CHLAMYDIA

Incidence of severe reproductive tract complications associated with diagnosed genital chlamydial infection: the Uppsala Women's Cohort Study

N Low, M Egger, J A C Sterne, R M Harbord, F Ibrahim, B Lindblom, B Herrmann

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See end of article for authors' affiliations

Correspondence to: Dr Nicola Low, Department of Social and Preventive Medicine, University of Bern, Finkenhubelweg 11, Bern, CH-3012, Switzerland; low@ispm.unibe.ch

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Objective: To estimate the cumulative incidence of severe complications associated with genital chlamydia infection in the general female population.

Methods: The Uppsala Women's Cohort Study was a retrospective population based cohort study in Sweden, linking laboratory, hospital, and population registers. We estimated the cumulative incidence of hospital diagnosed pelvic inflammatory disease, ectopic pregnancy, and infertility, and used multivariable regression models to estimate hazard ratios according to screening status.

Results: We analysed complete data from 43 715 women in Uppsala aged 15–24 years between January 1985 and December 1989. Follow up until the end of 1999 included 709 000 woman years and 3025 events. The cumulative incidence of pelvic inflammatory disease by age 35 years was 3.9% (95% CI 3.7% to 4.0%) overall: 5.6% (4.7% to 6.7%) in women who ever tested positive for chlamydia, 4.0% (3.7% to 4.4%) in those with negative tests, and 2.9% (2.7% to 3.2%) in those who were never screened. The corresponding figures were: for ectopic pregnancy, 2.3% (2.2% to 2.5%) overall, 2.7% (2.1% to 3.5%), 2.0% (1.8% to 2.3%), and 1.9% (1.7% to 2.1%); and for infertility, 4.1% (3.9% to 4.3%) overall, 6.7% (5.7% to 7.9%), 4.7% (4.4% to 5.1%), and 3.1% (2.8% to 3.3%). Low educational attainment was strongly associated with the development of all outcomes.

Conclusions: The incidence of severe chlamydia associated complications estimated from ours, and other population based studies, was lower than expected. Studies that incorporate data about pelvic inflammatory disease diagnosed in primary care and behavioural risk factors would further improve our understanding of the natural history of chlamydia. Our results provide reassurance for patients, but mean that the benefits of chlamydia screening programmes might have been overestimated.

Infection with *Chlamydia trachomatis* is the most common preventable cause of pelvic inflammatory disease in young women, and may lead to ectopic pregnancy and tubal infertility.[1] Reliable information about the complications of lower genital tract chlamydia infection is required so that patients can be better informed of the risks of infection, and the likely impact of preventive interventions can be determined. The fertility outcomes of women admitted to hospital with pelvic inflammatory disease have been studied in detail in Lund, Sweden,[2–4] although information about previous chlamydia infections is lacking. In addition, authoritative sources state that up to 40% of untreated endocervical chlamydia will progress to pelvic inflammatory disease.[5 6] There are several reasons, however, for questioning the generalisability of this information.[7] Firstly, data from studies of clinical populations might overestimate progression rates if they include more severe cases.[7 8] Secondly, the symptoms and signs of pelvic inflammatory disease are non-specific, and diagnosis without the aid of laparoscopy is difficult.[9] Thirdly, there are many causes of pelvic inflammatory disease and an aetiological role for *C trachomatis* cannot be unequivocally established or excluded, particularly after the acute infection has resolved. Finally, recorded numbers of chlamydia associated complications in population based studies are lower than would be expected from clinical research (table 1).[8 10–15]

Investigating the natural history of genital chlamydia remains problematic since prospective long term studies of untreated infection would clearly be unethical. The best opportunity to investigate associations between chlamydia and its long term consequences therefore comes from places in which chlamydia status and outcomes of chlamydia associated disease can be ascertained for large numbers of women. Sweden has the world's longest established chlamydia control activities: opportunistic screening has been undertaken nationwide since the late 1980s.[16–18] In Uppsala County (population 270 000), chlamydia screening is advised for women aged 15–29 years attending family planning clinics or other consultations for contraceptive purposes, pregnant women, and all attenders at five youth clinics,[17] but there is no stated screening interval and no monitoring of uptake. The objective of this study was to describe the frequency of hospital diagnosed complications of chlamydia and to estimate their incidence in young women in Uppsala County, Sweden.

METHODS

The Uppsala Women's Cohort Study included all 93 284 women resident in Uppsala and aged 15–39 years at any time between 1 January 1985 and 31 December 1989 (fig 1).[19] We attempted to follow the chlamydia screening histories and hospital diagnosed complications of these women from 1 January 1985 to 31 December 1999. We used the ''person number,'' a unique identifier assigned at birth or immigration to link the results of laboratory tests for chlamydia, hospital diagnoses, and sociodemographic data. The study was approved by the University of Uppsala research ethics committee. The source databases are described below.

Demographic and socioeconomic information

Statistics Sweden used population registers to construct a dataset of eligible women and provided data on country of

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Table 1 Population based estimates of chlamydia associated complications

Outcome and study setting	Ref	Period	Population	Study design	Cases	Age (years)	Incidence per 1000 woman years		
Pelvic inflammatory disease									
All women							Overall	Screened	Unscreened
Amsterdam, Netherlands	8	1990	Population based	Disease register	Hospital†	15–44	4.85	..	..
South Carolina, USA	10	1996–8	Military recruits	Cohort study	Clinical‡	80%<25 at entry	..	4.6	5.1
Aarhus, Denmark	11	1997–8	Population based	Randomised trial	Hospital§	16–17 at entry	6.5	2.4	11.5
					All cases§		31.2	19.2	53.2
Seattle, USA	12	1990–2	High risk women	Randomised trial	All cases¶	18–34 at entry	16.9‡	9.6	21.6
England and Wales	13	1991–2	Population based	Cross sectional	Primary care	16–46	16.7	..	..
Women with chlamydia									
Massachussetts, USA	14	1988–1	Population based	Cohort study	All cases¶	20–29 at entry	56.3†	..	..
Ectopic pregnancy							Overall	Chlamydia +	Chlamydia -
N Jutland, Denmark	15	1984–2003	Population based	Cohort study	Hospital**	15–43 at entry		3.5	8.6

†Data from city disease registry. Not clear if primary care cases are included. Authors estimated rate of chlamydial pelvic inflammatory disease as 1.7 cases per 1000 woman years.
‡Inpatient episodes only of pelvic inflammatory disease as a result of any cause.
§Hospital cases from hospital registers. All cases ascertained by patient report. Data collected at 1 year after intervention so assumed that each woman contributed 1 woman year of follow up. 45% lost to follow up. Includes pelvic inflammatory disease as a result of any cause.
¶Cases ascertained from health insurance records.
**From record linkage.

birth, migration, educational attainment, and numbers of births and deaths. We measured the material conditions of each woman based on her family's income recorded in the census closest to her 15th birthday because many women in the cohort were still at school or college during the study period. We did not have data about age at sexual debut, contraceptive practices, sexual behaviour, or healthcare seeking behaviour.

Chlamydia screening

All tests for *C trachomatis* are carried out at the University Hospital of Uppsala. Culture (sensitivity 75% compared to polymerase chain reaction[20]) was the diagnostic method for most samples until polymerase chain reaction (Amplicor CT Test, Roche Diagnostics, Basel, Switzerland) sensitivity compared to a combined reference standard 85–90%[20]) was introduced in 1996. We used a database of all chlamydia tests from 1985 to 1996, after which record linkage was not possible. Tests done outside Uppsala County were not available. Information about symptoms was not available: in this paper we refer to tests done for any purpose as screening tests.

Hospital diagnoses

The Centre for Epidemiology provided information about hospital diagnoses anywhere in Sweden from 1985 to 1999 so follow up for inpatient diagnoses was complete. We also used the Uppsala Hospital Discharge Database, which allowed us to include cases of ectopic pregnancy and pelvic inflammatory disease managed as outpatients from 1993 to 1999. We included all diagnoses of ectopic pregnancy (International Classification of Disease 10th Revision codes corresponding to ICD 10.00), pelvic inflammatory disease (N70, 71, 73, 74), and infertility (N97).

Record linkage

Statistics Sweden supplied a list of person numbers of the whole cohort to the Centre for Epidemiology and Uppsala University Hospital, both of which returned data on hospital diagnoses. Statistics Sweden then linked chlamydia test results, hospital diagnoses, and census data to the population register before deleting the person number and anonymising the dataset. For this study, we restricted the cohort to women resident in Uppsala who were 15–24 years old from 1985 to 1989 because chlamydia testing histories were most complete in this age group.

Statistical analysis

We restricted analysis to women with complete data on socioeconomic variables. We used survival analysis methods with age as the time axis and delayed entry at the date when each woman was first living in Uppsala County and aged 15–24 years. Each woman's screening test history was used to divide her follow up time into one or more of three exposure groups. Until the date of her first screening test, follow up time was classified as ''never tested.'' If the test was negative, subsequent follow up time was classified as ''negative.'' All follow up time subsequent to a positive test result was classified as ''positive.'' Follow up was censored when the woman experienced an outcome, when she left Uppsala County, or on 31 December 1999, whichever came first. We derived Kaplan-Meier estimates of the cumulative incidence (%, 95% confidence intervals, CI) of each outcome, and used Cox proportional hazards regression models to estimate the association of screening status with the hazard of developing each outcome, controlling for potential confounding by age, education, income, and housing. We used likelihood ratio tests to investigate interactions. Statistical analyses were

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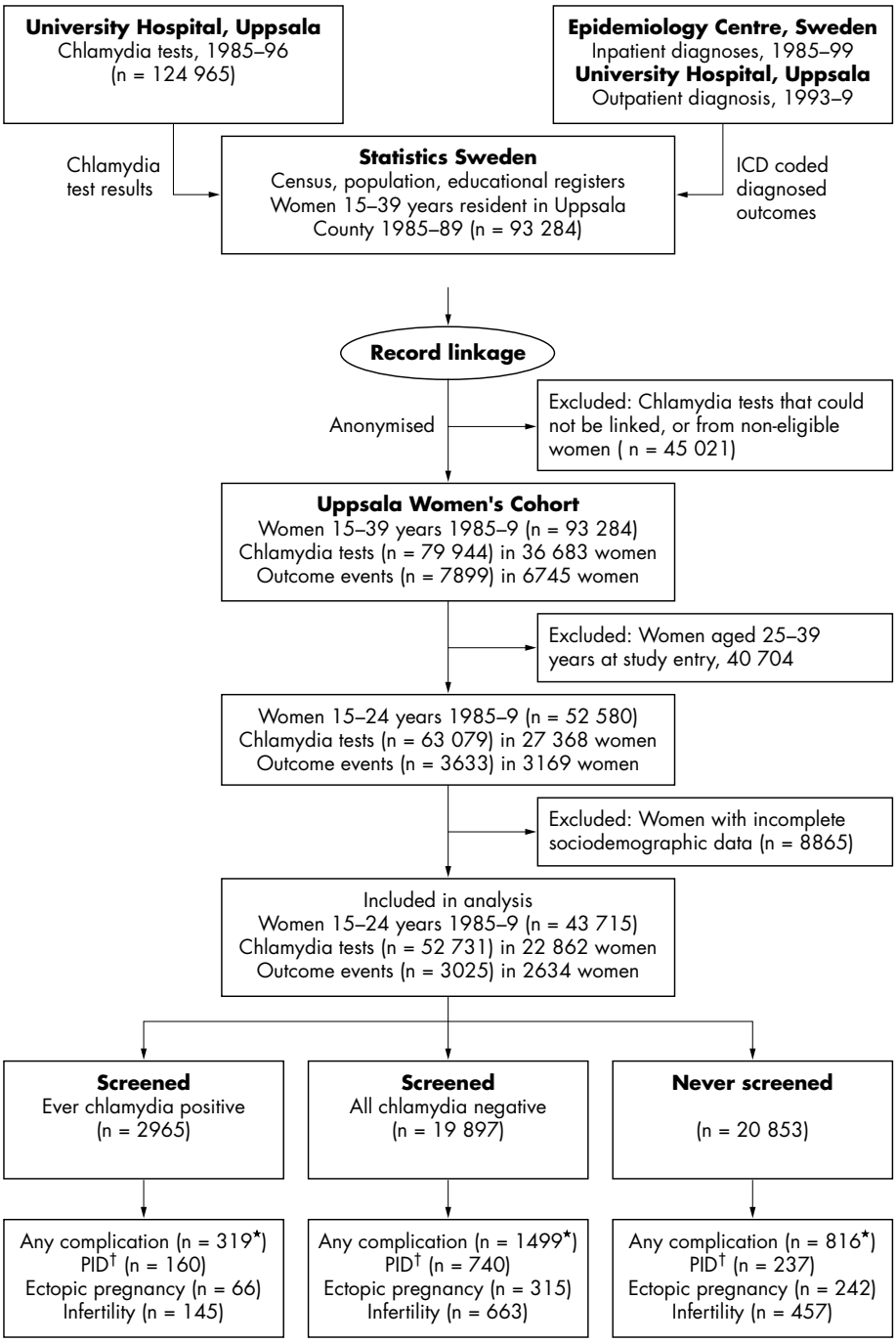


Figure 1 Record linkage in the Uppsala Women's Cohort Study. *Some women experienced more than one complication so the sum of individual complications is greater than the number with any of the three; †PID, pelvic inflammatory disease.

done using Stata (version 8.2, Stata Corporation, College Station, Austin, Texas).

RESULTS

Among the female resident population of Uppsala County from 1985 to 1989 there were 52 580 women aged 15–24 (fig 1). The subsequent analyses include 43 715 (83.1%) with complete information about socioeconomic characteristics, who contributed 709 000 (median 15 years) woman years of follow up until 31 December 1999. The characteristics of those with and without socioeconomic information were similar, although more younger women had complete data (data not shown).

The cumulative probability of ever being screened for chlamydia was 70.7% (95% CI 70.3% to 71.1%) by age 35 years. Of 22 862 women ever tested 47.8% (n = 10945) were tested once, 22.2% (n = 5081) had two tests, and 30.0% (n = 6877) had three or more tests. There were only 259 (1.1%) women who had 10 or more tests over the entire follow up period. Younger women, aged 15–19, were slightly more likely than 20–24 year olds to have been tested more than once (52.8% *v* 50.5%, p = 0.002). Among women screened, 11.5% (n = 2626) had one positive chlamydia test, 1.3% (n = 298) had two, and 0.2% (n = 41) had three or four episodes of infection.

During the study period 2634 women experienced any hospital diagnosed complication, including 1138 episodes of pelvic inflammatory disease, 623 ectopic pregnancies and 1265 women diagnosed with infertility (fig 1). Of these women, 816 (31.0%) had never been screened, 1499 (56.9%)

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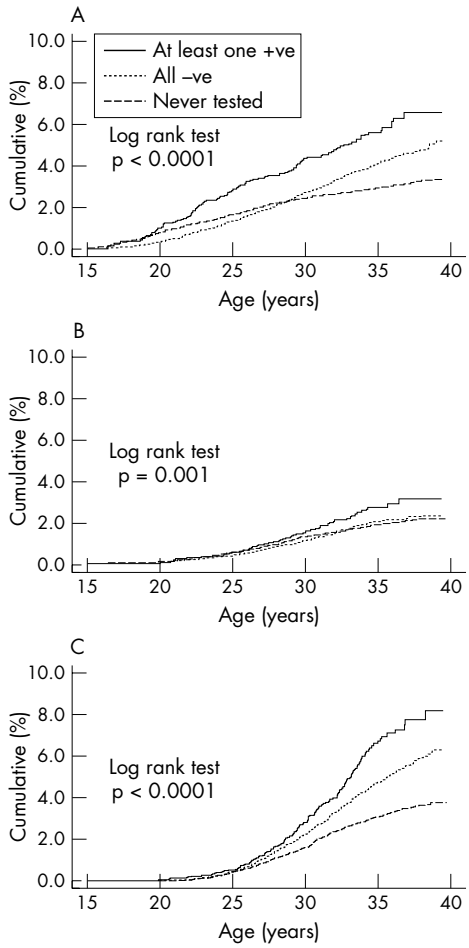


Figure 2 Incidence of hospital diagnosed conditions associated with chlamydia. (A) Pelvic inflammatory disease; (B) ectopic pregnancy; (C) infertility.

had only negative tests, and 319 (12.1%) had had a positive chlamydia test. The proportions of women experiencing any outcome among those who had had none, one, two, or three or more tests were 4.0%, 6.1%, 7.2%, and 11.3%, respectively (p for trend <0.0001). The odds of experiencing any complication were slightly higher in women with more than one episode of infection (odds ratio 1.35, 95% CI 0.97 to 1.9, p = 0.076).

Figure 2 shows the cumulative incidence of hospital diagnosed chlamydia associated conditions by age and time updated screening status. The cumulative incidence of experiencing pelvic inflammatory disease by age 35 years was 3.9% (95% CI 3.7% to 4.0%) overall: 5.6% (4.7% to 6.7%) in women who ever tested positive for chlamydia, 4.0% (3.7% to 4.4%) in those with negative tests, and 2.9% (2.7% to 3.2%) in those who were never screened. The corresponding figures were: for ectopic pregnancy, 2.3% (95% CI 2.2% to 2.5%) overall, 2.7% (2.1% to 3.5%), 2.0% (1.8% to 2.3%), and 1.9% (1.7% to 2.1%); and for infertility, 4.1% (95% CI 3.9% to 4.3%) overall, 6.7% (5.7% to 7.9%), 4.7% (4.4% to 5.1%), and 3.1% (2.8% to 3.3%).

Table 2 shows associations between chlamydia screening status and each outcome. In univariable analyses, the crude hazard of developing each event was higher in women with previous positive chlamydia tests than those with previous negative tests and in women with fewer years of schooling. These associations were attenuated after controlling for socioeconomic factors; the adjusted hazard of experiencing

Table 2 Associations between chlamydia screening, hospital diagnosed complications, and socioeconomic factors

	Pelvic inflammatory disease*			Ectopic pregnancy*			Infertility*		
	Hazard ratio (95% CI)			Hazard ratio (95% CI)			Hazard ratio (95% CI)		
Variable	Crude	Adjusted†	p value‡	Crude	Adjusted†	p value‡	Crude	Adjusted†	p value‡
Chlamydia test									
Never	0.69 (0.61 to 0.78)	0.72 (0.63 to 0.82)	<0.0001	0.98 (0.83 to 1.15)	0.95 (0.80 to 1.13)	0.160	0.60 (0.53 to 0.67)	0.65 (0.57 to 0.73)	<0.0001
All negative	1 (reference)	1 (reference)		1 (reference)	1 (reference)		1 (reference)	1 (reference)	
Positive	1.50 (1.23 to 1.82)	1.27 (1.04 to 1.55)		1.42 (1.06 to 1.88)	1.26 (0.94 to 1.67)		1.38 (1.15 to 1.66)	1.31 (1.09 to 1.57)	
Educational level									
Graduate	1 (reference)	1 (reference)	<0.0001	1 (reference)	1 (reference)	<0.0001	1 (reference)	1 (reference)	<0.0001
High school	1.52 (1.25 to 1.84)	1.48 (1.22 to 1.80)		1.22 (0.97 to 1.54)	1.28 (1.01 to 1.62)		1.26 (1.09 to 1.47)	1.23 (1.06 to 1.43)	
Vocational	3.20 (2.66 to 3.84)	2.86 (2.36 to 3.47)		2.32 (1.86 to 2.89)	2.16 (1.70 to 2.73)		1.88 (1.63 to 2.18)	1.85 (1.58 to 2.16)	
Basic	5.38 (4.39 to 6.59)	4.51 (3.62 to 5.61)		3.43 (2.64 to 4.45)	3.04 (2.29 to 4.04)		1.55 (1.25 to 1.92)	1.51 (1.20 to 1.89)	
Total numbers	1095 events			621 events			1265 events		

*Models restricted to 43715 women under 25 years at study entry with complete data. All models controlled for age.
†Adjusted models control for chlamydia test status, educational level, housing type, income, number of births, and census year.
‡p Value refers to adjusted model.

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each event was about 30% higher in women with previous positive compared to previous negative tests for all three complications. Low educational level remained strongly associated with developing complications before and after controlling for other factors, including chlamydia screening. There was no evidence of interaction between chlamydia screening status and educational level (likelihood ratio tests for pelvic inflammatory disease, p = 0.258; ectopic pregnancy, p = 0.223; infertility, p = 0.397).

DISCUSSION

In this large Swedish population based cohort, 71% of women aged 15–24 at study entry were screened for chlamydia and 13% of those screened had at least one episode of chlamydia. Nearly half of screened women had only one test. Between 2% and 4% overall and between 3% and 7% of women with a previously diagnosed episode of chlamydia experienced a hospital diagnosed episode of ectopic pregnancy, pelvic inflammatory disease or infertility by age 35 years. Low educational status was strongly independently associated with all three chlamydia associated complications.

Methodological issues

The strengths of this study are that it is a large long term population based cohort study that included all young women in a Swedish county from the time that widespread chlamydia testing was introduced. The level of record linkage was excellent, and ascertainment of both exposure and outcomes was high. Our longitudinal analyses took into account both age and the temporal sequence of chlamydia testing and development of outcomes.

The limitations of the study relate to the use of routine datasets and to inherent problems in studying the complications of a largely asymptomatic but curable condition. Firstly, our outcomes were defined by ICD coded hospital discharge records with diagnoses made by clinicians who might have applied different diagnostic criteria. Ectopic pregnancy diagnosis is objective and specific and our estimated incidence should be complete because we included outpatient cases from 1993, when methotrexate treatment became widespread.[21] The sensitivity and specificity of hospital diagnosed pelvic inflammatory disease and infertility are, however, imperfect. Complete ascertainment of infertility is not possible because it depends on women presenting for investigation. For pelvic inflammatory disease, 61% of ICD coded diagnoses in a recent Australian study were confirmed laparoscopically.[22] The largest source of underestimation of pelvic inflammatory disease is because up to 90% of cases could be diagnosed in primary care.[13 23] Although we were able to include outpatient diagnoses from 1993 we could not count these cases from 1985 to 1992 and we could not include cases managed in primary care. It would, however, be inappropriate to simply multiply the observed rate to account for under-ascertainment if hospital diagnosed cases differed from those diagnosed in primary care. Although there are similarities between acute and subclinical pelvic inflammatory disease,[24] mild cases treated in primary care might be less likely to cause tubal damage. Attributing all diagnosed cases of complications to chlamydia compensates for some under-reporting. For all three conditions we included all diagnosed cases although clinical diagnosis of pelvic inflammatory disease is known to be imprecise and chlamydia was only one possible cause.[9] Another source of under-ascertainment was that in women with diagnosed chlamydia, ascending infection might have been prevented by antibiotic treatment. We do not think that this led to a substantial underestimate in our study because of infrequent screening. Indeed, only 12% of complications occurred in women with a positive chlamydia test: the remainder were in women who had only negative tests or had never been tested. This indicates that the episode of chlamydia which might have caused the condition was untreated and that the natural history was unaffected by treatment. There is no evidence that single dose antibiotic treatment reduces the progression of lower genital tract chlamydia than multiple dose regimens so this is unlikely to have had an impact.[25]

Chlamydia test status is a proxy for the true exposure, chlamydia infection. A positive test might not indicate newly acquired infection, women with either no or only negative tests might have had test results that could not be linked or undiagnosed infection, and culture diagnosis will have missed some infections. Such misclassification would attenuate observed associations between chlamydia infection and its complications. This is suggested by our finding of a stronger association between the risk of sequelae and educational level than chlamydia status. The low risk of complications in women who were never screened suggests that this group of women were at low risk of chlamydia. Women who were not screened were different from women who underwent screening: they were more likely to have a university education and to be older and from families with high incomes (data not shown). These characteristics are partly a proxy for sexual behaviour, for which we did not have information. The incomplete coverage of screening also suggests an important contribution of both physicians' and women's perceptions of risk and decisions to offer, and accept, screening. The factors associated with chlamydia screening, and implications for screening programmes are a separate research question that will be addressed in a subsequent publication. These issues do not change the main finding of this study—that the risk of serious hospital diagnosed complications associated with chlamydia observed over a long period of time in the general population is lower than expected from studies in clinical populations.

Comparison with other prospective studies

Population based randomised controlled trials and cohort studies suggest that the overall incidence of hospital diagnosed pelvic inflammatory disease is 5–7 per 1000 woman years,[8 10 11] and 17–31 per 1000 woman years including cases diagnosed in primary care (table 1).[11–13] We estimated an incidence of hospital diagnosed pelvic inflammatory disease of 1.9 (95% CI 1.8 to 2.0) per 1000 woman years. In women with chlamydia, incidence rates of pelvic inflammatory disease diagnosed in all settings,[14] and hospital diagnosed ectopic pregnancy,[15] were estimated to be 56 and 4 per 1000 women years, respectively. While many of these studies suffer from the limitations outlined above, the estimated incidence rates of complications were consistently lower than from studies in clinical populations. These have found that up to 40% of untreated cervical chlamydial infections result in pelvic inflammatory disease within a few weeks,[26 27] and that 20–25% of women with pelvic inflammatory disease from any cause will have an ectopic pregnancy or become infertile.[2–4] This suggests that clinic based studies included women with more severe disease that was more likely to progress.[8]

Meaning of the study

A diagnosis of chlamydia makes women fearful about their future fertility.[28] Many asymptomatic infections detected during screening will have been present for some time and clinicians need to be able to give reliable advice to infected women about the probability of reproductive damage. Current advice suggests high rates of complications based on studies in clinic and hospital populations,[5 6] and higher risks of complications with repeated infection.[29] Our study, together with other population based data, provides

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Key messages

- Studies of hospital and clinic populations suggest that up to 40% of cases of untreated chlamydia progress to pelvic inflammatory disease within a few weeks of infection, and that 20–25% of women with pelvic inflammatory disease will have an ectopic pregnancy or become infertile
- In a long term observational cohort study of young women in Uppsala County, Sweden, the cumulative incidences of hospital diagnosed pelvic inflammatory disease, ectopic pregnancy, and infertility by age 35 were 2–4% overall and 3–7% in those with a history of diagnosed chlamydia
- These findings, which are consistent with the findings of other population based studies, should be used to reassure patients
- If the incidence of complications associated with chlamydia have been overestimated then the benefits and cost effectiveness of current screening programmes might also have been exaggerated

reassurance that the long term risks of being hospitalised with pelvic inflammatory disease, ectopic pregnancy, and infertility following a positive chlamydia test are lower than previously thought. Ectopic pregnancy and infertility are consequences of pelvic inflammatory disease, rather than the lower genital tract infection. We were unable to estimate these rates directly: our study was an observational cohort and, as observed in clinical practice, most episodes of ectopic pregnancy and infertility (about 85%) were not preceded by a documented episode of pelvic inflammatory disease. Furthermore, few women had repeated episodes of diagnosed chlamydia, probably because of the low frequency of screening, so we could not examine the association with repeated infections. There is now a need for ethical prospective studies to define the prognosis of genital chlamydial infection even better, by incorporating information about sexual behaviour and other risk factors, and about the aetiology of diagnosed complications.

Implications for research and health policy

Our findings suggest that the cost effectiveness of chlamydia screening might have been overestimated.[7 8] Economic evaluations typically assume that annual chlamydia screening uptake is 60–100% and apply estimates of disease progression based on clinical populations to all cases of asymptomatic chlamydia detected by screening.[30–33] An increasing number of studies show that about 50% of asymptomatic prevalent chlamydia infections resolve spontaneously within a year with little risk of pelvic inflammatory disease,[34–36] so the incidence of major outcomes is probably overestimated. These evaluations are also frequently based on static models that do not account for the effects of re-infections and spontaneous resolutions of chlamydia on population transmission.[37 38] In practice, the uptake of opportunistic chlamydia screening in target groups in the United States is well below 50%,[39 40] and our study suggests that complications in the general population are less common than in clinical settings. There is now a need for high quality dynamic economic modelling studies based on realistic assumptions about the uptake and frequency of screening, and the likelihood of severe reproductive tract morbidity. A low incidence of chlamydial complications is good news for individual patients but raises questions about the presumed cost effectiveness of current chlamydia screening programmes.

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CONTRIBUTORS

NL, ME, BL, and BH designed the study and obtained funding; BH supervised the data collection; RH and FI did the statistical analyses under the supervision of JS and NL; NL drafted the manuscript; all authors contributed to revising the manuscript.

Authors' affiliations

N Low, M Egger, Department of Social and Preventive Medicine, University of Berne, Finkenhubelweg 11, CH-3012, Switzerland
N Low, M Egger, J A C Sterne, R M Harbord, F Ibrahim, MRC Health Services Research Collaboration, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, UK
B Lindblom, Department of Women's and Children's Health, University of Uppsala, Uppsala, Sweden
B Herrmann, Department of Clinical Mirobiology, Uppsala University Hospital, SE-751 85 Uppsala, Sweden

Conflict of interest: none declared.

Ethical approval: The research ethics committee of the Uppsala University Hospital approved this project.

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