Randomised controlled trial of screening for *Chlamydia trachomatis* to prevent pelvic inflammatory disease: the POPI (prevention of pelvic infection) trial

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**ABSTRACT**

**Objective** To determine whether screening and treating women for chlamydial infection reduces the incidence of pelvic inflammatory disease over the subsequent 12 months.

**Design** Randomised controlled trial.

**Setting** Common rooms, lecture theatres, and student bars at universities and further education colleges in London.

**Participants** 2529 sexually active female students, mean age 21 years (range 16-27).

**Intervention** Participants completed a questionnaire and provided self taken vaginal swabs, with follow-up after one year. Samples were randomly allocated to immediate testing and treatment for chlamydial infection, or storage and analysis after a year (deferred screening controls).

**Main outcome measure** Incidence of clinical pelvic inflammatory disease over 12 months.

**Results** Baseline prevalence of chlamydia was 5.4% (68/1254) in screened women and 5.9% (75/1265) in controls. 94% (2377/2529) of women were followed up after 12 months. The incidence of pelvic inflammatory disease was 1.3% (15/1191) in screened women compared with 1.9% (23/1186) in controls (relative risk 0.65, 95% confidence interval 0.34 to 1.22). Seven of 74 control women (9.5%, 95% confidence interval 4.7% to 18.3%) who tested positive for chlamydial infection at baseline developed pelvic inflammatory disease over 12 months compared with one of 63 (1.6%) screened women (relative risk 0.17, 0.03 to 1.01). However, most episodes of pelvic inflammatory disease occurred in women who tested negative for chlamydia at baseline (79%, 30/38). 22% (527/2377) of women reported being tested independently for chlamydia during the trial.

**Conclusion** Although some evidence suggests that screening for chlamydia reduces rates of pelvic inflammatory disease, especially in women with chlamydial infection at baseline, the effectiveness of a single chlamydia test in preventing pelvic inflammatory disease over 12 months may have been overestimated.

**Trial registration** ClinicalTrials.gov NCT00115388.

**INTRODUCTION**

Genital infection with *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection in the United States and Europe, with over three million new infections diagnosed each year.12 But most chlamydial infections remain asymptomatic and undiagnosed.3 Untreated chlamydial infection in women can lead to pelvic inflammatory disease, causing scarring of the fallopian tubes, which can result in tubal infertility, chronic pelvic pain, and ectopic pregnancy. The annual cost of chlamydial infection and its sequelae in the United States has been estimated to exceed $2bn.9

In many developed countries, screening programmes for chlamydia have been set up to reduce transmission and reproductive tract morbidity.2 The US Centers for Disease Control and Prevention recommend annual screening of all sexually active women aged 25 or less.1 In England the recommendation applies to women aged 24 or less.2 But controversy remains about the evidence base. The results of the landmark trial by Scholes et al1 have been questioned,5-7 and the continuing search for supporting evidence from other randomised controlled trials and epidemiological studies has not been always fruitful.8-11 The UK National Institute for Health and Clinical Excellence recommended improvements in the quality of randomisation, allocation concealment, and blinding of assessment of outcome in any future trials of chlamydia screening.12 A more accurate estimate of the rate of progression of genital chlamydial infection to pelvic inflammatory disease is also urgently needed to evaluate the cost effectiveness of screening programmes.12 However, neither of the two previous trials13 tested all the control women. No trials of chlamydia screening have taken place in a British population.

The national chlamydia screening programme was progressively rolled out across England from 2003 to 2008. This left a window of opportunity from 2004 to 2007 to carry out a community based trial in a non-healthcare setting using self taken samples. In the
POPI (prevention of pelvic infection) trial we investigated whether screening young sexually active female students for chlamydial infection and treating those found to be infected reduced the incidence of pelvic inflammatory disease in the subsequent 12 months. We also carried out an exploratory study to investigate the incidence of pelvic inflammatory disease in women with untreated chlamydial infection.\(^1\)

**METHODS**

The design and recruitment methods have been published elsewhere.\(^1\) Briefly, women were eligible for inclusion if they were aged 27 or less and were sexually active. We excluded women who had never had sexual intercourse, had been tested for chlamydial infection in the past three months, or were pregnant. Female nurses, research assistants, the principal investigator (PO), and peers recruited women in bars, common rooms, and lecture theatres at 20 London universities and further education colleges. (Further education colleges take students from age 16 and teach both academic subjects and vocational subjects, such as hairdressing.)

Participants provided written informed consent.\(^1\) They were warned of the risks of chlamydial infection and that their samples might not be tested for a year and were advised to get checked independently if they thought they had been at risk.

**Procedures**

Participants were asked to complete a brief confidential questionnaire on sexual health; to provide self taken vaginal samples in the nearest lavatory; and to allow access to their medical records, with follow-up after a year.\(^1\) Within two weeks of recruitment we randomly allocated sealed sample packs, which contained the completed, unopened questionnaires and consent forms, into two groups using random number tables. Vaginal swabs from packs allocated to the intervention group were tested for *C trachomatis* using transcription mediated amplification (TMA; Gen-Probe, San Diego, CA). Vaginal swabs from packs allocated to deferred screening were stored at $-80^\circ\mathrm{C}$ and analysed one year later. PO contacted infected women within two weeks of diagnosis and asked them to attend their local gynecological clinic or general practitioner for treatment and partner notification. Vaginal swabs made at baseline were Gram stained and examined for bacterial vaginosis using Nugent’s criteria.\(^1\)\(^1\)

A year after recruitment, we asked the participants to complete a secure online questionnaire about possible symptoms of pelvic inflammatory disease (pelvic pain, dyspareunia, bleeding between menstrual periods, or abnormal vaginal discharge) and sexual behaviour during the past year. Those who did not respond or provide an email address were sent the questionnaire by post, backed up by telephone reminders. We followed up non-responders through their general practice records. For all women (or their general practitioner) who reported that during the past 12 months they had had treatment for pelvic inflammatory disease, we endeavoured to obtain copies of the clinical findings from medical records of general practitioners, hospitals, family planning clinics, and gynecological clinics. After anonymisation of data, three gynecological doctors blinded to group allocation and baseline chlamydia status used modified Hager’s criteria\(^1\) and Centers for Disease Control guidelines\(^3\) to classify cases into probable, possible, or not pelvic inflammatory disease.\(^1\) Cases were categorised independently by two doctors, with review by a third for disagreements.

**Masking**

Participants were blind to group allocation except for those in the intervention group with baseline samples that tested positive for chlamydia and who were referred for treatment, and 38 women with indeterminate test results who were asked to post a repeat sample. Investigators were blind during recruitment and follow-up except PO when she referred women with chlamydial infection for treatment. Categorisation of pelvic inflammatory disease status was also blind.\(^1\)

**Statistical analysis**

Assuming a 2% incidence of pelvic inflammatory disease in the control group, we needed a sample of 4122 women to detect a relative risk of 0.48 with 80% power and 5% significance. We had difficulty with recruitment.\(^1\)\(^1\) however, as we were asking women who were not attending college for health reasons to provide vaginal samples that might not be tested for a year. Two studies\(^9\)\(^9\) suggested a higher rate of pelvic inflammatory disease, enabling us to revise down our sample size calculations. Assuming a 3% incidence of pelvic inflammatory disease in the control group,\(^9\)\(^9\) we...
Sixty eight (5.4%) women in the screened group tested positive for chlamydia at baseline. PO contacted 65 of the women to ask them to attend their local genitourinary medicine clinic or general practitioner for treatment and partner notification. Two women could not be contacted directly as their mobile telephone number was not working, they did not provide an email address, and they had requested no post to the home address. The college nurses contacted them for us. A further chlamydia positive sample from the 35 intervention samples unintentionally put in the freezer was not tested for 12 months. When telephoned after 1-2 months, 59 women confirmed they had been treated: 36 at a genitourinary medicine clinic, 12 by their general practitioner, and three at a community sexual health clinic. Eight women did not provide details. When control samples were tested 12 months after recruitment, 75 (5.9%) were positive for chlamydia.

### RESULTS

Between September 2004 and October 2006, 2563 eligible women were recruited and randomised (figure). We were unable to obtain information on all non-participants, but recruitment forms completed early in the study suggested 41% of 956 ineligible women had never had sexual intercourse, 24% were outside the age range, and 13% had been tested for chlamydial infection in the previous three months.\(^13\) A survey during three recruitment sessions suggested that eligible women refusing to participate were more likely than responders to be from ethnic minority groups.\(^14\) After 34 exclusions (figure), 2529 women (mean age 20.9 years) were included in the study. Baseline characteristics of participants were similar between the screened and deferred screening groups except that more women in the screened group reported symptoms in the six months before recruitment (table 1).

### Table 1 | Baseline characteristics of 2529 women allocated to immediate or deferred screening for Chlamydia trachomatis. Values are percentages (numbers) unless stated otherwise

| Characteristics | Screened women (n=1259) | Deferred screening controls (n=1270) |
|-----------------|-------------------------|-------------------------------------|
| Age (years):    |                         |                                     |
| <20             | 44.2 (557)              | 44.6 (567)                          |
| 20-24           | 46.5 (585)              | 43.3 (550)                          |
| ≥25             | 9.3 (117)               | 12.0 (153)                          |
| Ethnicity:      |                         |                                     |
| White           | 63.0 (787)              | 60.1 (758)                          |
| Black Caribbean| 8.5 (106)               | 9.5 (120)                           |
| Black African   | 15.3 (191)              | 17.4 (220)                          |
| Black other     | 2.3 (29)                | 1.7 (22)                            |
| South Asian     | 3.0 (35)                | 2.8 (35)                            |
| Chinese         | 1.0 (11)                | 0.7 (9)                             |
| Other           | 7.3 (91)                | 7.8 (98)                            |
| Recruited at university*| 69.5 (875) | 66.7 (847)                          |
| Cigarettes smoked per day: | n=1253 | n=1265 |
| None            | 66.9 (838)              | 69.9 (884)                          |
| 1-10            | 26.6 (333)              | 24.0 (304)                          |
| >10             | 6.5 (82)                | 6.1 (77)                            |
| Mean (SD) age at sexual debut | 16.4 (1.8); n=1233 | 16.5 (1.8); n=1247 |
| No of sexual partners in past year: | n=1251 | n=1262 |
| None            | 3.4 (42)                | 4.2 (53)                            |
| 1               | 52.0 (650)              | 54.6 (689)                          |
| 2               | 23.1 (289)              | 21.2 (268)                          |
| >2              | 21.6 (270)              | 20.0 (252)                          |
| Contraception:  |                         |                                     |
| None            | 7.6 (95)                | 8.0 (101)                           |
| Condoms         | 53.4 (664)              | 55.2 (695)                          |
| Contraceptive pill | 49.1 (610) | 46.4 (585) |
| Implant, injection, or patch | 5.1 (63) | 5.3 (67) |
| Coil            | 1.7 (21)                | 1.7 (22)                            |
| Douching        | 0.2 (2)                 | 0 (2)                               |
| Symptoms in past 6 months: | n=1242 | n=1254 |
| Pelvic pain     | 13.7 (170)              | 11.8 (148)                          |
| Dyspareunia     | 13.1 (163)              | 10.0 (125)                          |
| Bleeding between menstrual periods | 14.1 (175) | 11.3 (142) |
| Abnormal vaginal discharge | 12.6 (157) | 10.7 (134) |
| Any symptoms    | 36.6 (455)              | 31.3 (393)                          |
| Reported history of sexually transmitted infection ever: | n=1190 | n=1219 |
| Chlamydia†      | 5.9 (70)                | 6.6 (80)                            |
| Genital warts   | 1.2 (14)                | 1.2 (15)                            |
| Genital herpes  | 0.6 (7)                 | 0.9 (11)                            |
| Bacterial vaginosis | 0.9 (11) | 0.5 (6) |
| Gonorrhoea      | 0.3 (4)                 | 0.2 (2)                             |
| Reported history of pelvic inflammatory disease: | n=1252 | n=1265 |
|                 | 2.1 (26)                | 0.9 (12)                            |

*Not further education colleges.
†No results were available for 10 baseline samples (five intervention, five control). Three intervention samples were indeterminate or inhibitory and participants failed to return a repeat baseline postal sample, four samples leaked, and three control samples were either lost or the labels were illegible after defrosting.
Follow-up
Overall, 94% (2377/2529) of the women were followed up after 12 months. Nearly half (47%, 1108) replied by email, 32% (n=760) by postal questionnaire, 8% (n=199) by telephone, and 13% (n=310) were followed up by questionnaire to their general practitioner. The 152 women lost to follow-up were younger (mean age 20.0 years [SD 2.5] vs 21.0 [SD 2.8]; P<0.01) and more likely to be of black ethnicity (46% (68/149) vs 26% (620/2363); P<0.01) than the remainder. Table 2 gives details of the 396 women who were selected, on the basis of questionnaire responses, for more detailed assessment and search of medical records.

Incidence of pelvic inflammatory disease
The incidence of pelvic inflammatory disease was 1.3% (15/1191) in screened women compared with 1.9% (23/1186) in controls (relative risk 0.65, 95% confidence interval 0.34 to 1.34) (table 3). After adjustment for symptoms at baseline the relative risk was 0.57 (0.29 to 1.11). The overall incidence of pelvic inflammatory disease over 12 months was 1.6% (38/2377, 95% confidence interval 1.1% to 2.1%).

Rates of pelvic inflammatory disease were examined in the 137 women with chlamydial infection at baseline who were followed up for 12 months. Seven of 74 women in the deferred screening group developed clinical pelvic inflammatory disease (incidence 9.5%, 4.7% to 18.3%). All seven women were tested for C trachomatis at the time pelvic inflammatory disease was diagnosed and five tested positive. By comparison, only one of 63 (1.6%) screened and treated women positive for chlamydia developed clinical pelvic inflammatory disease (relative risk 0.17, 0.03 to 1.01).

Table 2 | Details of follow-up for potential pelvic inflammatory disease (PID) over 12 months. Values are numbers unless stated otherwise

| Variables | Screened women (n=1259) | Deferred screening controls (n=1270) |
|-----------|------------------------|-----------------------------------|
| % (No) followed up by questionnaire to participant or general practitioner | 94.6 (1191) | 93.4 (1186) |
| % (No) selected for additional record search for clinical details of potential PID: | 17.3 (218) | 14.0 (178) |
| Participant or general practitioner reported PID* | 12 | 9 |
| Laporoscopy | 16 | 24 |
| Visited doctor for abdominal or pelvic pain | 108 | 95 |
| Treated for urinary tract infection | 50 | 22 |
| Reported 3 of 4 symptoms† but did not report seeing doctor | 32 | 28 |

*Some participants were in more than one category, but each is included only once, in hierarchical order.
†Pelvic pain, dyspareunia, bleeding between menstrual periods, or abnormal vaginal discharge.

Table 3 | Incidence of pelvic inflammatory disease (PID) in 2377 women followed up for 12 months. Values are percentages (numbers) unless stated otherwise

| Variables | Screened women | Deferred screening controls | Relative risk (95% CI) | P value |
|-----------|----------------|----------------------------|------------------------|---------|
| All PID: probable* and possible† | 1.3 (15/1191) | 1.9 (23/1186) | 0.65 (0.34 to 1.22) | 0.19 |
| Probable PID | 0.80 (10/1191) | 1.3 (16/1186) | 0.62 (0.29 to 1.34) | 0.24 |
| Rate of PID in women who were positive for chlamydia at baseline | 1.6 (1/63) | 9.5 (7/74) | 0.17 (0.03 to 1.01) | 0.07 |

*Doctor assessed as probable—that is, clinical diagnosis of PID and treated; modified Hager’s criteria—pelvic pain, cervical motion tenderness, uterine or adnexal tenderness, and per rectum symptoms.
†Abdominal pelvic pain with features of PID, which may have responded to antimicrobial therapy, but no record of cervical excitation or uterine or adnexal tenderness; or long standing abdominal pain consistent with endometriosis, but some features of PID—for example, uterine tenderness, and unable to confirm if antimicrobial therapy had a benefit.
were positive for chlamydia at baseline were more likely than those who were negative to report having been tested independently (43%, 29/67 v 24%, 229/968; P<0.001).

DISCUSSION

The risk of clinical pelvic inflammatory disease over 12 months in women screened for C trachomatis was non-significantly reduced by 35%. The overall incidence of pelvic inflammatory disease was, however, low (1.6%). In 137 women with chlamydial infection at baseline, 9.5% in the deferred screening control group developed pelvic inflammatory disease compared with only 1.6% in the screened group. Over 90% (67/74) of control women with chlamydial infection at baseline did not develop clinical pelvic inflammatory disease; and most cases (79%, 30/38) of pelvic inflammatory disease, including 10 cases of chlamydia positive pelvic inflammatory disease, occurred in women who were negative for chlamydia at baseline, suggesting these were incident infections.

Strengths and limitations of the study

This is the first trial of chlamydia screening to obtain samples for delayed chlamydia testing from the control women. Analysis of these samples enabled us to provide novel data on the risk of pelvic inflammatory disease in untreated women positive for chlamydia in the community, which can now be used for modelling and cost effectiveness studies. Second, this is the first UK study to provide prospective data on the overall risk of clinical pelvic inflammatory disease in a large cohort of sexually active young women in the community. Thirdly, this is the most robust trial to date. Randomisation was done blind and after recruitment and the main outcome was assessed blind. The 94% follow-up was a major achievement in this young, mobile, mainly inner city population, requiring repeated telephone calls and emails. We also obtained data on independent chlamydia testing and treatment in both groups. Participants came from a wide range of backgrounds and included 1124 sexually active teenagers of whom 46% came from ethnic minorities. As in the English national chlamydia screening programme, we used self taken samples and routine management of infected women. Vaginal swabs are more sensitive than urine samples for the detection of chlamydia.

The main weakness is that despite a similar sample size (2529 v 2607) and incidence of pelvic inflammatory disease (1.6% v 1.7%) to the Scholes trial, screening twice as many women (1259 v 643) and treating more women with chlamydial infection (67 v 44), the trial was underpowered. The annual incidence of pelvic inflammatory disease was less than the 3% used in the sample size calculations, and screening did not reduce the risk by at least 50%. Secondly, participants were advised to be screened independently, and the one in five who acted on this advice had a high prevalence of chlamydial infection. The rate of independent testing reported by women in the deferred screening group who were positive for chlamydia at baseline was even higher (43%). It is likely that this reduced the effect of the intervention. Thirdly, the clinical diagnosis of pelvic inflammatory disease lacks sensitivity and specificity, which is also likely to attenuate the effect size. The diagnosis of pelvic inflammatory disease depended on the women seeing a health professional, and the women’s reports of possible symptoms or consultations for pelvic inflammatory disease may be unreliable, particularly for those who could be followed up only by telephone questionnaire (10% of controls, 7% of screened women), and who might tend to respond negatively to questions. We were able to obtain detailed medical records only of the 17% of women with potential pelvic inflammatory disease. In addition, the medical records were sometimes incomplete and many women changed address and general practitioner during the study period or attended different hospitals and clinics. Finally, as with all randomised clinical trials, the study has limited generalisability and may not apply to different populations such as women attending healthcare facilities, those from different ethnic groups, higher risk women such as sex workers, or non-UK populations.

Comparison with other studies

Only two trials have been carried out on chlamydia screening to prevent pelvic inflammatory disease in non-pregnant women. These were done in the United States and Denmark and started in 1990 and 1997. The trial by Scholes et al involved 2607 women from a health maintenance organisation. However, over a third of the women (n=364) in the intervention group were not screened, and these women had a lower rate of pelvic inflammatory disease (0.5%, 2/364) leading to a relative risk of pelvic inflammatory disease in those allocated to screening compared with usual care of 0.44 (95% confidence interval 0.20 to 0.90). Pelvic inflammatory disease is polymicrobial, but in many cases no pathogens are isolated. If chlamydial infection is implicated in only about 30% of cases of pelvic inflammatory disease, even if screening and treatment prevented all cases of pelvic inflammatory disease due to chlamydia, it would be unlikely to halve the overall risk of pelvic inflammatory disease. Recently, the

Table 4 | Reported symptoms of potential pelvic inflammatory disease and sexual behaviour over 12 months in 2057 women who completed follow-up questionnaires

| Reported symptoms and behaviour | Screened women (n=1029) | Deferred screening controls (n=1028) | % (No) of women |
|---------------------------------|----------------------------|-------------------------------------|----------------|
| Pelvic pain                     | 11.0 (113)                 | 10.2 (105)                          |                |
| Dyspareunia                     | 10.9 (112)                 | 9.3 (96)                            |                |
| Bleeding between menstrual periods | 13.5 (139)               | 12.8 (132)                          |                |
| Abnormal vaginal discharge      | 15.2 (156)                 | 13.0 (134)                          |                |
| Any symptom                     | 34.0 (350)                 | 31.3 (322)                          |                |
| >2 sexual partners in past 12 months | 36.7 (367); n=1001        | 37.6 (377); n=1003                  |                |
| Condom use                      | 56.5 (557); n=9985         | 56.5 (557); n=9985                  |                |
| Sexually transmitted infection in past 12 months | 4.8 (48); n=1007 | 5.2 (52); n=1000                   |                |
WHAT IS ALREADY KNOWN ON THIS TOPIC

Chlamydia trachomatis can cause pelvic inflammatory disease (PID) leading to tubal infertility and ectopic pregnancy.

Annual testing of all sexually active women aged 24 or less is widely recommended and many developed countries have set up chlamydia screening programmes.

The evidence base has been questioned.

WHAT THIS STUDY ADDS

While screening and treatment of chlamydial infection might reduce the risk of clinical PID over 12 months, especially in women with chlamydial infection at baseline, most cases of PID occurred in women who tested negative for chlamydia at baseline, suggesting incident infection.

The effectiveness of a single chlamydia test in preventing PID over 12 months might have been overestimated.

Policy makers might consider focusing on more frequent testing of those at higher risk, such as those with a recent change of sexual partner or history of chlamydial infection in the past three months.

Findings by Scholes et al have been suggested as fortuitous.

In a later trial in 1700 female high school students, Ostergaard et al found that 2.1% of those in the home sampling group and 4.2% in the usual care group reported treatment for pelvic inflammatory disease when interviewed after a year. Ascertainment of pelvic inflammatory disease was, however, unblinded and nearly 50% of the women were lost to follow-up. In addition, reports by the women might be unreliable, as masked analysis of clinical data in our trial confirmed pelvic inflammatory disease in only 11 of the 21 women whose questionnaires reported that they had had pelvic inflammatory disease. Finally, the incidence of pelvic inflammatory disease in our trial was slightly lower than the 2.3% found in similar aged women attending English and Welsh general practices. The women in our study with pelvic inflammatory disease were assessed by doctors in genitourinary medicine, and both coding and diagnosis may be more reliable. It is, however, likely that the incidence of pelvic inflammatory disease would be higher in those lost to follow-up, sexually active teenagers aged <16, or those not in education.

Implications

This is the only chlamydia screening trial with this design ever likely to be done in a developed country. This is because of ethical issues with delayed chlamydia testing and the widespread introduction of chlamydia screening programmes. Although some evidence shows that screening reduced rates of pelvic inflammatory disease, especially in women with chlamydial infection at baseline, the absolute number of cases prevented was small. Our findings suggest that to prevent one case of clinical pelvic inflammatory disease over 12 months, it may be necessary to screen 147 women for chlamydial infection or to treat 13 women who are positive for chlamydia. These numbers are greater than previously suggested. If the incidence of pelvic inflammatory disease in women with chlamydial infection has been overestimated, and particularly if it is less than 10%, then the cost effectiveness of screening might be exaggerated.

Most cases of pelvic inflammatory disease over 12 months were not prevented by a single chlamydia screen and occurred in women who were negative for chlamydia at baseline. This suggests the importance of incident infection. Policy makers might consider focusing on more frequent testing of those at higher risk, such as women with a new sexual partner or a recent history of chlamydial infection.

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Ethical approval: This study was approved by Wandsworth research ethics committee (reference 03.0012).

Data sharing: No additional data available.

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