Frequency Of Nondiagnostic Findings On Colposcopy: Implications For Management

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Background: **This study examines the frequency of nondiagnostic findings from colposcopic biopsies at the University of Washington Family Medical Center Colposcopy Clinic and reviews the literature for any current recommendations for management of such cases.**

Methods: **We reviewed 138 consecutive colposcopy reports covering the period from January 1990 to August 1991 from the Colposcopy Clinic at the University of Washington Family Medical Center. Nondiagnostic results were defined as those negative for dysplasia (atypia, inflammation, hyperkeratosis, and parakeratosis).**

Results: **Of 138 endocervical curettages 25 (18.1 percent) had nondiagnostic findings, while of 206 ectocervical biopsies 104 (50.5 percent) had nondiagnostic findings. Of the 138 patients examined, 41 (29.7 percent) had a nondiagnostic biopsy as the most notable finding.**

Conclusion: **Nondiagnostic colposcopic biopsy results occur frequently at the University of Washington Family Medical Center. The meaning of these equivocal results remains unclear. We need a further study of the natural history of such patients to determine appropriate recommendations for management. (J Am Board Fam Pract 1993; 6:209-214.)**

It is well established that regular Papanicolaou smears are a necessary part of a woman's health maintenance. The decline in cervical cancer since the 1930s has been attributed in part to this test.[1,2] Much has been published on the management of an abnormal Papanicolaou smear result. It is generally recommended that a patient with either dysplasia on a Papanicolaou smear or two consecutive smears with atypical findings undergo a colposcopic evaluation. Management after colposcopy is based on the histopathologic results. For patients with dysplasia, treatment options include cryotherapy, laser ablation, low-voltage loop diathermy, and excisional cone biopsy.[3-6] In the case of a marked discrepancy between findings on the Papanicolaou smear and the colposcopic biopsy, it is generally recommended to repeat the colposcopy. What is not clear is the proper care for patients who fall into neither of these groups, i.e., those whose biopsy result is nondiagnostic. The purpose of our study was to examine the frequency of such an occurrence at the University of Washington Family Medical Center Colposcopy Clinic and to review the literature for any current recommendations on management of these patients.

Methods

We reviewed 138 consecutive colposcopy reports covering the period from January 1990 to August 1991 from the Colposcopy Clinic at the University of Washington Family Medical Center. Patients were referred to the clinic for the following reasons: a Papanicolaou result was consistent with dysplasia, or two consecutive Papanicolaou smears had atypical findings. Patients excluded from the Colposcopy Clinic included those who were pregnant and those with a history of diethylstilbestrol exposure. All colposcopy procedures were done by a family practice attending physician assisted by a family practice resident.

Information from the examination was recorded on a standard form for each patient. Abnormal findings on the ectocervix that led to biopsies were defined as any of the following: white epithelium, mosaicism, punctation, atypical vessels, and leukoplakia. An endocervical curettage was done on all patients. Biopsy specimens were fixed in a buffered formalin solution

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and sent to the University of Washington Medical Center Pathology Department for histologic diagnosis. After the final pathology report was returned to the patient's chart, the information was tabulated.

Abstracted data from each patient's chart included the following: identification number, birth date, date of colposcopy, and indication for colposcopy. Descriptions of each biopsy were recorded, including the colposcopic appearance of the cervix as well as the biopsy location. These data were correlated with the pathology report. Each biopsy result was categorized into one of the following groups: normal, dysplasia (cervical intraepithelial neoplasia groups I through III), or nondiagnostic. Nondiagnostic findings were defined by the following criteria from pathology reports: atypia, inflammation, hyperkeratosis, and parakeratosis. Finally, a MEDLINE search was conducted to obtain reports on the care of patients whose colposcopic findings were nondiagnostic.

Statistical analysis was done to assess the following: to determine whether the number of ectocervical biopsies affected the chance of finding dysplasia, we used the Student t-test. We compared the number of biopsies done on patients who had no evidence of dysplasia with the number of biopsies done on patients in whom dysplasia was detected. To address the relation between Papanicolaou smear cytology results (atypical or dysplastic) and colposcopic histopathology results (normal, dysplastic, or nondiagnostic), we used the chi-square test.

Results

A total of 138 consecutive cases were reviewed. The mean patient age was 29.2 years (range 16–60 years). Seventy-two (52.2 percent) had dysplastic findings on an earlier Papanicolaou smear as the reason for colposcopy, and 66 (47.8 percent) had a history of atypical findings on two Papanicolaou smears. Ten (7.2 percent) patients had only an endocervical curettage. One hundred twenty-eight (92.8 percent) patients had both ectocervical biopsies and endocervical curettage. The mean number of ectocervical biopsies per patient was 1.5 (range 0–4).

The results of the 138 endocervical curettages are presented in Table 1. Ninety-four (68.1 percent) were read as normal. Dysplasia (all grades) was seen in 19 (13.8 percent), and nondiagnostic results were reported in 25 (18.1 percent).

Table 1. Biopsy Results from All Patients Undergoing Colposcopy.

Results	No.	Percent
Endocervical curettage		
Total	138	100
Normal	94	68.1
Dysplasia (all grades)	19	13.8
Nondiagnostic	25	18.1
Inflammation	13	
Atypia	12	
Ectocervical biopsies		
Total	206	100
Normal	42	20.4
Dysplasia (all grades)	60	29.1
Nondiagnostic	104	50.5
Inflammation	48	
Atypia	50	
Hyperkeratosis or parakeratosis	6	

The results of the 206 ectocervical biopsies are also presented in Table 1. Of these 42 (20.4 percent) were considered normal, 60 (29.1 percent) had dysplasia (all grades), and 104 (50.5 percent) were nondiagnostic. Of the 138 patients examined, 41 (29.7 percent) had a nondiagnostic biopsy as the most notable finding (Table 2). Overall, there was no difference in the number of ectocervical biopsies when comparing those patients who had a diagnosis of dysplasia with patients who had normal or nondiagnostic findings ($P < 0.01$). In comparing Papanicolaou smear cytology results with colposcopic histopathology results (Table 3), we found the following: patients with atypical findings on a Papanicolaou smear were less likely to have a biopsy

Table 2. Most Notable Biopsy Findings for All Patients (Includes Ectocervical Biopsy and Endocervical Curettage).

Result	No.	Percent
Total	138	100.0
Normal	30	21.7
Dysplasia (all grades)	67	48.6
Nondiagnostic	41	29.7
Inflammation	19	
Atypia	20	
Hyperkeratosis or parakeratosis	2	

Table 3. Correlation of Papanicolaou Smear Cytology Findings with Colposcopic Histopathology Results.

Papanicolaou Smear Result	Number	Percent	Colposcopy Result
Atypical	26/66	39.4	Normal
Dysplastic	4/72	5.6	
Atypical	19/66	28.8	Dysplastic
Dysplastic	48/72	66.7	
Atypical	21/66	31.8	Nondiagnostic
Dysplastic	20/72	29.2	

positive for dysplasia and more likely to have a biopsy read as normal ($P < 0.001$). The reverse was true of patients with dysplasia on a Papanicolaou smear. There was no detectable increased likelihood that a patient with atypical or dysplastic findings on a Papanicolaou smear would have the most notable biopsy read as nondiagnostic ($P < 0.001$).

Discussion

The purpose of this study was to determine the frequency of nondiagnostic findings on colposcopic-directed biopsies done for further evaluation of an abnormal Papanicolaou smear. In this study of 138 endocervical curettages, 25 (18.1 percent) were nondiagnostic, whereas 104 (50.5 percent) of the 206 ectocervical biopsies were nondiagnostic. Of 138 patients 41 (29.7 percent) had the most notable biopsy finding as nondiagnostic. Our findings are similar to those reported in other studies. Pfenninger[7] reported the results of the first 200 colposcopies done at the Mid-Michigan Regional Medical Center Family Practice Residency Program. Twenty-nine percent of cervical biopsy specimens had "miscellaneous" changes. These changes included atypia, hyperkeratosis, and parakeratosis. Nuovo, et al.[8] reported a 1-year series of 130 biopsy specimens of colposcopically identified epithelial cervical lesions that turn white upon application of acetic acid (acetowhite) from 100 patients being followed up for abnormal Papanicolaou smears. Of these 130 specimens 59 (45.4 percent) were classified as nondiagnostic for cervical intraepithelial neoplasia (CIN). From the results of these three studies, two from a family practice training program and the other from a tertiary care setting, it can be concluded that nondiagnostic findings are a common occurrence.

The meaning of these nondiagnostic findings remains unclear. The group of biopsies labeled nondiagnostic probably represents a heterogeneous group with different causes and different outcomes. It is also possible, however, that some overlap occurs among the categories labeled nondiagnostic. With respect to the category of atypia, it is important to understand the criteria used to differentiate CIN from atypia. The histologic criteron for CIN is koilocytotic atypia with perinuclear halos and nuclear atypia (binucleate and multinucleate forms). For low-grade lesions mitotic activity is minimal. In high-grade lesions the perinuclear halos are typically less prominent, whereas the nuclear atypia is more evident. In addition, mitotic activity (often with one to two mitoses per medium-power field), atypical mitotic figures, and nuclear crowding are increased. In the group labeled equivocal for CIN, which is synonymous for squamous cell atypia, perinuclear halos are often evident, but the degree of nuclear atypia is not considered sufficient for a diagnosis of CIN.[9-12] From our study sample 50 biopsies had such squamous atypia. What is the importance of these findings? There are two possible explanations: (1) the lesion is not due to the human papillomavirus but mimics it as a result of inflammation, repair, or squamous metaplasia, or (2) the lesion could be related to the human papillomavirus, but because of inadequate sampling, host factors, or stage of the lesion, the diagnostic features are not evident.[8]

Regarding the latter possibility of a nondiagnostic lesion representing human papillomavirus infection, we must consider that the cytologic and histologic features associated with human papillomavirus constitute a spectrum that ranges from no recognizable changes to the diagnostic features that include perinuclear halos and variation in nuclear size, shape, and chromaticity.[9,13] It is possible that the biopsies labeled atypia represent an early infection or one from a less oncogenic type of human papillomavirus (e.g., types 6 and 11). Nuovo, et al.[13] found that women with these types of human papillomavirus were more likely to have a Papanicolaou smear demonstrating atypia, and those women with oncogenic strains (e.g., types 16, 31, 33, 35) were more likely to have Papanicolaou demonstrating CIN. It is possible that the same process holds true when examining cervical specimens histopathologically.

From the published literature on Papanicolaou smear cytology, atypia is clearly a marker for CIN. Data on repeat Papanicolaou smears for atypia show a high association with CIN (10 to 25 percent), particularly for those who have atypia without inflammation.[14] In follow-up studies this association could increase. Reiter[15] found that of 110 patients who had atypical findings on a Papanicolaou smear, 44.5 percent were subsequently found to have dysplasia.

Biopsies with findings of hyperkeratosis and parakeratosis were also labeled as nondiagnostic. Histologically hyperkeratosis is defined by a thickened keratin layer above the surface squamous epithelium, and parakeratosis as pyknotic nuclei within the keratin layer. Clinically both hyperkeratosis and parakeratosis can manifest as leukoplakia. The changes of hyperkeratosis and parakeratosis are sometimes observed histologically in cell samples of CIN. Other hypotheses include that the changes could simply be the response to uterine prolapse, inflammation, or chemical or physical trauma.[16]

How important are these findings? The report by Andrews and Miyazawa[16] could help answer this question. They studied 170 women who had hyperkeratosis or parakeratosis on Papanicolaou smears but who did not have other abnormal findings. All patients underwent colposcopy. Sixty-four percent had either a cervical biopsy or an endocervical curettage. Six women (3.5 percent) had CIN documented histopathologically. Given the reported general prevalence of CIN to be between 1.2 and 3.2 percent, it was believed that the cytologic finding of hyperkeratosis or parakeratosis in the presence of normal squamous epithelial cells on a Papanicolaou smear did not appear to result in an increased finding of biopsy-proven CIN. Nevertheless, 38 (22 percent) had histologic evidence of human papillomavirus. Johnson, et al.[17] reported a similar high rate of human papillomavirus histologic findings (19 percent) in the presence of hyperkeratosis or parakeratosis. Although specific human papillomavirus testing was not done, classic histologic features of human papillomavirus are strongly correlated with the presence of the virus. When the typical cytologic and histologic findings associated with human papillomavirus infection are noted, more than 95 percent of the patients will have the virus.[10,11] It could be that a substantial number of patients show hyperkeratosis or parakeratosis as an early manifestation of human papillomavirus infection.

Another nondiagnostic finding was that of inflammation. Histologically inflammation is determined by an increased number of histocytes, polymorphonuclear leukocytes, and the presence of transformed lymphocytes. Kiviat, et al.[18] studied the cytologic manifestations of cervical and vaginal infections, specifically looking at epithelial and inflammatory cellular changes. They found the following: increased numbers of histocytes and polymorphonuclear lymphocytes were associated with a *Chlamydia trachomatis* infection, increased lymphocytes were associated with *Trichomonas vaginalis* infection, minimal squamous atypia was associated with a yeast infection, and moderate squamous atypia and koilocytosis were associated with cervical condylomata. It is clear that a number of patients with inflammation on colposcopy could indeed have similar infections. A study similar to that of Kiviat, et al.[18] has not been researched using histopathologically examined cervical specimens from colposcopic-directed biopsies. There was inadequate information from our study sample to assess this issue.

When trying to account for possible contributing causes of ambiguous results, the technical skill of the colposcopist must be considered. Variation in interpretation of what constitutes an abnormal colposcopic finding can result in a variation of biopsy sites. In addition, there is also observer variability as well as reporting variability found in each pathology laboratory. The cytologic and histologic features assessed when looking for cervical disease include cell size, nuclear size, nuclear chromatin, nuclear contour, cytoplasmic characteristics, and presence of mitotic cells.[18] Although abnormal findings have specific requirements, subjective judgment influences the pathologist's final report. Another important issue for the pathologist is that of sampling from the tissue presented by the colposcopist. The tissue obtained could in fact contain CIN that was not represented in the sections reviewed by the pathologist; only a small portion of a lesion is examined histologically, and CIN lesions are often very focal and sharply demarcated from uninvolved tissues.[19]

There were several other important observations from the data analysis. The first relates to

the relation of Papanicolaou smear cytology and colposcopic histopathology. Those patients with an atypical Papanicolaou smear were more likely to have normal biopsy findings and less likely to have dysplasia. This finding is not surprising given the potential for inflammation or repair to produce cellular atypia. The second observation relates to those patients with a dysplastic Papanicolaou smear. The majority of these patients (48 of 72) had dysplasia on biopsy. There was no relation between the number of ectocervical biopsies and the discovery of dysplasia. Certainly of concern were the 24 patients with dysplasia on a Papanicolaou smear that had either a normal (4 of 72) or a nondiagnostic (20 of 72) biopsy result. In all of these patients the Papanicolaou smear showed low-grade dysplasia. It was our policy to see these patients for a Papanicolaou smear every 3 to 4 months for 1 year. A repeat colposcopy would be performed on those patients with persistently abnormal findings on a Papanicolaou smear. Long-term follow-up data on this subset of patients are not yet available. At 6 months, however, none of the 24 patients had dysplasia on a Papanicolaou smear.

The third observation relates to those patients with nondiagnostic findings from an endocervical curettage. Overall, 25 of 138 (18.1 percent) endocervical curettages were nondiagnostic. Given that 10 percent of cervical cancers are adenocarcinomas, the majority arising within the endocervical canal, and that coexistent CIN could be present in up to 48 percent of cases, should this group be approached differently?[20] Although there is literature to support concern for false-negative Papanicolaou smears in the diagnosis of cervical adenocarcinoma, there is no literature to suggest that endocervical curettage is insensitive. An adequate endocervical curettage without evidence for adenocarcinoma should be considered reassuring.[21]

A review of the medical literature was done to find out what recommendations should be given for the care of patients with nondiagnostic findings. Much is written concerning treatment options for CIN, including cryotherapy, laser ablation, low-voltage loop diathermy, and cone biopsy.[3-6] For those patients with a normal biopsy result, recommendations range from close follow-up with repeat Papanicolaou smears or repeat colposcopy. No specific literature, however, supports a general recommendation concerning the care of the patient with a nondiagnostic result. All of the management options (repeat colposcopy and frequent Papanicolaou smears) come with substantial financial and emotional consequence to the patient.

Those patients whose Papanicolaou smears show high-grade dysplasia and who have normal or nondiagnostic biopsy results should undergo repeat colposcopy. It is assumed that the dysplastic lesion was missed in this set of patients. In those patients who had a Papanicolaou smear showing low-grade dysplasia and normal or nondiagnostic biopsy results, possible options include repeat colposcopy versus frequent Papanicolaou smear follow-up. For those with an atypical Papanicolaou smear and a recognizable white epithelial lesion found during colposcopy, human papillomavirus testing should be considered. The technique of in situ hybridization allows the clinician to use the fixed paraffin-imbedded cervical tissue for this analysis. Testing, therefore, can be considered after the biopsy report is completed.

Human papillomavirus testing can provide useful information in determining which patients are high risk for subsequent CIN. Further, it can be a useful adjunct in the analysis of genital tract lesions that are clinically suggestive of a human papillomavirus lesion but for which the histologic information is equivocal. Nuovo, et al.[8] found that patients with acetowhite epithelial changes but nondiagnostic biopsy results who were human papillomavirus positive had an increased rate of developing CIN within 1 year. Those patients with an atypical Papanicolaou smear who are human papillomavirus positive should have a more conservative follow-up plan (i.e., repeat colposcopy in 6 to 12 months). Those who are human papillomavirus negative could be cared for with follow-up Papanicolaou smears. All those patients with inflammation as the diagnostic finding should undergo specific testing to detect the presence of other infectious agents (e.g., chlamydia, gonorrhea, trichomonas, yeast, and bacterial vaginosis).

Conclusion

The following observations can be made based on our study results: nondiagnostic findings from colposcopic-directed biopsies are common. As a substantial number of patients are affected by

such findings, to clarify the meaning of such ambiguous results would be invaluable to the clinical colposcopist. Human papillomavirus testing might be of value in the nondiagnostic group with white epithelial lesions, because those who are human papillomavirus positive will be more likely to develop CIN. We need more follow-up studies with these patients to determine the natural history of such findings and to establish reasonable management recommendations.

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