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Nondiagnostic And Inconsistent Results From Colposcopy

"Frequency of Nondiagnostic Findings on Colposcopy: Implication for Management" by Nuovo and Kreiter in this issue of *JABFP* presents the histologic findings of a series of patients (nonpregnant, not exposed to diethylstilbestrol) who underwent colposcopic-directed biopsies. The primary indication for the colposcopic procedure included two sequential Papanicolaou smears indicating atypical cellular changes or one Papanicolaou smear with evidence of dysplasia. Their data suggest that clinicians can be faced with nondiagnostic histology reports in nearly one-third (29.7 percent) of patients undergoing colposcopic examination for these indications. Much of this dilemma stems from inconsistent terminology and confusion regarding the meaning of nondiagnostic reporting. Reconsideration of some of the data in light of problems with terminology and careful review of the basic tenants of colposcopic examination will help address this dilemma and in most cases will guide therapy towards desirable outcomes.

First, it is the clinician who must ultimately decide how to care for a patient whose Papanicolaou smear is interpreted as abnormal.[1] Few argue that dysplasia of any grade on a screening Papanicolaou smear report warrants colposcopic evaluation, and in most cases ectocervical biopsy and endocervical curettage (ECC). Furthermore, a Papanicolaou smear report of persistent cellular atypia prompts many clinicians to evaluate these women's cervices with colposcopy and biopsy as well. Both the Papanicolaou smear and the colposcopic appearance of the cervix share one feature in common, however; *neither* procedure is diagnostic. Only the histologic interpretation of the colposcopic-directed biopsy provides an opportunity to diagnose or explain the abnormal smear and guide appropriate intervention (i.e., expectant management, cryotherapy, electrosurgery, laser surgery, cone biopsy). When such biopsies appear to explain or to correlate inadequately with the Papanicolaou smear findings and colposcopic impression, the clinician is compelled to make management decisions that are not as clearly defined. Clinicians are routinely presented with ambiguous, nondiagnostic, or nonconfirmatory test results during the work-up of many medical conditions. Nondiagnostic results as defined by Nuovo and Kreiter are those negative for dysplasia, but showing atypia, inflammation, hyperkeratosis, and parakeratosis. As defined, histologic examination would find nondiagnostic results by failing to explain the cause for abnormal findings on screening cell studies.

This notion of nondiagnosis can be misleading, however. At a minimum, what the nondiagnostic biopsy findings actually show is atypia, inflammation, hyperkeratosis, or parakeratosis of squamous tissue *without* dysplasia. The results can be nondiagnostic in the sense that they fail to explain the abnormal cytologic findings; nonetheless, they also do not show dysplasia. The ultimate purpose of the colposcopic-directed biopsy is to rule out invasive (or microinvasive) cervical cancer and to guide

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therapy when preneoplastic conditions are found. Assuming reasonable skill level with colposcopy and adequate tissue sampling and preparation, the finding of nondiagnostic tissue helps substantiate the clinical impression that the patient does not have a malignant process. Each biopsy sample must first be interpreted in terms of its origin, implying that the ectocervix was sampled and that the sample was of sufficient size and quality to allow for a histologic diagnosis. Atypia, inflammation, etc. are generally descriptive conditions that can cohabit or sometimes imply dysplasia but are not diagnostic for dysplasia. With adequate colposcopy performed by a skilled individual, nondiagnostic histologic findings can be reassuring because dysplasia or malignancy was not found. In other instances, nondiagnostic reports can be so inconsistent with either the Papanicolaou screening or the colposcopic appearance that more accurate terms would be perhaps inconclusive, inconsistent, or ambiguous.

In the authors' discussion, one method of dealing with this diagnostic dilemma is offered: "It was our policy to see these patients [with normal or nondiagnostic biopsy results] for a Papanicolaou smear every 3 to 4 months for 1 year." In essence, this approach amounts to rescreening these patients to see whether the confirmatory test (colposcopy and biopsy) was warranted in the first place. This approach relegates the Papanicolaou smear as a diagnostic back-up to the finding of nondiagnosis, which might be questioned on theoretical considerations, especially in regard to concern about false-negative rates for Papanicolaou smears. If subsequent smears return to normal, can they be trusted? Furthermore, it might be more expensive and inconvenient to repeat Papanicolaou smears every 3 months with the expectation that a large number of these women could eventually require a repeat biopsy anyway. The psychological impact of not knowing or delaying a diagnosis must be contrasted with the anxiety of a repeat biopsy procedure. It is especially important for physicians to offer information to facilitate their patients' inclusion in the management decisions necessary to choose the best follow-up method when nondiagnostic results are obtained. The authors did not present further data regarding the patients who were cared for by the strategy of repeating Papanicolaou smears, and it would be worthwhile to know how many of them ultimately either resolved their atypia (should you believe this?) or in fact had a repeat biopsy (and what were their repeat results?). The authors further point out that they will repeat colposcopy and biopsy for patients whose original Papanicolaou smears indicate high-grade cervical dysplasia and whose initial biopsy result was nondiagnostic. This strategy certainly has empirical appeal, yet at best there still remains only fair correlation between the grade of cellular dysplasia on Papanicolaou smear and the histologic grade on biopsy. Experienced colposcopists can readily recall patients whose Papanicolaou smear indicated only minimal change, yet whose biopsy showed advanced disease. It would be helpful if data were also presented regarding the histologic diagnosis and outcomes of those patients whose colposcopy was repeated when their findings on Papanicolaou smear implied a high grade of squamous atypia or dysplasia.

The adequate colposcopic examination requires not only consistency between the Papanicolaou smear and the histology report from biopsy, but both must be consistent with the colposcopic appearance observed at the time of biopsy.[2] In Nuovo and Kreiter's study, mention is made regarding data that included correlation of Papanicolaou sampling and histologic grading, as well as the colposcopic appearance. Apparently colposcopic appearance data were not tabulated. Despite the fact that the colposcopic appearance of the cervix is not diagnostic, appearance is still a critical feature of the work-up of patients with abnormal Papanicolaou smears, and there is a high likelihood that it would help address management confusion imparted to patients whose biopsies were nondiagnostic. What were the colposcopist's visual impressions of the cervices, especially those of patients included in the nondiagnostic category? If a colposcopist determines an area of the cervix as being consistent with cervical dysplasia and a subsequent biopsy of this area is deemed nondiagnostic, the colposcopist is well advised to discuss this inconsistency with the pathologist. Such a discussion typically allows for further sample preparation, review, and reinterpretation. The colposcopist should maintain open communication channels with the pathologist to address

problematic pathology results. Typically, if the pathologist has access to the histologic findings and the original indexed Papanicolaou smear and can be involved in the discussion regarding nondiagnostic results, enhanced patient care will result.

Testing for human papillomavirus (HPV) has been advocated by some to help clinicians with the diagnostic dilemma presented by the patient who has nondiagnostic results from cervical biopsy.[3] In-situ hybridization techniques can pinpoint whether a given tissue sample has incorporated HPV-DNA. Despite the generally accepted observation that cervical cancer is highly correlated with HPV infection, it is the histologic expression of dysplasia (or certainly carcinoma) that directs therapeutic intervention. The mere presence of viral HPV-DNA in cervical tissue does not warrant therapy. Accordingly, given the added expense of in-situ HPV hybridization testing, it remains less clear that this strategy will be clinically useful or cost effective. Women who have persistently atypical Papanicolaou smears are more likely to have cervical dysplasia, and its management mandates enhanced follow-up, which in most cases eventually results in some form of definitive tissue sampling. Nondiagnostic or, more correctly, nonconfirmatory or ambiguous histologic findings do little to abolish concern about the increased risk, and this subset of women will likely require increased monitoring despite HPV-DNA in-situ testing.[4]

The finding of nondiagnostic ECC sampling as defined in Nuovo and Kreiter's study (18 percent) has an entirely different connotation than a nondiagnostic ectocervical biopsy report. Currently, ECC is considered an essential part of the colposcopic examination for the evaluation of an abnormal Papanicolaou smear (in nonpregnant woman). The challenge to a colposcopist is to distinguish normal from abnormal tissue based upon visual cues and to provide direct sampling of observed abnormal areas. This strategy cannot be equally applied to the endocervical canal, however. Simply stated, it is often difficult to examine adequately the canal that in many patients is closed, composed mostly of endocervical epithelium, obscured by mucus or blood, and friable on manipulation. Given the epidemiological consideration that nearly 10 percent of cervical carcinoma originates from glandular epithelium, often from within the endocervical canal, a strategy different from direct observation and selective biopsy is necessary to rule out the possibility of occult disease in this area.[5] The ECC is used as a blind procedure to sample the endocervical canal for occult disease because, generally, directed biopsies cannot be performed. Even though the ECC sample is prepared and reviewed as if it were a histologic biopsy, in reality it is little more than a blended mash of tissue elements, mucous, and blood. Results of the ECC are traditionally interpreted in terms of (1) adequacy (containing tissue elements representing an endocervical origin), and (2) whether these elements display any evidence of atypia, dysplasia, or carcinoma. ECC results are not usually diagnostic in the same sense as results from ectocervical biopsies, because it is much more difficult to grade abnormal results (especially of glandular origin), and one rarely knows the exact position of an abnormality other than it most likely originates from the endocervical canal. The finding of dysplasia in the endocervical canal is considered to be due to inadequate colposcopy, and further definitive sampling of the canal is then warranted (e.g., cone biopsy). Accordingly, the implications to the clinician of a nondiagnostic ECC are much different from those of nondiagnostic ectocervical sampling. For instance, if patients' ECCs are nondiagnostic because they are inadequate, i.e., lacking cellular elements consistent with an endocervical origin, then *all* of these patients should undergo repeat canal sampling prior to definitive therapy. If on the other hand an ECC is nondiagnostic because of atypia, many colposcopists argue that definitive resampling is likewise indicated because many adenocarcinomas of high degree can present as simple adenomatous or glandular atypia of endocervical elements. Finally, the finding of parakeratosis or hyperkeratosis from an ECC sample is unusual and might imply contamination from ectocervical material or a serious canal lesion mandating a need for further histologic correlation. Simply stated, the presented criterion for nondiagnostic ectocervical sample interpretation as defined in Nuovo and Kreiter's paper should not be equated to those of ECC sample interpretation. It is not clear from the review of the presented

data what strategy was adopted to care for the nearly 18 percent of patients whose ECC reports were described as nondiagnostic. These patients require very close follow-up and definitive repeat biopsy.

To what extent does overreading or lack of precision of the Papanicolaou smear terminology contribute to the finding of nondiagnostic biopsy reports?[1] In reviewing the data, it is interesting to note that of the 138 cases, the indications for performing colposcopy were roughly split between the finding of dysplasia on Papanicolaou smear (52.2 percent) and a history of two atypical Papanicolaou smears (47.8 percent). Colposcopy performed on a patient whose Papanicolaou smear indicated dysplasia was less likely to produce nondiagnostic histologic results than a patient whose indication was for two consecutive atypical Papanicolaou smears. In some instances, the high rate of nondiagnostic histologic readings might result from overreading or interpretation of the original Papanicolaou smear screening. The importance of the atypical Papanicolaou smear remains an interpretive enigma. The so-called Bethesda System of Papanicolaou smear nomenclature attempted to address this debate by reserving the classification of atypical smear only when other likely explanations for atypia (infection, inflammation) had been considered.[6] It would be noteworthy to know what the atypical Papanicolaou rate was for the population screened in this study. Samples from such patients who undergo a colposcopic examination could yield nondiagnostic biopsy results. Furthermore, if cytological Papanicolaou smear reporting was not problematic enough, the issue of histological grading contributes to confusion. In this study the diagnosis of low-grade dysplasia requires koilocytic atypia with perinuclear halo and nuclear atypia. Some pathologists consider the findings of koilocytes with minimal nuclear changes as an indication of low-grade dysplasia. Among colposcopists, it has often been muttered that "one pathologist's koilocyte is another's low-grade dysplasia." To what extent can interpretive variation contribute to the issue of nondiagnostic histology? It would be interesting to review the current data in regard to how many nondiagnostic biopsies actually displayed koilocytes yet were not judged severe enough to warrant the diagnosis of low-grade cervical dysplasia.

In summary, the ultimate goal of Papanicolaou smear screening is to prevent cervical cancer. It is the challenge of the contemporary family physician to be aware of women who are at higher risk for cervical cancer and to recommend and offer careful long-term follow-up for them. Despite the confusion regarding terminology and, at times, lack of a clearly defined indication for a particular therapeutic course, it is unlikely that women who are known to be at increased risk and who are cared for by a combination of increased Papanicolaou screening frequency and colposcopy services will develop cervical cancer. It is hoped that further standardization of nomenclature and histological grading will help address much of the confusion or ambiguity discussed with these data. Further study is necessary to clarify the issues raised by the important work of Nuovo and Kreiter.

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