports that in 7.4 percent[5] of the cases no cervical or vaginal lesion consistent with the cytologic diagnosis was found. Such false-positive results are most commonly due to an error in cytodiagnosis. One of the main reasons for such an error is the exfoliation of atypical cells by inflammatory lesions of the cervix (eg, Trichomonas vaginalis) which may be confused cytologically with neoplastic-type cells. Less frequent causes of false-positive results are loss of a portion of the tissue specimen intended to document the cytologic findings, destruction of the lesion by biopsy, and inadequate histologic sampling of the biopsy specimen.

Table 1. Cytologic Screening

	Routine
Annual:	Every sexually active female
	All females 18 years old or older
	Females exposed to stilbesterol in utero, beginning at menarche or by 14 years old if not menarchal
Biennial or Triennial:	Females having had hysterectomy for benign disease
	Indicated
	Females with cervical abnormalities
	Females with abnormal uterine bleeding or discharge
	More frequent cytologic examinations in patients with history of abnormal cytology or treatment of uterine or vaginal malignancy

The incidence of false-negative cervical cytology is commonly believed to be about 15 percent, although it has been reported to be as high as 45 percent or more.[6] Inadequate cytologic sampling is the most common reason for false-negative cytology. Errors in cytodiagnosis involve a much smaller number of cases. The incidence of false-negative smears increases when a single cytologic specimen is obtained, when a cotton swab or wooden spatula fails to release all of the material it has collected, or when the vaginal pool is depended upon to reveal abnormalities of the cervix.

In spite of the relatively high incidence of false-positive and false-negative smears, cervical cytology remains the most effective and most

practical method of screening for CIN and early invasive cancer. Cytology should not be depended upon to diagnose visible lesions of the cervix. These lesions require direct punch biopsy. They are often bulky, secondarily infected, and partially necrotic. Such changes, which accompany invasive cancer, affect the cytologic specimen adversely by interfering with the study of nuclear and cytoplasmic detail.

Cytologic Sampling

To obtain the best possible results from cervical cytology, the patient should be instructed not to douche, insert vaginal medications, or use tampons for at least 24 hours prior to having a Pap test. Digital pelvic examination, the use of intravaginal lubricants, and cleansing of the vagina and cervix may compromise the quality of the cytologic specimen. It is recommended that a bivalved speculum be inserted carefully into the vagina using vaginal secretions or warm tap water to overcome the resistance of the tissues. The cytologic specimen should be taken under direct visual control and should consist of endocervical *and* ectocervical samples. The endocervical sample is best obtained by endocervical aspiration, using a taper-pointed disposable plastic pipet connected to a 25 cc suction bulb. The ectocervical sample should be obtained by scraping the entire squamocolumnar junction and the transformation zone of either side of it with a shaped plastic spatula. It has been shown that by endocervical aspiration and ectocervical scraping 99 percent of cellular abnormalities of the cervix can be diagnosed.[7]

Lateral vaginal wall specimens are usually not a part of routine cervical cytologic screening. They are essential, however, for the cytologic detection of adenosis or clear cell carcinoma in the stilbesterol-exposed female and for the cytologic evaluation of the patient's hormonal status. They are also a better source of material for the study of the microbiology of the vagina.

Interpretation and Follow-Up

It is no longer considered acceptable for cytology laboratories to submit final reports using only the five-point Roman numeral classification or the words "suspicious" or "positive" for malignancy. Such broad categories conceal important information. Cytologic reports should use specific histocytologic terminology. If colposcopy and biopsy be indicated, it is possible for the clinician to correlate the findings of all three methods of diagnosis concerning the type and degree of tissue abnormality.

The cytology report form used at the Medical College of Virginia is shown in Figure 1. When completed, it provides an adequate data base for cytologic interpretation and permits recommendations by the cytopathologist. Using this form as an outline, the follow-up of the cervical cytologic report will be discussed.

Negative cytologic smears on patients having a normal history and clinically normal pelvic examination should be repeated on an annual basis. Cytologic smears with evidence of cervicitis may be quantitated as to the degree of inflammatory response. Often the etiologic microorganism or its identifiable byproduct (intranuclear inclusions) can be detected on the smear. The groups most commonly encountered are the bacteria (cocci, diplococci, Corynebacterium vaginalae), protozoans (trichomonads), fungi (candida species), and viruses (herpes, condyloma accuminata). Although the microbiologic classification of cytologic findings may be clinically useful, it should not serve as a substitute for direct gram-stain smears or specific bacteriologic cultures.

The process of squamous metaplasia that occurs within the transformation zone, usually in response to the acidity of the vagina, is detectable cytologically. On occasion, the cervix may shed atypical cells as a result of a reparative and/or inflammatory process. When such is indicated, it is the cytologist's opinion that these do not represent early cervical neoplasia.

The degree of cervical dysplasia should be quantitated as mild, moderate, or severe. Mild dysplasias are common and blend imperceptibly with the atypical squamous metaplasias already mentioned. They may be the result of an inflammatory process within the cervix and may not be part of an early cervical neoplasia. If a causative microorganism can be identified, therapy should be prescribed and the cytologic examination should be repeated when the inflammation has disappeared. A report of mild dysplasia of the cervix is no cause for alarm. Many of these lesions will regress spontaneously; only rarely will one progress to a more advanced form of cervical neoplasia. Therefore, neither colposcopic evalua-

tion nor biopsy is essential in the follow-up of a report indicating mild dysplasia; cervical cytology may be repeated at intervals of three to six months. Should a more advanced form of dysplasia be detected upon subsequent cytologic examination, there should still be adequate time for the documentation and erradication of the lesion.

A method for investigating smears showing moderate dysplasia, severe dysplasia, carcinoma in situ, or invasive carcinoma is outlined in Figure 2. In accordance with current opinion, follow-up relies heavily upon colposcopy in evaluating such smears.

The colposcope is essentially a binocular microscope of 10 to 25 power that enables the colposcopist to detect epithelial lesions by their surface alterations, junctional changes, and disturbances in vasculature. Colposcopy requires special equipment, training, and experience; there-

Name _____ Age____ Race____ Sex____ Special Request Hormone Eval._____

Address_____ Other _____

Source of Material_____ Date_____ Important Clinical History:

Doctor_____ Address_____ LMP:

Endocrine Therapy:

Radiation Therapy:

Cytologic Interpretation

_____Negative (Malignant cells not identified)

_____Smear not entirely satisfactory due to:
_____Limited Cells
_____Drying Artifact
_____No endocervical sample
_____No vaginal pool

_____Smear entirely unsatisfactory

Cellular changes consistent with:

Cervicitis: Mild Moderate Severe Presence of: Cocci, Trichomonas, Monilia, Herpes

Squamous Metaplasia Atypical cells derived from reparative/inflammatory process

Dysplasia: Mild Moderate Severe Description: _____

Carcinoma in situ Description: _____

Invasive carcinoma Description: _____

Other: _____

Recommendation: ____None ____Immediate Repeat
____Colposcopy
____Biopsy
____Conization
____D&C

____Repeat in: ____Months/Years
To include: ____Endocervical sample
____Endometrial sample
____Other_____

Figure 1. Cytologic Report.

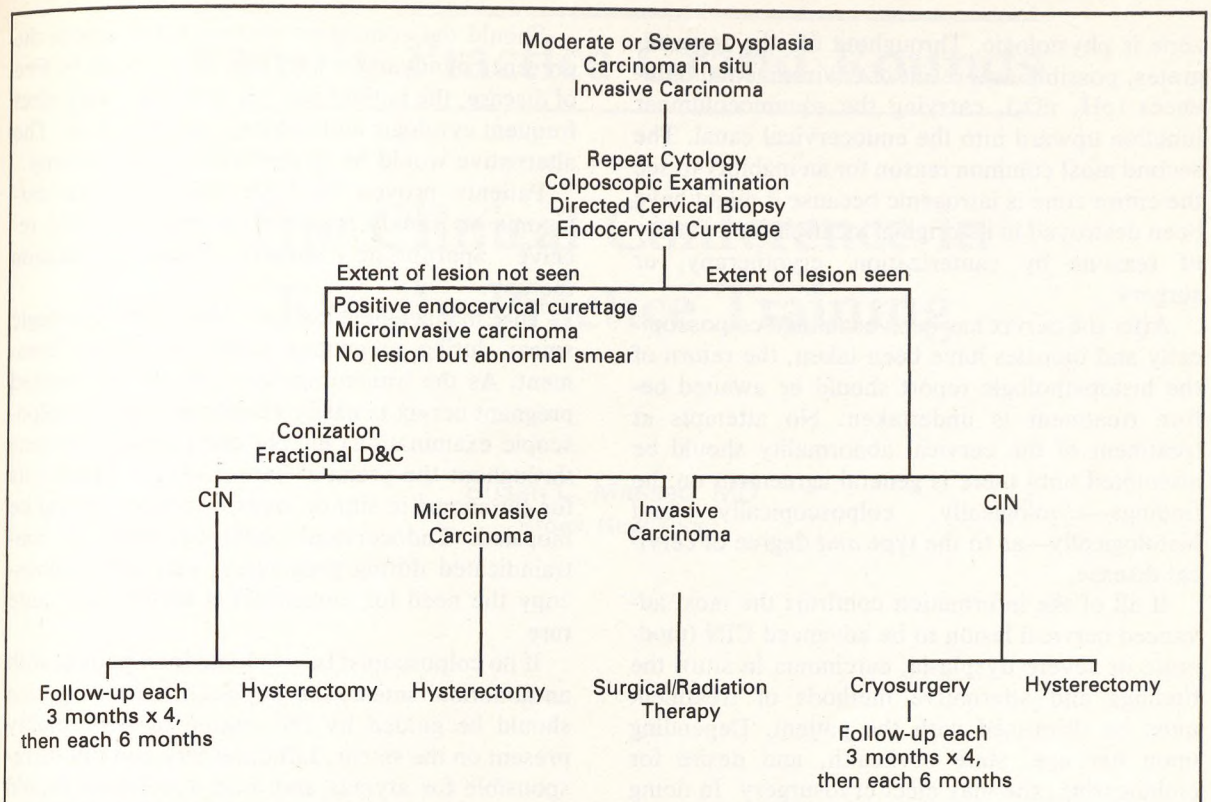

Figure 2. Cervical Cytology Follow-Up.

fore, it is not in the patient's best interest to have a physician who is not a colposcopist undertake the colposcopic evaluation of an abnormal smear. A skilled colposcopist, on the other hand, may be expected to identify and document by directed biopsy the most advanced area of cervical neoplasia in at least 90 percent of the cases examined. To do this in a simple and efficient manner reduces trauma to the cervix, patient morbidity, and overall medical costs when compared to diagnostic routines requiring multiple random punch biopsies or cervical cold knife conization with or without fractional uterine curettage.

A description of colposcopic findings and their significance is beyond the scope of this article. It is important to point out, however, that while there is histocytologic terminology for lesions of the cervix, there also is corresponding colposcopic terminology for such lesions. Both sets of terminology are based upon histologic findings. The colposcopist must correlate his findings with the cytologist's report and the report of the surgical pathologist.

It is recommended that all patients having cervical cytology reports indicating moderate dysplasia or worse be examined by a skilled colposcopist. His examination can be completed in a relatively short period of time and causes the patient little inconvenience or discomfort.

Initially, a repeat cytologic smear is taken for confirmation of a previous abnormal report. Then a complete colposcopic examination of the cervix is performed. The location and detail of each lesion should be diagramed in the patient's record. The visual examination is followd by a colposcopically directed punch biopsy of all the different lesions. In cases in which no abnormality is observed, or when there is endocervical extension of a lesion, endocervical curettage may be indicated.

For a colposcopic examination to be satisfactory, it is essential that the entire transformation zone be observed and the borders of every lesion be examined. Any examination that does not meet these criteria should be termed "unsatisfactory," and other diagnostic methods, usually conization and dilatation and curettage, should be undertaken. The most common cause of an inability to adequately visualize the entire transformation

zone is physiologic. Throughout life the zone migrates, possibly as a result of environmental influences (pH, pO_2), carrying the squamocolumnar junction upward into the endocervical canal. The second most common reason for an inability to see the entire zone is iatrogenic because it might have been destroyed in its original location for a variety of reasons by cauterization, cryotherapy, or surgery.

After the cervix has been examined colposcopically and biopsies have been taken, the return of the histopathologic report should be awaited before treatment is undertaken. No attempts at treatment of the cervical abnormality should be attempted until there is general agreement on the findings—cytologically, colposcopically, and histologically—as to the type *and* degree of cervical disease.

If all of the information confirms the most advanced cervical lesion to be advanced CIN (moderate or severe dysplasia, carcinoma in situ), the findings and alternative methods of treatment must be discussed with the patient. Depending upon her age, state of health, and desire for childbearing, she may elect cryosurgery. In doing so, she must understand the need for frequent repeat smears and colposcopy in order to detect possible recurrence of the cervical lesion. The alternative form of therapy would be an extrafascial hysterectomy.

A histologic diagnosis of invasive cancer requires that the patient be treated in an appropriate manner using surgery and/or radiation therapy.

In approximately ten percent of cases, the colposcopic examination will be unsatisfactory, or it will produce information that indicates the need for additional diagnostic procedures. Basically, there are four reasons for performing a cold knife conization of the cervix and fractional curettage subsequent to colposcopy: (1) borders of all lesions not seen due to endocervical extension, (2) positive endocervical canal curettage, (3) microinvasive carcinoma, and (4) no lesion detected colposcopically to account for the abnormal smear. In the case of a positive endocervical curettage, the specimen is fragmented and is not accompanied by sufficient stroma to judge the depth of the cancer invasion. This is also the case with microinvasive cancer; frankly invasive cancer may be found in areas adjacent to the biopsy site or in lymphatic or vascular channels.

Should the conization specimen document the presence of advanced CIN and the margins be free of disease, the patient and her physician may elect frequent cytologic and colposcopic follow-up. The alternative would be to perform a hysterectomy.

Patients proven to have microinvasive carcinoma or frankly invasive carcinoma should receive appropriate surgery and/or radiation therapy.

The management of an abnormal cytologic smear during pregnancy deserves special comment. As the transformation zone of the everted pregnant cervix is easily visualized, repeat colposcopic examinations enable one to follow lesions throughout the prenatal period. Areas suspicious for carcinoma in situ or invasive cancer should be biopsied. Endocervical canal curettage is contraindicated during pregnancy, and with colposcopy the need for conization is fortunately quite rare.

If no colposcopist be available for a patient with an abnormal smear, the physician's investigation should be guided by the degree of abnormality present on the smear. Inflammatory conditions responsible for atypias and mild dysplasias should be treated medically if the cause can be identified. Repeat smears in three to six months are indicated. Advanced CIN requires immediate attention. Visible lesions should be biopsied. If there are no visible lesions, iodine staining of the cervix with biopsy of the nonstaining areas *and* endocervical canal curettage is recommended. Failure to demonstrate a suspicious area by iodine staining or to document a lesion by biopsy that corresponds to the cytologic diagnosis is usually an indication for cold knife conization and fractional curettage prior to beginning therapy.

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