Association of Lower Genital Tract Inflammation With Objective Evidence of Endometritis

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ABSTRACT

The purpose of this report is to evaluate the association between lower genital tract inflammation and objectively diagnosed endometritis. We analyzed the first 157 patients enrolled in the PEACH study, a multicenter randomized clinical trial designed to compare the effectiveness of outpatient and inpatient therapy for PID. Women less than 38 years of age, who presented with a history of pelvic discomfort for 30 days or less and who were found to have pelvic organ tenderness (uterine or adnexal tenderness) on bimanual examination, were initially invited to participate. After recruitment of the first 58 patients (group 1) we added the presence of leukorrhea, mucopurulent cervicitis, or untreated positive test for *N. gonorrhoeae* or *C. trachomatis* to the inclusion criteria (group 2, N = 99). We compared rates of endometritis in the two groups and calculated the sensitivity, specificity, and predicted values of the presence of white blood cells in the vaginal wet preparation. The rate of upper genital tract infection in group 1 was 46.5% (27/58) compared to 49.5% (49/99) in group 2. Microbiologic evidence of either *N. gonorrhoeae* or *C. trachomatis* increased from 22.4% in group 1 to 38.3% in group 2. The presence of vaginal white blood cells or mucopus has a high sensitivity (88.9%), but a low specificity (19.4%) for the diagnosis of upper genital-tract infection. Assessment of the lower genital tract for evidence of infection or inflammation is a valuable component of the diagnostic evaluation of pelvic inflammatory disease. The presence of either mucopus or vaginal white blood cells is a highly sensitive test for endometritis in patients with pelvic pain and tenderness. Infect. Dis. Obstet. Gynecol. 8:83–87, 2000. © 2000 Wiley-Liss, Inc.

Pelvic inflammatory disease (PID) causes more morbidity and mortality to women between the ages of 15 and 25 than all other infections combined.[1] In fact, PID affects almost 11% of United States women during their reproductive years.[2] The reproductive sequelae of PID can be devastating and can include infertility, chronic pelvic pain, ectopic pregnancy, and recurrent infections.[3,4]

The clinical diagnosis of PID is inaccurate. The Centers for Disease Control and Prevention's minimal criteria for the diagnosis of PID have low sensitivity and specificity.[5,6] These criteria do not reliably discriminate infectious from other genital-tract etiologies of pelvic pain. In the diagnostic criteria for PID, the CDC lists "additional criteria" which may improve the specificity of the diagnosis in women who present with the "minimum crite-

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ria" for PID (abdominal tenderness, cervical motion tenderness, and adnexal tenderness). One of the additional supportive criteria listed is the presence of abnormal cervical or vaginal discharge.[7]

The evaluation of vaginal discharge is one of the most underutilized, yet consistent, predictors of upper genital-tract infection. The largest cohort study to date, in which Swedish women suspected of having PID underwent a laparoscopic evaluation, found that a marked increase in the number of inflammatory cells (i.e., inflammatory cells outnumbering all other cellular elements in the smear) was associated with laparoscopic salpingitis.[4] In addition, the absence of white blood cells in the vaginal discharge plus clear cervical mucus is felt to reliably exclude upper genital-tract infection (high negative predictive value).[8]

The purpose of this preliminary report is to evaluate the association between lower genital-tract inflammation (mucopus or vaginal white blood cells on saline microscopic preparation) and objectively diagnosed upper genital-tract infection. The hypothesis of this study is that evidence of lower genital-tract inflammation is a sensitive test in women presenting with pelvic pain and tenderness.

SUBJECTS AND METHODS

The PID Evaluation and Clinical Health (PEACH) study, funded by the Agency for Health Care Policy and Research, is a multicenter randomized clinical trial designed to compare inpatient versus outpatient antimicrobial therapy for the treatment of PID. It is the largest prospective study of PID ever conducted in North America, and the first trial to evaluate the effectiveness and cost-effectiveness of currently recommended antibiotic regimens in terms of preventing long-term reproductive sequelae.

The methods of the PEACH study have been fully described in a prior publication,[9] so an abbreviated overview is provided here. Patients are recruited from eight clinical sites (Charleston, Providence, Birmingham, Atlanta, Philadelphia, Pittsburgh, Detroit, and Dallas). Prior to recruitment, the study was approved by the institutional review board at each center. Women less than 38 years of age who present with a history of pelvic discomfort for 30 days or less and who are found to have pelvic organ tenderness (uterine or adnexal tenderness)

on bimanual examination are invited to participate. At the launch of the trial, these criteria were the only inclusion criteria. If an initial review showed that the rate of upper-tract infection in the cohort was relatively low, we added the presence of one or more of the following as inclusion criteria: (1) leukorrhea (finding more white blood cells than epithelial cells in at least four high power fields of a saline vaginal wet mount); (2) mucopurulent cervicitis (yellow or green mucus discharge from the endocervix); and (3) untreated positive test for *N. gonorrhoeae* or *C. trachomatis* from the cervix. These additional criteria represented evidence of lower genital-tract infection or inflammation. This change in methodology provided an opportunity to evaluate the association of lower genital-tract inflammation (mucopus or vaginal white blood cells) and objective evidence of upper genital-tract infection. In the initial group recruited between February and May, 1996, (group 1), evidence of lower genital-tract infection or inflammation was not part of the inclusion criteria. In the subsequent group recruited between June and October, 1996, (group 2), evidence of lower genital-tract inflammation or positive test for *N. gonorrhoeae* or *C. trachomatis* was required for patient inclusion in the study.

Women were excluded from participation for the following reasons: (1) positive test for beta human chorionic gonadotropin; (2) inability to tolerate oral antibiotic therapy; (3) presence of a tubo-ovarian abscess; (4) surgical emergency (e.g., appendicitis or suspected ovarian torsion) requiring immediate operative intervention; (5) pain present for more than 30 days; (6) severe allergy to penicillins, cephalosporins, or tetracyclines; (7) antimicrobial therapy within seven days of presentation; (8) delivery, abortion, or gynecologic surgery within the last 30 days ; (9) prior hysterectomy or bilateral salpingectomy; and (10) homelessness.

Baseline data collection included standard demographic and reproductive characteristics, including education, insurance, contraceptive use, douching, history of gynecologic infections and sexually transmitted diseases, and sexual history. Clinical data collected included degree and duration of pain.

Baseline examination included pelvic examination and scoring of pelvic tenderness. Assessment of vaginal discharge for presence of trichomonads, bacterial vaginosis, and candidal infection was per-

formed using microscopy of saline and potassium hydroxide preparations. Vaginal fluid was also tested for pH and release of amine odor with the addition of potassium hydroxide (whiff test). A vaginal gram stain was also performed. Bacterial vaginosis was considered present when three out of four clinical criteria for the diagnosis were obtained as outlined by Amsel.[10] Trichomonas was diagnosed by examining numerous high-power fields for motile trichomonads.

After cleansing the ecto- and endócervix with providone iodine, cervical swabs were obtained for gram stain and for polymerase chain reaction (PCR) testing for *N. gonorrhoeae* and *C. trachomatis*. An endometrial biopsy was performed with a flexible suction cannula and assessed by *N. gonorrhoeae* culture *C. trachomatis* PCR, and with histologic evaluation. Blood samples were sent for white blood cell count and erythrocyte sedimentation rate. Urinalyses were obtained and were sent for culture when suspicious. Because laparoscopy was not a feasible method of evaluation for all participants, we used histologic evidence of endometritis as the diagnostic criteria for upper-tract infection. Histologic evidence of acute or chronic endometritis was considered present when there was ≥1 plasma cell in the stroma and/or ≥5 neutrophils in the endometrial epithelium.[11,12]

We analyzed the baseline data from the first 157 patients enrolled in the PEACH study. We chose this group as a relatively homogeneous sample, because after this time additional clinical sites were added. Incorporating the additional clinical sites would introduce site and patient characteristic variability. We stratified this pool into two groups: leukorrhea, mucopus, and positive evidence for cervical infection not required (group 1) and lower genital-tract inflammation or infection as inclusion criteria (group 2); and we evaluated the change in the rate of upper genital-tract infection. Categorical variables were analyzed by χ^2 tests. In group 1, we then calculated the sensitivity, specificity, and predictive values of mucopurulent cervicitis and the presence/absence of white blood cells in the vaginal discharge from two-by-two tables. The 95% confidence intervals of the diagnostic indices were calculated from formula described by Snedecor and Cochran.[13] Diagnostic indices could not be calculated from group 2 since lower genital-tract inflammation was an inclusion criteria in this group.

RESULTS

The demographic and reproductive characteristics of the initial 157 patients stratified by group is shown in Table 1. There were no significant differences in demographic or reproductive characteristics by group.

In group 1, the rate of upper genital-tract infection was 46.5% (27/58). After leukorrhea was added to the inclusion criteria (group 2), the rate of upper-tract infection was 49.5% (49/99). The percentage of women with microbiologic evidence of *C. trachomatis* increased from 8.6% in group 1 to 17.4% in group 2 (N = 150). Microbiologic evidence of either *N. gonorrhoeae* or *C. trachomatis* increased from 22.4% in group 1 to 38.3% in group 2 (N = 157). Furthermore, *N. gonorrhoeae* and *C. trachomatis* were isolated from the upper genital tract in 18.5% of patients in group 1 and from 25.3% of patients in group 2. Mucopurulent cervical discharge was also much more common in group 2 (31.0 vs. 57.6%). The findings of an increased prevalence of positive tests for *N. gonorrhoeae* or *C. trachomatis* and mucopurulent cervical discharge is expected since these criteria were part of the inclusion criteria for group 2.

The diagnostic test characteristics for the presence of either vaginal white blood cells or mucopurulent cervicitis and the presence of both findings are presented in Table 2. In group 1, the presence of vaginal white blood cells in the vaginal discharge or mucopus has a high sensitivity (88.9%; 95% confidence interval (CI) 75.2%, 100%), but a low specificity (19.4%; 95% CI 3.8%, 34.9%). In the total cohort, the presence of either mucopus or vaginal white blood cells had a sensitivity of 96.1% (95% CI 91.0%, 100%).

DISCUSSION

The clinical interpretation of these results is as follows: the presence of lower genital-tract inflammation (either mucopus or white blood cells in the vaginal discharge) is a sensitive test for upper genital-tract infection (histologic endometritis). In other words, there are relatively few false negatives (no mucopus and no vaginal white blood cells) in patients with endometritis. Therefore, one should suspect other causes of pelvic pain in a woman who presents with pain and tenderness but is found to have no white blood cells in the vaginal discharge and no mucopus.

TABLE I. Demographic and reproductive characteristics by group

Characteristic	Group I (N = 58)		Group 2 (N = 99)		Total (N = 157)		P value
	N	%	N	%	N	%	
Age							
<20	11	19.0	24	24.2	35	22.3	NS
20–24	22	37.9	36	36.4	58	36.9	
25–29	13	22.4	20	20.2	33	21.0	
30–34	9	15.5	14	14.1	23	14.6	
>34	3	5.2	5	5.1	8	5.1	
Race (N = 157)[a]							
Black	38	65.5	65	65.7	103	65.6	NS
White	12	20.7	16	16.2	28	17.8	
Hispanic	3	5.2	14	14.1	17	10.8	
Other/unknown	5	8.6	4	4.0	9	5.7	
Marital status (N = 146)[a]							
Never married	37	67.3	60	65.9	97	66.4	NS
Separated	5	9.1	10	11.0	15	10.3	
Married/remarried	7	12.7	12	13.2	19	13.0	
Divorced	5	9.1	9	9.9	14	9.6	
Widowed	1	1.8			1	0.7	
Education							
<high school diploma	26	44.8	36	36.4	62	39.5	NS
≥high school diploma	32	55.2	63	63.6	95	60.5	
Uninsured (N = 145)[a]	20	36.4	40	44.4	60	41.4	NS
History of STD (N = 156)[a]	36	62.1	57	58.2	93	59.6	NS
History of PID (N = 156)[a]	20	34.5	34	34.7	54	34.6	NS
Trichomoniasis (N = 157)[a]	5	8.6	12	12.1	17	10.8	NS
Bacterial vaginosis (N = 155)[a]	17	30.4	27	27.3	44	28.4	NS

[a]Some data missing; percent based on known data.

TABLE 2. Sensitivity, specificity, and predictive values of mucopurulent cervicitis and presence of vaginal white blood cells for predicting upper genital-tract infection

Group I (N = 58)	Either mucopus or vaginal WBCs (%)	Both mucopus and vaginal WBCs (%)
Sensitivity	88.9	51.9
Specificity	19.4	87.1
Positive predictive value	49.0	77.9
Negative predictive value	66.7	67.5
Total Cohort (N = 157)		
Sensitivity	96.1	61.8
Specificity	4.4	65.4
Positive predictive value	49.3	62.3
Negative predictive value	66.7	64.6

Evaluation for lower genital-tract inflammation is one of the most valuable tests for the diagnosis of upper genital-tract infection. Other studies have shown that saline wet prep is one of the most sensitive tests for the diagnosis of upper-tract infection.[14] The test is inexpensive and relatively easy to perform.

This finding is consistent with results presented from previous studies of diagnostic testing for PID.[15] In a cohort of women evaluated for classic and "non-classic" signs and symptoms of upper-tract infection, Peipert and colleagues noted that the evaluation of microscopic preparation for vaginal white blood cells (WBCs) was the most sensitive test for objective evidence of upper-tract infection.[14] The results of the present study differ from the this previous study[14] due to the different inclusion criteria. All participants in the present study had pelvic pain while subjects in the 1996 report[14] had a wider spectrum of symptoms. In the largest cohort of suspected PID studied, Westrom and colleagues noted that the combination of clear cervical mucus and the absence of WBCs in the vagina could reliably exclude PID in almost all cases.[8]

This study goes beyond previous reports in the literature evaluating lower genital-tract inflammation as a marker of upper-tract infection. As a multicenter clinical trial, this study is more readily be generalized to U.S. populations than can the Swedish cohort or other studies with recruitment limited

to a specific geographic area. In addition, this study includes patients that meet the CDC's minimal criteria for PID and patients who may not meet the CDC criteria, but have more subtle signs of upper-tract infection (i.e., any pelvic tenderness).

The limitations of this report include the small sample size of group 1; there were only 58 patients in this group prior to our inclusion criteria mandating evidence of lower-tract inflammation or testing positive for *N. gonorrhoeae* or *C. trachomatis*. As a result, the 95% confidence interval is fairly wide. Secondly, the most severe cases of upper-tract infection (e.g., tubo-ovarian abscesses) were excluded from participation. Thus, our results may apply to more mild to moderate infection.

In conclusion, the evaluation of the lower genital tract for inflammation is a necessary component of a careful evaluation of a women suspected of having upper genital-tract inflammation.[16] The evaluation is inexpensive, quick, and provides a sensitive test for the diagnosis of upper genital-tract infection. Future studies should evaluate the diagnostic test characteristics of mucopus and vaginal WBCs compared to other simple and inexpensive tests in large populations with suspected upper-tract infection. Only then can we develop accurate diagnostic algorithms that maximize sensitivity and aid in rapid and accurate diagnosis and treatment of PID.

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