Empiric Treatment of Minimally Abnormal Papanicolaou Smears with 0.75% Metronidazole Vaginal Gel

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Background: **The purpose of this study was to compare the efficacy of 0.75% metronidazole vaginal gel with no treatment in patients who have had a minimally abnormal Papanicolaou smear.**

Methods: **One hundred forty-five patients whose initial Papanicolaou smears were limited by inflammation or benign cellular changes, reactive cellular changes, or atypical squamous cells of undetermined significance that did not favor a neoplastic process were randomized to 5 days of treatment with 0.75% metronidazole vaginal gel or to a control group receiving no treatment. Papanicolaou smears were repeated after 3 to 4 months.**

Results: **Cytologic findings of the follow-up Papanicolaou smears were normal in 61 of 114 (54%) of patients. Sixty-two percent (n = 37) of the Papanicolaou smears in the control group converted to normal on follow-up, whereas 44% (n = 24) of the Papanicolaou smears in the treatment group converted to normal ($P = .07$). Only one follow-up Papanicolaou smear worsened to low-grade squamous intraepithelial lesion. In no subgroup was treatment effective.**

Conclusions: **Empiric treatment for an asymptomatic, minimally abnormal Papanicolaou smear with 0.75% metronidazole vaginal gel before a repeated cytologic examination did not improve the rate of reversion to normal cytologic findings. (J Am Board Fam Pract 2002;15:347–54.)**

More than 50 million Papanicolaou smears are performed annually in the United States. Of these, approximately 2.5 million are reported as having low-grade cytologic abnormalities.[1] Since the standardization of cervical cytologic reporting by the Bethesda system, a great many Papanicolaou smears have been classified as minimally abnormal.[2] Findings include benign cellular changes, reactive cellular changes associated with inflammation, atypical squamous cells of undetermined significance (ASCUS), and low-grade squamous intraepithelial lesions (LSIL).

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Although the evaluation and management of high-grade squamous intraepithelial lesions or carcinoma are clear, there is a lack of consensus among physicians about the most appropriate approach for the minimally abnormal Papanicolaou smear.[3,4] Some clinicians empirically prescribe a topical or systemic antimicrobial therapy, such as povidone-iodine gels or douches, sulfa vaginal cream, metronidazole vaginal gel, or oral antibiotics.[5,6] Papanicolaou smears are then repeated in 3 to 6 months. Other clinicians recommend evaluations with slide preparations of the vagina and cultures of the cervix in women with inflammation.[1,7] In contrast, some experts advocate simply monitoring patients with mildly abnormal cervical findings with serial Papanicolaou smears and performing colposcopy if subsequent Papanicolaou smears continue to show mild abnormalities or worsening cytologic findings.[1,8] Still, others promote immediate colposcopic examinations and biopsy for all women with minimally abnormal Papanicolaou smears.[3,9] There is currently no accepted standard of care

for women with minimally abnormal Papanicolaou smears.

Recent data have shown an association between Papanicolaou smears with inflammation and bacterial vaginosis.[10–13] Bacterial vaginosis, the most common cause of vaginal symptoms in adolescent and adult women,[14] is characterized by an overgrowth of anaerobic and gram-negative bacteria in the vagina, *Gardnerella vaginalis* in particular.[15] Up to 50% of cases are asymptomatic.[16] The reported prevalence of bacterial vaginosis varies widely, ranging from 5% to 25% of college students and from 10% to 30% of typical obstetric populations,[17] to more than 60% of patients visiting sexually transmitted disease clinics.[18] In a study of premenopausal women with cytologic findings showing cervical inflammatory changes, 43% were found to be infected with *G vaginalis*.[10]

Other studies have found inflammatory epithelial changes on cytologic examination to be significantly associated with clue cells in rehydrated wet smears and bacterial vaginosis.[11,12] In addition, Eltabbakh et al[13] found a statistically significant association between bacterial vaginosis and Papanicolaou smears with inflammation and ASCUS. Interestingly, data also suggest an association between bacterial vaginosis and cervical intraepithelial neoplasia (CIN). Platz-Christensen et al[19] found that patients who had clue cells representing bacterial vaginosis on a Papanicolaou smear were more likely to develop CIN.

Recognizing the common finding of bacterial vaginosis in women of reproductive age and the association of bacterial vaginosis in Papanicolaou smears with inflammation, ASCUS, and CIN, we believed it seemed reasonable to treat bacterial vaginosis empirically in the patient who has a minimally abnormal Papanicolaou smear. For these patients, revision to normal cytologic findings with inexpensive drug therapy represents time and cost savings when compared with further evaluation entailing slide preparations, cultures, and colposcopy for the patient who continues to produce abnormal Papanicolaou smears. In only one published study were patients with initial atypical smears randomized to receive antibiotic therapy before a repeated cytologic examination.[6] Triple sulfa cream, the drug used for treatment in the above study, failed to show superior results compared with placebo. A retrospective observational study, however, found that in patients with inflammatory atypia on Papanicolaou smears, rate of reversion to normal cytologic findings improved significantly after treatment with 0.75% metronidazole vaginal gel.[20]

The purpose of this study was to compare the efficacy of 0.75% metronidazole vaginal gel with no treatment in asymptomatic patients who have had a minimally abnormal Papanicolaou smear. We hypothesized that the Papanicolaou smears of patients with minimally abnormal cytologic findings who apply 0.75% metronidazole vaginal gel will more likely convert to normal than will those of patients in the control group. In addition, we examined possible relations of continued abnormal Papanicolaou smears with demographic and behavioral characteristics.

Methods

The Institutional Review Board of the Health Sciences Center of the University of South Florida (USF) approved the proposal for study. The sample consisted of women who had routine Papanicolaou smear screening from 1 August 1997 until 30 June 2000 at the USF Family Practice Clinic, a primary care clinic operated by USF faculty physicians. Two additional sites, Lifetime Cancer Screening Center, a nurse practitioner-staffed cancer screening clinic operated by H. Lee Moffitt Cancer Center and Research Institute, and Planned Parenthood were added in September 1998 and January 1999, respectively.

Patients were eligible for the study if their screening Papanicolaou smear result was minimally abnormal, defined as limited by inflammation (including partially obscured inflammation and moderate-to-marked inflammation), benign cellular changes, reactive cellular changes, or ASCUS. Because up to 40% of patients with LSIL will be found to have CIN II or III,[7] we excluded those patients from the study.

Other exclusion criteria included the following: age younger than 18 years; symptoms or signs of vaginal or cervical infection at the initial Papanicolaou examination; a gross cervical lesion; benign cellular changes associated with infection (*Trichomonas vaginalis*, *Candida albicans*, predominance of coccobacilli, or other); reactive cellular changes associated with atrophy, radiation, or intrauterine contraceptive device; glandular cell abnormalities; Papanicolaou smear reports with "koilocytosis," "changes consistent with human

papillomavirus (HPV)," or "favors neoplastic process," or when "dysplasia cannot be excluded"; history of abnormal Papanicolaou smear in the past year; previous squamous intraepithelial lesion (low-grade or high-grade) or carcinoma; previous cryosurgery or other cervical surgery; infection with gonorrhea or chlamydia; pregnancy, lactation, or plans for pregnancy within 6 months; history of hysterectomy; use of a vaginal antibacterial or antifungal treatment or treatment for any pelvic infection since the initial Papanicolaou smear; a serious medical disorder, such as human immunodeficiency virus; and known allergy or hypersensitivity to metronidazole.

Sample Size Considerations

An initial target sample size of 250 was chosen based on the following assumptions. The z test for differences in proportions was used to compare the proportion of abnormal Papanicolaou smears that revert to normal among treatment and control groups. As there was no reasonable expectation that treatment would worsen Papanicolaou smears, analyses assumed a one-tailed P value with $\alpha = 0.05$. Previous studies had indicated that between 50% and 75% of minimally abnormal Papanicolaou smears would spontaneously revert to normal. A sample size of 250 patients would allow more than 80% power to detect a 20% difference in reversion rates if the rate among the control group was 50% (ie, 50% vs 70%). A sample size of 250 patients would have more than 80% power to detect a 15% difference in reversion rates if the rate for the control group was instead 75% (ie, 75% vs 90%). In both cases the target sample size of 250 would be sufficient to allow for more than 20% loss to follow-up.

Entry criteria were met by 332 patients. Of that number, 145 agreed to participate and provided informed consent. Participating patients subsequently completed a questionnaire that elicited demographic data and information about smoking, alcohol consumption, use of recreational drugs, sexual preference, age of first sexual intercourse, number of sexual partners in the past 5 years, new partner in the past year, contraceptive use, history of sexual abuse or assault, and history of sexually transmitted disease, pelvic infection, or tubal pregnancy. Patients were randomized to treatment (n = 68) or control (n = 77) groups using a table of random numbers. Treatment consisted of 0.75% metronidazole vaginal gel, 1 applicator full at bedtime for 5 consecutive days. The control group received no treatment. Papanicolaou smears were repeated 3 to 4 months after enrollment. Neither the patients' medical providers nor the pathologists who reviewed the cytological slides were aware of the treatment status. A follow-up questionnaire that elicited information on sexual habits, contraceptive use, douching habits, other vaginal product use, vaginal symptoms, medications, and side effects of treatment was distributed and to be returned at the follow-up appointment.

Statistical Analysis

To determine whether randomization resulted in equivalent treatment and control groups, univariate relations between predictor variables and treatment groups were obtained using the t test for continuous variables. The primary statistical test used for the analysis of categorical measures was the chi-square test, and cross-tabular frequencies were performed to ascertain demographic comparisons of treatment with control groups. Variables of interest included race-ethnicity, marital status, educational level, sexual history, and condom use. We also examined the distribution of initial Papanicolaou smear findings among the treatment and control groups.

The main outcome of our study was a normal Papanicolaou smear at the follow-up examination. Investigation into the effects of 0.75% metronidazole vaginal gel on the likelihood of a normal follow-up Papanicolaou smear was conducted using the z test for differences in proportions.

Results

The study enrolled 145 women, 75.0% of whom were seen in the USF Family Practice Clinic, 19.3% of whom were seen at Lifetime Cancer Screening, and 5.5% of whom were seen at Planned Parenthood. A total of 31 women were lost to follow-up (14 from the treatment group and 17 from the control group), leaving 114 women (54 in the treatment group and 60 in the control group) for evaluation. Reasons for lost to follow-up included patients relocating or not returning for follow-up examinations and follow-up examinations being performed outside the 3- to 4-month study period.

Table 1. Demographic Characteristics of Patients Initially Enrolled in Study (N = 145).

Characteristics	Control (n = 77)	Treatment (n = 68)	*P* Values
Mean age (years)	42.7	40.4	.27
Mean age at first sexual encounter (years)	19.7	18.5	.08
Race, ethnicity	*% (No.)*	*% (No.)*	.29
White	80.5 (62)	73.1 (49)	
Nonwhite	19.5 (15)	26.9 (18)	
Marital status			.44
Single	29.3 (22)	25.0 (17)	
Married	45.3 (34)	55.9 (38)	
Separated, divorced or widowed	25.3 (19)	19.1 (13)	
Educational level			.15
High school	41.3 (31)	32.8 (22)	
2-year degree	18.7 (14)	35.8 (24)	
4-year degree	22.7 (17)	17.9 (12)	
Advanced degree 1	17.3 (13)	13.4 (9)	
New sexual partner			.34
Previous year	14.3 (11)	9.1 (6)	.15
Sexual partners previous 5 years			
0	10.5 (8)	4.5 (3)	
1	56.6 (43)	71.6 (48)	
2–3	27.6 (21)	16.4 (11)	
4 or more	5.3 (4)	7.5 (5)	
Condom use			.34
Always	9.2 (7)	15.5 (10)	
Most of the time	7.9 (6)	15.5 (10)	
Half of the time	1.3 (1)	3.0 (2)	
Rarely	11.8 (9)	12.1 (8)	
Never	69.7 (53)	54.5 (36)	

When comparisons were made between the study participants, the treatment and control groups were found to be similar in age, marital status, educational level, age at first sexual encounter, number of sexual partners in the previous 5 years, new sexual partner in the previous year, and condom use (Table 1). There were no demographic or clinical differences found between patients who were lost to follow-up and those who completed the study.

The distribution of patients according to initial Papanicolaou smear result is shown in Table 2 and was similar for the treatment and control groups. As shown by the table, reactive cellular changes and inflammation were the most frequently observed cytologic abnormalities. Reactive cellular changes were distributed among 19% of the treatment group and 18.3% of the control group, whereas inflammation accounted for 17% for both treatment and control groups.

Follow-up cytologic findings were normal in 61 of 114 (54%) of patients (Table 3). Sixty-two percent (n = 37) of the Papanicolaou smears in the control group converted to normal on follow-up, whereas only 44% (n = 24) of the Papanicolaou smears in the treatment group converted to normal ($z = -1.84$ testing the hypothesis that treatment was superior to control, one-tailed $P = .97$). A

Table 2. Distribution of Cytologic Findings on Initial Papanicolaou Smear.

Cytologic Findings	Control (n = 77) No. (%)	Treatment (n = 68) No. (%)	Total (n = 145) No. (%)
Inflammation	24 (17.0)	24 (17.0)	48 (33.8)
ASCUS	16 (11.3)	8 (5.6)	24 (17.0)
Reactive cellular changes	26 (18.3)	27 (19.0)	53 (37.3)
Benign cellular changes	9 (6.3)	8 (5.6)	17 (12.0)
Total	75 (52.8)	67 (47.2)	142 (100.0)

Note: $P = .51$ for overall distribution of cytologic findings among control and treatment groups.
ASCUS = atypical squamous cells of undetermined significance.

Table 3. Comparison of Patients with Normal Cytologic Findings on Follow-Up Papanicolaou Examination, by Treatment Groups and Findings on Initial Papanicolaou Report.

Findings on Initial Papanicolaou Report	Treatment (n = 54) Normal Findings No. (%)	Control (n = 60) Normal Findings No. (%)	Total (n = 114) Normal Findings No. (%)	*P* Value
Inflammation	13 (62.0)	11 (61.1)	24 (61.5)	.96
ASCUS	6 (46.2)	1 (12.5)	7 (33.3)	.17*
Reactive cellular changes	14 (73.7)	9 (45.0)	23 (59.0)	.07
Benign cellular changes	4 (66.7)	3 (37.5)	7 (50.0)	.59*
Total	37 (61.7)	24 (44.4)	61 (54.0)	.07

*P value obtained using Fisher's exact test.
ASCUS = atypical squamous cells of undetermined significance.

chi-square test examining whether either group was superior was 3.39 (two-tailed $P = .07$). In subgroup analysis, the rates of reversion to normal cytologic findings were the same among both groups of patients having inflammation on their initial Papanicolaou smear. In patients with reactive cellular changes, benign cellular changes, or ASCUS on initial Papanicolaou smear, however, there was a statistically nonsignificant trend toward higher resolution rates among patients in the control group compared with the treatment group ($P = .17$). Only one follow-up Papanicolaou smear worsened to LSIL. This patient, who was randomized to the treatment group, had an initial Papanicolaou smear categorized as reactive cellular change with inflammation. No subgroup of patients was found for whom metronidazole vaginal gel was beneficial (data not presented).

Our final sample size of 114 patients provided approximately 80% power to detect a 20% difference in reversion rates using a one-tailed test (whether treatment was superior to control) and 80% power to detect a 25% difference between the two groups using a two-tailed test (either group superior to the other).

Discussion

In this study, treatment with 0.75% metronidazole vaginal gel did not improve the rate of reversion of asymptomatic minimally abnormal cervical cells to normal cytologic findings. This finding is in contrast to results of a retrospective study by Randell,[20] who reported increased reversion rates from inflammatory atypia to normal with the use of 0.75% metronidazole vaginal gel compared with triple sulfa cream or no treatment. Our results are similar to those of one other randomized prospective study,[6] which found that triple sulfa vaginal cream did not improve reversion rates of the atypical Papanicolaou smear when compared with control.

The plausibility of bacterial vaginosis contributing to the finding of a minimally abnormal Papanicolaou smear is supported by the increased prevalence of bacterial vaginosis in high-risk populations and in Papanicolaou smears showing inflammatory changes or ASCUS.[10–13,18] Furthermore, bacterial vaginosis is now understood to be a syndrome in which the normal vaginal flora is disrupted and dominated by anaerobic bacteria, including *G vaginalis*. Because this abnormal microflora can produce carcinogenic nitrosamines, it has been postulated to be a major cofactor in the development of CIN.[19,21,22] Wilson et al[10] reported that 44 of 102 premenopausal women whose Papanicolaou smears showed inflammatory changes tested positive for *G vaginalis*. Fifty percent of these patients subsequently had abnormal colposcopic findings, ranging from mild to severe dysplasia, 6 weeks later. Similarly, Platz-Christensen et al[19] found that patients who had clue cells representing bacterial vaginosis on Papanicolaou smear were more likely to develop CIN. If bacterial vaginosis was present, the relative risk for having any CIN was 8.0, and the relative risk for having CIN III-carcinoma in situ was 5.0.

Other studies have refuted the relation of bacterial vaginosis to inflammation or cervical dysplasia on Papanicolaou smears. In a study of asymptomatic women undergoing routine Papanicolaou smears, inflammation on cytologic smears had a relatively low predictive value for the presence of vaginal pathogens, including *G vaginalis*.[23] Frega et al,[24] in a study of 1,008 women, one half of whom had a diagnosis of CIN, found no significant dif-

ference in the incidence of bacterial vaginosis between the CIN and non-CIN groups. The conflicting findings in the above studies might be due to the variation in patient populations studied, the differences in study designs, the variations of diagnostic criteria for bacterial vaginosis, and the differences in interpretation and classification of abnormal Papanicolaou smears among cytopathologists.

Our study suggests that bacterial vaginosis is not an important factor in the development of Papanicolaou smears that are limited by inflammation or those with benign cellular changes, reactive cellular changes, or ASCUS that does not favor a neoplastic process. More than 50% of the patients, regardless of whether they received treatment, had cytologic findings that reverted to normal in 3 to 4 months, with the patients with no treatment having a slightly higher reversion rate. Our findings parallel the reported high spontaneous resolution rates of more than 50% for ASCUS and LSIL.[2,25,26]

It appears that most minimally abnormal Papanicolaou smears do not have any clinically pathologic importance. For patients whose Papanicolaou smears show persistent inflammation, two thirds have been found to be normal or have only chronic inflammation on biopsy.[3] In a study by Bertolino et al,[23] women who had intercourse at least once during the week before a Papanicolaou smear were more likely to have inflammation. In a study of Papanicolaou smears with benign cellular changes, Malik et al[27] found specific infections in only 8% of cases. In patients without a history of CIN or cervical carcinoma, benign cellular changes were due to a wide spectrum of nonneoplastic and nonspecific inflammatory processes that can probably be ignored.

Current interim guidelines developed by a National Cancer Institute workshop for the management of ASCUS and LSIL smears recommend repeating Papanicolaou smears at least every 6 months for 2 years until 3 consecutive negative smears are found. Colposcopy is reserved for those with repeated smears showing persistent abnormalities or for a patient at high risk (previous abnormal Papanicolaou tests, poor compliance for follow-up).[1] Using decision analysis, however, Melnikow et al[28] showed that a hypothetical cohort of 100,000 women with squamous atypia treated in this way would cost between $14 million and $33 million. In addition, the guidelines do not make recommendations for management of smears that are satisfactory but limited by inflammation, or those that have benign cellular changes or reactive cellular changes with inflammation. In our study, only 1 patient progressed to LSIL. Because the progression from low-grade CIN lesions to invasive squamous cell carcinoma of the cervix is estimated in most cases to take 10 to 15 years,[29] it would appear that annual screening is a prudent and cost-effective way to approach patients with minimally abnormal Papanicolaou smears.

This study has several limitations. The patients were not tested for bacterial vaginosis because we wanted to test the efficacy of empiric treatment; therefore, we do not know how many patients in the treatment or control groups did indeed harbor bacterial vaginosis. It was interesting that, compared with the treatment group, there was a trend for the control group to have a higher reversion rate to normal. We do not know whether treatment failed to eradicate bacterial vaginosis, the use of 0.75% metronidazole vaginal gel impeded reversion, or bacterial vaginosis was in some way protective in this patient population and eradicating bacterial vaginosis was actually detrimental. A protective effect has been suggested by a prospective cohort study of 46 patients evaluated for ASCUS found on Papanicolaou smears. In that study, women with bacterial vaginosis had less than one half the incidence of cervical dysplasia and abnormal cervical biopsies compared with women without bacterial vaginosis.[30]

Perhaps treatment did eradicate bacterial vaginosis, but the time from treatment to the follow-up Papanicolaou smear was too short. All the women had follow-up Papanicolaou smears 3 to 4 months after enrollment. In the study by Reiter,[6] repeating Papanicolaou smears at 3 to 4 months significantly increased the rate of reversion of atypical to normal cytologic findings compared with repeating smears at 1 to 2 months or 5 to 6 months. We did not have a placebo group, so the patients were not blinded. Follow-up questionnaires showed, however, that behaviors among the treatment and control groups were similar. Although we did not meet our initial target sample size, our final sample size of 114 patients provided approximately 80% power to detect a 20% difference in reversion rates.

It could be that bacterial vaginosis does not play a role in the development of cervical dysplasia in women at low risk, and it is only a cofactor when

other oncogenic agents, such as human papillomavirus, are present. Our study group, as well as that of Bertolino et al,[23] consisted mostly of low-risk women who were middle-aged, white, monogamous, and highly educated, and thus who were less likely to be infected with human papillomavirus. These demographic characteristics are probably representative of a number of settings, however. Further studies are indicated to ascertain the role of bacterial vaginosis in the development of cervical dysplasia. In addition, larger randomized controlled studies are indicated to develop guidelines for the management of the minimally abnormal Papanicolaou smear.

In conclusion, our study indicates that the empiric use of 0.75% metronidazole vaginal gel does not improve the rate of reversion of minimally abnormal Papanicolaou smears, characterized by those limited by inflammation, benign cellular changes, reactive cellular changes with inflammation, or ASCUS that does not favor a neoplastic process. It seems that the syndrome of bacterial vaginosis does not substantially contribute to this minimally abnormal clinical finding in our relatively low risk population. The current practice of some clinicians to treat empirically the minimally abnormal Papanicolaou smear with 0.75% metronidazole vaginal gel before follow-up smears is not supported by this trial. In low-risk patients, repeating Papanicolaou smears in 1 year is probably sufficient. We agree with Everett and Chesebro,[4] in that emphasis needs to be placed on screening unscreened women, who account for 70% of cases of invasive cervical cancer, than on frequent follow-up screening of women with minimally abnormal Papanicolaou smears.

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