

PREVENTION OF PELVIC INFLAMMATORY DISEASE BY SCREENING FOR CERVICAL CHLAMYDIAL INFECTION

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Abstract Background. *Chlamydia trachomatis* is a frequent cause of pelvic inflammatory disease. However, there is little information from clinical studies about whether screening women for cervical chlamydial infection can reduce the incidence of this serious illness.

Methods. We conducted a randomized, controlled trial to determine whether selective testing for cervical chlamydial infection prevented pelvic inflammatory disease. Women who were at high risk for disease were identified by means of a questionnaire mailed to all women enrollees in a health maintenance organization who were 18 to 34 years of age. Eligible respondents were randomly assigned to undergo testing for *C. trachomatis* or to receive usual care; both groups were followed for one year. Possible cases of pelvic inflammatory disease were identified through a variety of data bases and were confirmed by review of the women's medical records. We used an intention-to-screen anal-

ysis to compare the incidence of pelvic inflammatory disease in the two groups of women.

Results. Of the 2607 eligible women, 1009 were randomly assigned to screening and 1598 to usual care. A total of 645 women in the screening group (64 percent) were tested for chlamydia; 7 percent tested positive and were treated. At the end of the follow-up period, there had been 9 verified cases of pelvic inflammatory disease among the women in the screening group and 33 cases among the women receiving usual care (relative risk, 0.44; 95 percent confidence interval, 0.20 to 0.90). We found similar results when we used logistic-regression analysis to control for potentially confounding variables.

Conclusions. A strategy of identifying, testing, and treating women at increased risk for cervical chlamydial infection was associated with a reduced incidence of pelvic inflammatory disease. (N Engl J Med 1996;334:1362-6.)

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PELVIC inflammatory disease is the most serious sexually transmitted bacterial infection affecting women.¹ Recent studies have more clearly defined the ascending route of infection. Lower genital tract infection can lead to endometrial and tubal infection (i.e., pelvic inflammatory disease) and, in turn, to complications such as infertility, ectopic pregnancy, and chronic pelvic pain.²⁻⁵ There is general agreement that efforts to prevent pelvic inflammatory disease must address the earliest parts of this causal chain — that is, they must emphasize the primary prevention or early detection of infections of the lower genital tract.⁵⁻⁸

In the United States, *Chlamydia trachomatis* is the most common sexually transmitted bacterial pathogen and a major cause of pelvic inflammatory disease.^{1,9,10} It is thus a logical focus for prevention efforts, but timely detection and control are hampered by the large number of asymptomatic cervical infections.^{1,5-11} Efforts to control chlamydial infection have been aided in recent years by the development of screening criteria for use in situations where there is a low prevalence of infection.¹²⁻¹⁷ Direct evidence that screening programs can contribute to the secondary prevention of pelvic inflammatory disease is still lacking, however. To our

knowledge, no studies have experimentally verified that testing and treating women with early chlamydial infection affects their risk of subsequent pelvic inflammatory disease.

We developed criteria to identify women at increased risk for chlamydial infection in a low-prevalence population — the enrollees of a health maintenance organization (HMO).¹⁷ We now report on a randomized, controlled trial in the same population that was designed to evaluate whether the use of these criteria to select women to be tested for cervical chlamydial infection would reduce the incidence of pelvic inflammatory disease.

METHODS

Study Population

This study was conducted between October 1990 and May 1992 at Group Health Cooperative of Puget Sound, a staff-model HMO located in western Washington State. Group Health Cooperative provides comprehensive health care to approximately 380,000 enrollees and has numerous computerized and manually maintained data bases linked by the permanent medical-history numbers assigned to each person on enrollment.¹⁸ All study procedures were reviewed and approved by the institutional review board at the HMO.

An earlier study at Group Health Cooperative of 1692 largely asymptomatic young women attending primary care clinics found a prevalence of chlamydial infection of 3.5 percent.¹⁷ An age of less than 25 years, black race, nulligravidity, two or more sexual partners in the past year, douching within the past year, the presence of cervical ectopy, and being unmarried were independently associated with an increased risk of chlamydial infection.

We then designed a randomized, controlled intervention trial to examine whether testing and treating women identified by the risk factors would affect the subsequent occurrence of pelvic inflammatory disease. We adapted the earlier predictive model to exclude married women, in whom the prevalence of chlamydial infection was very low, and to exclude cervical ectopy as a criterion for screening, since this required an examination. We then developed a brief, self-adminis-

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tered questionnaire that we could use to classify women according to risk status. All women from 18 to 34 years of age who were Group Health Cooperative enrollees as of October 1, 1990, were selected from the computerized enrollment file. After excluding enrollees whose records listed a spouse, we mailed questionnaires to the remaining 36,547 women over a 10-month period. Duplicate surveys were mailed to those who did not respond. We also telephoned some of the nonresponders each month to request that they return the questionnaire or give their responses by telephone. Emphasis was placed on calling nonresponding women assigned to the intervention group in order to expedite setting up their clinic appointments for testing.

Once the questionnaires were returned, we excluded women who were currently pregnant, who had never had sexual intercourse, who had undergone hysterectomy, who regularly used antibiotics, or who were married. We then used an algorithm (in which we assigned the following values: age $\leq 24 = 1$, black race = 2, nulligravidity = 1, douching in the preceding 12 months = 1, and two or more sexual partners in the preceding 12 months = 1) to assign each woman a risk score. Those with scores of 3 or more were eligible for the study, since they were considered to be at increased risk for asymptomatic chlamydial infection.

Randomization

The women were randomly assigned to either the screening group or the usual-care group at the time the original sample was selected in October 1990; the ratio of women in the screening group to women in the control (usual-care) group was 1:2.

Study Intervention

As soon as their surveys were scored, all eligible respondents in the screening group were invited to come to one of the study clinics to be tested for *C. trachomatis*. At the clinic, after informed consent was obtained, we collected two cervical samples. A swab was tested by enzyme-linked immunosorbent assay (Kallested Pathfinder kit) performed according to the manufacturer's instructions. A second specimen, obtained with a cytobrush, was placed in transport medium and sent to the University of Washington for chlamydial cell culture, as previously described.¹⁹ All women with positive results on either test were treated for chlamydial infection by their primary care provider.

Women assigned to the usual-care group saw their providers at Group Health Cooperative as needed. They were not contacted further by the study team until the follow-up evaluation.

Evaluation of Outcomes

Participants were followed for 12 months to assess end points of interest. Because funding for this study limited follow-up to a relatively brief period, the end point was the incidence of pelvic inflammatory disease. We used several methods to identify potential cases of pelvic infection in the study population. Each participant received a follow-up questionnaire one year after enrollment in which she was asked about urogenital infections, diagnosed pelvic inflammatory disease, and other health-related events and behavior. The Group Health Cooperative's outpatient data base was used to identify study participants who had been assigned a diagnostic code indicating pelvic inflammatory disease or cervicitis during follow-up. Similarly, we used the inpatient data base to identify participants who had been assigned a diagnosis of acute pelvic inflammatory disease or salpingitis at discharge from the hospital. Information on participants with positive tests for chlamydia or gonorrhea during follow-up was obtained from the laboratory records. Finally, women who had not otherwise been identified as having pelvic infection but who had received 10-day courses of doxycycline were identified from pharmacy records.

The medical records of the women with possible cases of pelvic inflammatory disease were then reviewed. We determined whether there was evidence of a diagnosis of pelvic inflammatory disease in the chart and recorded any available information on specific signs and symptoms (principally abdominal pain of less than one month's duration, cervical-motion or uterine tenderness, and adnexal tenderness); laboratory findings (positive tests for gonorrhea or chlamydia);

and subsequent diagnoses invalidating the diagnosis of pelvic inflammatory disease. The abstracters were unaware of the participants' study-group assignments.

Statistical Analysis

On the bases of the responses to the initial survey, we determined the distributions of prognostic factors and other variables in the two groups and compared them by means of chi-square tests and t-tests. An intention-to-screen analysis was used to compare the groups with respect to the incidence of pelvic inflammatory disease. The incidence of pelvic inflammatory disease in each group was calculated according to total follow-up time (12 months or until the women underwent hysterectomy or left the HMO). For all analyses, we included only cases of pelvic inflammatory disease that were confirmed by the medical-records review. That is, in addition to the listing in the data base that was used to identify a potential case of pelvic inflammatory disease, the diagnosis had to be noted in the medical record. We then evaluated by rate ratios the risk of pelvic inflammatory disease among the women assigned to the screening group relative to that among the women assigned to usual care.

We also used unconditional logistic-regression analysis to estimate odds ratios and 95 percent confidence intervals while controlling for the potentially confounding effects of other base-line variables. Variables considered singly and in combination in the logistic-regression models were age, marital status, douching practices, gravidity, and number of sexual partners.

RESULTS

Final Study Population

We received responses from 20,836 (57 percent) of the 36,547 women to whom we mailed the initial survey; 17,725 (85 percent) of those responding were ineligible because they had a low risk score or another reason for exclusion, and 504 women (2 percent) declined to participate. Of the remaining 2607 eligible women (13 percent), 1009 had been randomly assigned to the screening group and 1598 to the usual-care group.

Base-Line Characteristics

The distribution of prognostic variables and other characteristics in the screening and usual-care groups at base line is shown in Table 1. The two groups were very similar in terms of the variables used to evaluate risk status and in their educational level, annual income, and history of Pap tests.

A total of 645 (64 percent) of the women in the screening group were tested for cervical chlamydial infection; 44 (7 percent) had positive tests. All 44 women with positive results received treatment for chlamydial infection from their primary care providers. The 645 women in the screening group who underwent testing were similar in terms of the prognostic variables to the 364 who were not tested (data not shown).

Incidence of Pelvic Inflammatory Disease

At the end of the 12-month follow-up period, we received completed follow-up questionnaires from 76 percent of the 2607 participants. Ninety-six of the women reported an episode of pelvic inflammatory disease. The computerized data bases of Group Health Cooperative identified 57 participants who had received a diagnosis of pelvic inflammatory disease. Of the 142

Table 1. Prognostic Variables in the Screening and Usual-Care Groups at Base Line.

VARIABLE	SCREENING (N = 1009)	USUAL CARE (N = 1598)
Mean age (yr)	22	22
	<i>no. (%)</i>	
Age		
18–24 yr	817 (81.0)	1289 (80.7)
25–34 yr	192 (19.0)	309 (19.3)
Marital status*		
Single	850 (84.2)	1320 (82.6)
Married or living as married	85 (8.4)	188 (11.8)
Separated, divorced, or widowed	74 (7.3)	90 (5.6)
Gravidity†		
0	776 (76.9)	1271 (79.7)
≥1	233 (23.1)	324 (20.3)
Use of douching in the past yr‡		
No	324 (32.1)	579 (36.3)
Yes	685 (67.9)	1016 (63.7)
No. of sexual partners in the past yr§		
0	28 (2.8)	39 (2.4)
1	311 (30.9)	440 (27.6)
2	348 (34.6)	580 (36.4)
≥3	319 (31.7)	534 (33.5)
Race or ethnic group¶		
Asian	20 (2.0)	39 (2.4)
Black	230 (22.8)	331 (20.8)
Hispanic	21 (2.1)	23 (1.4)
Non-Hispanic white	695 (68.9)	1145 (71.8)
Other	42 (4.2)	57 (3.6)
Pap test		
No	58 (5.7)	82 (5.1)
Yes	951 (94.3)	1515 (94.9)
Risk score		
3	709 (70.3)	1158 (72.5)
4	235 (23.3)	339 (21.2)
≥5	65 (6.4)	101 (6.3)
Income**		
≤\$14,999	387 (39.9)	571 (37.1)
\$15,000–24,999	259 (26.7)	391 (25.4)
\$25,000–34,999	135 (13.9)	236 (15.3)
\$35,000–49,999	93 (9.6)	165 (10.7)
≥\$50,000	96 (9.9)	177 (11.5)
Education††		
Some high school or less	57 (5.7)	82 (5.1)
High-school graduate	243 (24.1)	411 (25.8)
Some college or technical school	530 (52.6)	815 (51.1)
College graduate	150 (14.9)	234 (14.7)
Graduate school	27 (2.7)	54 (3.4)

*P=0.01 for the comparison between the study groups, by the chi-square test.

†Data on gravidity and use of douching were missing for three women in the usual-care group.

‡P=0.03 for the comparison between the study groups, by the chi-square test.

§Data on the number of partners were missing for three women in the screening group and five in the usual-care group.

¶Data on race or ethnic group were missing for one woman in the screening group and three in the usual-care group.

||Data on Pap-test history were missing for one woman in the usual-care group. This variable measured whether women had ever had a Pap test.

**Data on income were missing for 39 women in the screening group and 58 in the usual-care group.

††Data on education were missing for two women in each group.

women identified in these two ways as having pelvic inflammatory disease, a review of the medical records showed a clinical diagnosis of pelvic inflammatory disease in 37. Five more women with a recorded diagnosis of pelvic inflammatory disease were identified by our review of the charts of 486 women who reported symptoms typical of pelvic inflammatory disease, had a di-

agnosis of cervicitis, filled prescriptions for doxycycline, or had positive tests for chlamydia or gonorrhea during follow-up.

There were 9 confirmed cases of pelvic inflammatory disease among the women in the screening group and 33 among the women assigned to receive usual care. Seven of the nine cases in the screening group were in women who had been tested for chlamydia. Additional information on symptoms, other evidence of infection, or indications of severe disease included the following: abdominal pain (noted for 13 women); the presence of two of three symptoms (abdominal pain, cervical-motion or uterine tenderness, and adnexal tenderness, noted for 18); and the presence of all three symptoms (noted for 6). Seven women had positive tests for chlamydia or gonorrhea. Three women, all in the usual-care group, were hospitalized for pelvic inflammatory disease.

Follow-up totaled 11,563 woman-months for the 1009 women in the screening group and 18,265 woman-months for the 1598 women in the usual-care group. The incidence of pelvic inflammatory disease was 8 per 10,000 woman-months in the screening group and 18 per 10,000 in the usual-care group (relative risk, 0.44; 95 percent confidence interval, 0.20 to 0.90)(Table 2). In logistic-regression models adjusting for base-line variables, the odds ratios ranged from 0.42 (95 percent confidence interval, 0.20 to 0.88) after adjustment for race or ethnic group or gravidity to 0.44 (95 percent confidence interval, 0.21 to 0.91) after adjustment for the number of sexual partners in the past 12 months. Simultaneous adjustment for the potentially confounding effects of douching, marital status, and age (odds ratio, 0.42; 95 percent confidence interval, 0.20 to 0.89) (Table 2) and other combinations of the base-line variables did not substantially alter the reduction in the risk of pelvic inflammatory disease associated with screening.

DISCUSSION

Reducing the incidence of pelvic inflammatory disease is a goal of the Public Health Service for the year 2000.²⁰ Efforts to control this disease are hampered, however, by many problems, including the fact that a variety of pathogens can cause infection, the difficulty of making the diagnosis, the frequency of asymptomatic infections, and the lack of adequate surveillance systems. The greatest hope for progress lies in the prevention and early detection of lower genital tract infections, which often lead to pelvic inflammatory disease.

The importance of cervical chlamydial infection in the pathogenesis of pelvic infection is well recognized.^{1,3,9} More than 4 million chlamydial infections are estimated to occur annually in the United States, and their early detection and treatment clearly represents an important avenue for the prevention of pelvic inflammatory disease. To date, the effects of programs to control chlamydia on the incidence of pelvic inflammatory disease

Table 2. Incidence and Risk of Pelvic Inflammatory Disease According to Study Group.*

	SCREENING	USUAL CARE	RELATIVE RISK (95% CI)	ODDS RATIO (95% CI)
No. of cases	9	33		
Rate	8	18	0.44 (0.20–0.90)	0.42 (0.20–0.89)

*Rates are expressed per 10,000 woman-months. CI denotes confidence interval. The relative risk is unadjusted. The odds ratio is adjusted for age, marital status, and use of douching.

have been evaluated primarily through the use of decision analysis or other models estimating the cost effectiveness of selective screening strategies in various populations of patients.^{13,21-26} Although very useful, these models rely on assumptions about the prevalence of chlamydia, the characteristics of tests, the efficacy of treatment, patients' compliance, and the risks of subsequent pelvic inflammatory disease.

In an earlier study, we identified several readily ascertainable characteristics that were associated with an increased risk of cervical chlamydial infection.¹⁷ We then conducted a randomized, controlled trial to study the effect of screening and treating women for these infections on the incidence of pelvic inflammatory disease. Using confirmed clinical diagnoses of pelvic inflammatory disease as the outcome measure, we found that the women assigned to the screening group had a 56 percent lower incidence of pelvic inflammatory disease than those in the usual-care group.

The selection of Group Health Cooperative as the research setting had a number of advantages. The well-defined patient population of this HMO allowed us to identify and contact all female enrollees of the appropriate age and enabled us to recruit high-risk participants efficiently from a large pool of women at low risk. Enrollees also received most of their health care within the Group Health Cooperative system.¹⁸ Rather than rely solely on the women's reports in the follow-up questionnaire or review the charts of the entire study group, we used a variety of computerized data bases to identify potential cases of pelvic inflammatory disease. This disease is difficult to identify; therefore, we also used manually maintained medical records as a method of verifying its occurrence.

National surveillance systems can monitor only the incidence of pelvic inflammatory disease in hospitalized patients, yet the great majority of women with this condition are not admitted to hospitals. Women with chlamydial pelvic inflammatory disease may be particularly likely to have relatively mild symptoms and to be treated as outpatients.^{2,3,20} A recently completed outpatient reporting system at Group Health Cooperative made it easier for us to identify women receiving ambulatory care for pelvic inflammatory disease.

HMOs also offer advantages from the standpoint of integrating the control of chlamydia with routine patient care. Both screening for risk factors and testing can be initiated by either the HMO or the provider. In the latter case, women who come into contact with the

health care system for a variety of reasons can be evaluated for risk and tested if necessary. Alternatively, the population-based approach that we used to assess the efficacy of screening could be continued at selected intervals. This approach has been adopted at Group Health Cooperative for mammography²⁷ and has the potential advantage of reaching women who use health care services infrequently.

Our study had limitations that deserve discussion. The one-year follow-up period did not allow us to evaluate the frequency of delayed or uncommon sequelae of chlamydial infection. Time constraints also dictated our decision to assign women randomly to study groups before mailing the first questionnaire. In order to have enough time to bring participants into the clinics for testing and still allow 12 months for follow-up, we concentrated on making telephone reminder calls to nonresponders assigned to the screening group. The final ratio of women in the screening group to women in the usual-care group was 1:1.6, rather than the initially assigned ratio of 1:2. This smaller proportion of women assigned to the usual-care group who actually participated in the study suggests the possibility of selection bias. More women assigned to screening than to usual care may have responded to the reminder calls, and those who agreed to participate in response to telephone calls may have differed in some ways from those who responded to the initial mailings. However, the script used for the reminder telephone calls was identical for both study groups, said nothing about group assignment, and contained the same information as the cover letters. Our examination of base-line variables also showed the two groups to be very similar.

We were able to screen only 64 percent of the 1009 women in the intervention group who were invited to undergo testing. This relatively low rate of participation is probably a feature of using a population-based approach to identifying and testing high-risk women.

The use of pelvic inflammatory disease as a study outcome is problematic. Given the invasiveness and cost of laparoscopic visualization, the vast majority of cases must be diagnosed on the basis of clinical signs and symptoms, indicators of inflammation, and laboratory-test results.^{28,29} In this analysis, we used medical records to confirm cases of pelvic inflammatory disease identified through the women's reports or in computer data bases. Nonetheless, some of the women may not have had pelvic inflammatory disease. It is also possible that some cases of asymptomatic pelvic infection did not come to our attention. It is unlikely, however, that the identification and verification of pelvic inflammatory disease varied greatly between the screening group and the usual-care group. The same diagnostic codes were used to identify women with potential cases, and the medical-records reviewers were unaware of the participants' group assignments.

This study was conducted in a managed-care setting; the optimal factors for use in screening and the effects of screening and treating women for chlamydial infec-

tion on the incidence of pelvic inflammatory disease could differ in other health care settings. However, a number of screening criteria (for example, age, number of sexual partners, and marital status) have been consistently identified and provide a basis for evaluating risk status. Our study provides evidence that, once women at high risk are identified and tested, the incidence of pelvic inflammatory disease can be reduced.

The costs of pelvic infection in terms of human suffering and use of health resources are large, and the components of successful programs to prevent pelvic inflammatory disease remain elusive. Several pieces of the prevention puzzle have been put in place in recent decades. The prevention of sexually transmitted infections that can cause pelvic inflammatory disease has received deservedly increased attention. The elucidation of the role of cervical chlamydial infections, along with the development of more sensitive diagnostic tests and more effective treatment, was also important, as was the development of efficient ways to target high-risk women through selective screening. Our study further shows that a population-based approach to identifying and testing women at increased risk for cervical *C. trachomatis* infection can reduce the risk of pelvic inflammatory disease.

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