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Title: Pelvic Inflammatory Disease and Salpingitis: incidence of primary and repeat episodes in England

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Running Head: Incidence of PID in England

Summary

Pelvic Inflammatory Disease (PID) and more specifically salpingitis (visually confirmed inflammation) is the primary cause of Tubal Factor Infertility and is an important risk factor for Ectopic Pregnancy. The risk of these outcomes increases following repeated episodes of PID. We develop a homogenous discrete time Markov model for the distribution of PID history in the UK. We use a Bayesian framework to fully propagate parameter uncertainty into the model outputs. We estimate the model parameters from routine data, prospective studies, and other sources. We estimate that for women aged 35-44, 33.6% and 16.1% have experienced at least one episode of PID and salpingitis respectively (diagnosed or not). 10.7% have experienced 1 salpingitis and no further PID episodes, 3.7% one salpingitis and one further PID episode, and 1.7% one salpingitis and 2 or more further PID episodes. Results are consistent with numerous external data sources, but not all. Studies of the proportion of PID that is diagnosed, and the proportion of PIDs that are salpingitis together with the severity distribution in different diagnostic settings and of overlap between routine data sources of PID would be of great value.

INTRODUCTION

Pelvic Inflammatory Disease (PID) is the primary cause of Tubal Factor Infertility (TFI) and an important risk factor for Ectopic Pregnancy (EP). It comprises a spectrum of upper genital tract inflammatory disorders among women, which includes any combination of endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis.[1] PID is difficult to diagnose and the criteria for a clinical diagnosis of PID have changed over time with the recognition that atypical milder clinical manifestations are common,[2, 3] but may still be associated with reproductive damage. In the UK national PID guideline 2011, recent onset of lower abdominal pain in association with local tenderness on bimanual examination is considered sufficient to establish a diagnosis and initiate treatment.[4] Clinical information can also be used to classify PID as "possible", "probable" and "definite" PID based on Hager's criteria.[5, 6] This classification is often used in clinical trials (e.g. POPI[7]) and in studies of patient data, such as the General Practice Research Database (GPRD).[6-8]

Over 50% of diagnosed PID episodes in England are treated in primary care, the remainder being treated in sexually transmitted infection (STI) clinics or hospital. Diagnosed PID underestimates true PID incidence as a relatively high proportion of PID is undiagnosed because of the range of clinical manifestations and difficulty in making a diagnosis [3, 9]. However, a cross-sectional study found that whilst 66% of TFI cases reported no previous diagnosis of PID, only 11% reported *never* having had clinical symptoms;[10] suggesting that whilst a large proportion of the PID that causes TFI is undiagnosed it usually isn't completely asymptomatic.

PID is mostly caused by sexually transmitted infections (STIs), such as *Chlamydia trachomatis* (CT), gonorrhoea, or bacterial vaginosis–associated microbes; by respiratory and

enteric pathogens that colonise the female genital tract, and, more rarely, infections introduced during surgery, abortion, or parturition[3, 11]

Much of our knowledge of the impact of PID on reproductive health is based on the Lund study[2, 12-14]. The study was based on laparoscopic examination of women with hospital-diagnosed PID. Women with clinical PID but with no salpingitis, defined as visible inflammation of the fallopian tubes, experienced EP and TFI at no more than the background rate. Incidence of EP and TFI among women with salpingitis depended on age and severity of index salpingitis, and increased markedly with the number of subsequent PID episodes.

On the basis of these findings, the present study sets out to provide estimates of population level age-specific mean incidence of PID and salpingitis, with a particular focus on the incidence of repeat episodes, as these appear specifically associated with poor reproductive outcomes. Our primary interest lies in natural history in the absence of screening for STI infections so we use data for 2002. We develop a homogenous Markov model to describe PID and salpingitis history in women in England. The estimates offer opportunities to validate risk estimates for infections that cause PID. Provide estimates of cumulative exposure for population attributable fraction calculations. And estimates of the exposure distribution allow results from cohort studies following patients with PID/salpingitis to be validated against population sequealea estimates. We estimate the model parameters using a variety of data sources and methods and validate the model against a number of external data sources.

MATERIALS AND METHODS

We develop an 8-state discrete time homogenous Markov structure with 1-year cycles to describe the distribution of PID and salpingitis (Figure. 1). The model is designed to estimate not only the cumulative incidence of episodes, but also the age-specific proportions of the population who have experience 1, 2, 3 or more episodes. Separate estimations are generated for three kinds of "episode": PID, salpingitis, and PID in women who have experienced salpingitis.

We assume women who have an episode of the type(s) specified in the model have a different (higher) rate of subsequent episodes for the next two years. This is based on the observation in the Lund cohort that the majority of women who experienced a second PID did so within 2 years. To allow the rate of progression to change with time since last episode the model includes 8 states and women may transition between these states as described in figure 1. The model does not consider what happens to women who have more than 3 episodes because data on the risk distribution of sequelae, and external validation data, do not distinguish between such women. The key model outputs from each model are the proportions of women in age group a in the general population who have experienced $i = 0,1,2,3+$ previous episodes or diagnosed episodes. These are simple functions of the model parameters (Web Supplementary Digital Content 1).

Model 1 – Distribution of clinical PID in the English general population

In this model episodes represent clinical PID. We make the assumption that the ratio of the incidence rate of PID in women who have had a PID in the last two years to women who have not is independent of age. We performed a literature search to identify all relevant sources of evidence for the model parameters and functions of the model parameters in England [9] (see Supplementary Digital Content 2). Note that these estimates are correlated

because they are estimated from the same data, and are therefore incorporated into the Markov model as a multivariate lognormal likelihoodwith co-variances calculated from the synthesis model.

Models 2 - distribution of salpingitis in the English population

In this model an episode represents salpingitis. We make the assumptions that the proportion of Clinical PID episodes that are salpingitis is independent of age and PID/salpingitis history. Note that in this model the higher rate only applies to women who have had a salpingitis within the previous two years and not women who have had a non-salpingitis PID. In addition to the data described above we require information on the proportion of clinical PID episodes that are salpingitis (see Supplementary Digital Content 2).

Models 3: distribution of PID in women with salpingitis history in the English population

A final model considers the proportion of women by age in England who have had at least 1 salpingitis episode. And the number of subsequent clinical PID episodes 0, 1, 2+ that they have had. So the first episode is salpingitis and the 2^{nd} and 3^{rd} episodes are PID. This model produces estimates that are comparable to the form of the data from the Lund studies allowing external validation of the model against these data.

Methodology for estimation and computation

Estimation is carried out using a Bayesian approach using Markov chain Monte Carlo (MCMC) simulation in WinBUGS Version 1.4.3[15] and the add-on package WBDev .

Posterior means and 95% credible intervals for parameters and model outputs are reported. This method ensures that all the uncertainty in the data and estimates for all parameters is fully propagated into the model outputs. Unless otherwise stated vague priors are employed throughout, so that results are dominated by the data. Further details are given in Supplementary Digital Content 3

Summary of assumptions

We have made the following key assumptions

1. The incidence rate for PID is the same within the age groups 16-19, 20-24, 25-34 and 35-44.
2. The incidence rate for PID in women younger than 16 is zero.
3. Women who have a PID episode have a different (higher) rate of subsequent PID episodes for the next two years and the ratio of these rates is independent of both age. Furthermore the pattern of infection and re-infection in CT, is the same as the pattern of PID and repeat PID, for PID from any cause.
4. Conditional upon assumption 3, PID incidence is independent of PID history.
5. Estimated incidence of diagnosed PID from routine data sources is uniformly distributed between the total observed in STI clinics + the maximum from HES and scaled GPRD data and the total from STI, HES, and scaled GPRD data.
6. The probability that a clinical PID episode is diagnosed to be independent of age and PID history.
7. The probability that a clinical PID episode is salpingitis is independent of age and PID/salpingitis history.

External Validation

We validate our results against the Lund study[2], which reports data on the distribution of numbers of PID episodes in women who have had salpingitis, for a mean follow-up period of approximately 8 years, separately for women under and over 25. The Markov model was run separately for women starting at each of the 22 one-year age bands 16-37, in each case starting in state 2, for an 8 year time-horizon. The average predicted number of women with a single, and 2+ subsequent PID episodes were obtained by averaging across the age ranges 16-24, and 25-37 respectively. Results for all PID and diagnosed PID only are shown alongside the Lund data (Table 1).

Sensitivity analysis

We have developed a fully probabilistic model which accounts for all of the uncertainty in the data that has been used to estimate the parameters. However, the sensitivity of the results to some key structural assumptions are assessed in Supplementary Digital Content 4.

RESULTS

Table 2a gives the predicted numbers of women who have had 0, 1, 2, or 3+ previous PID episodes, whether diagnosed or not, by age. Exactly analogous sets of predictions are shown for diagnosed PID (Table 2b) and for salpingitis (Table 2c). These tables show that 33.6% of women aged 25-44 have experienced at least one episode of PID, and at 16.1% have experienced at least one episode of salpingitis, again all-cause and whether diagnosed or not. Finally Table 2d shows the proportions of the population that have experienced at least one episode of salpingitis, followed by 0, 1, or 2 or more episodes of PID. Here we see that, while

16.1% have experienced at least one episode of salpingitis, 10.7% have experienced 1 salpingitis and no further PID episodes, 3.7% one salpingitis and one further PID episode, and 1.7% one salpingitis and 2 or more further PID episodes. Figure 2 gives essentially the same results respectively in one-year bands from age 16 to age 44.

External validation

Table 1 shows the correspondence between the results from the Markov model run for an 8-year period and the Lund data. The comparisons between observed and predicted distributions only concern the proportions of PIDs that are 2nd or 3rd (or more) PIDs, because only women who have a PID were recruited into the Lund study. Note that there is no reason to expect the credible intervals to agree. The first column shows the proportions of women in the study that the model predicts would develop 1, or 2+ PIDs, whether diagnosed or not, during the follow-up period. Column 2 shows how many PIDs would be expected to be observed (diagnosed) in these women. The Lund study results (column 3) lie between the results in the first two columns, which is exactly what is to be expected as it seems reasonable that subsequent PIDs in women who have had a previous, relatively recent, hospital diagnosed PID are more likely than average to be diagnosed, on the basis that (i) these women will be more likely to recognise the symptoms, and (ii) such PIDs may be more severe than average. On the other hand, the Lund study is not technically a cohort study: unlike the POPI trial participants, women recruited into the Lund study will not have been told specifically to look out for symptoms, and the follow-up time was much longer, so we would not necessarily expect all, or even most, symptomatic PID to be diagnosed.

DISCUSSION

This paper proposes, as far as we are aware for the first time, a methodology for estimating the proportion of incident PID episodes, and salpingitis episodes, that are first, second, or third PIDs, by age. The method is based on assumptions about the CT *re*-infection to infection rate ratio, and the length of time after which the re-infection rate applies. With these two assumptions, the results are compared to data on the distribution of 2^{nd} and 3^{rd} episodes in women with an index episode. We used a variety of high quality data-sources to estimate the parameters and where possible assessed their consistency. The impact of key structural assumptions was assessed in sensitivity analysis.

In the Lund study 22.1% of women aged 16-24 with an index salpingitis were observed to have a further PID episode within 8 years, and 6.2% had more than one further episode. In women aged 25-44 11% had a further PID episode, and 2% more than one. The Lund study follows women whose index PID was sufficiently severe to be diagnosed and treated in hospital. So our estimate of the proportion of PIDs that are diagnosed in the general population will likely be lower than the proportion in the Lund dataset. So our external validation with this data must be informal. All we can say is that the Lund results should lie somewhere between our estimates for the numbers of subsequent PIDs and the numbers of subsequent PIDs likely to be diagnosed in the general population.

Within year and diagnostic pathway repeat PID rates are available for Hospital and GUM settings[16, 17]. 3.2-3.4% of PID cases recorded in HES annually are within-year repeat cases. The population at risk of a first annual HES diagnosis is far higher than for a second or subsequent, so the HES PID diagnosis rate is nearly 20-fold higher in the latter. Gum data are similar. This is higher than our base-case average rate-ratio which covers a 2-year period, and slightly higher than our sensitivity analysis. So we may have over-estimated ever PID and

underestimated repeat episodes. However, it's unknown how long this repeat case rate persists past 6 months (average).

We use data from the UK study by Taylor-Robinson to estimate the proportion of PID cases that are salpingitis[18]. Although the study was published fairly recently the data were collected in the 90s and cases were diagnosed in hospital, so it is unclear how applicable it is to all PID in 2002. Over time, clinical guidance has changed to treat women with possible or probable PID instead of only treating women with probable PID so this is likely to be an overestimate for the proportion in all PIDs in 2002. Although we only included PID cases from the GPRD database that are definite and probable it is unclear whether the Taylor-Robinson study provides an overestimate for clinical PID cases diagnosed in GUM clinics. We also assume the same proportion of salpingitis in undiagnosed PID cases and there is no real evidence to say whether this is reasonable. On the one-hand, undiagnosed women are likely to have less severe symptoms and symptoms are likely to correlate to severity of inflammation and presence of salpingitis. However, laparoscopy identifies the presence of salpingitis at a single point in time. Some of the women in the Taylor-Robinson study may have developed inflammation that would be visible on laparoscopy at a later date had they not been treated as would be the case if they were undiagnosed.

Our estimates of cumulative incidence of diagnosed PID are considerably higher than the National Survey of Sexual Attitudes and Lifestyles (NATSAL)[19] which reported that 2.2% (1.8%,2.6%) of female respondents aged 16 to 44 said they have ever been treated for PID compared to our estimate of about 10% in 31 year-olds (Figure 2). However, NATSAL is also highly inconsistent with other UK data sources. The POPI trial[7] observed all-cause PID incidence to be 2% *in a single year*. Furthermore, HES data alone report a total of approximately 15,000 PIDs in women by the age of 35. If the 20-fold repeat case PID rate persists throughout a woman's reproductive life after diagnosis this would be consistent with

NATSAL. But this would be at odds with the Lund data and this doesn't consider GP or GUM diagnoses. Recruitment and participation biases in surveys like NATSAL may selectively under-sample those who would be considered at increased risk (and some groups at reduced risk). On top of this there may be a tendency among responders to under-report health problems linked to sexually transmitted disease, and it may be that not everyone diagnosed with PID is told this diagnosis and remembers it. In fact GPRD codes for PID often do not mention PID specifically. The discrepancy between NATSAL and our results is, nevertheless, large and requires further investigation.

Our projections can also be compared with the 2002 US National Survey of Family Growth in which 5.1% of women aged 16-44 reported having been treated for PID[20]. This figure is sharply down on the 1995 Survey which reported 8% had been treated for PID, with 11% in the 1988 and 14% in the 1982. Our average estimate for this age range is around 10%. In the Uppsala study, the cumulative incidence of hospital-diagnosed PID was reported as 3.9% by 35 years[21]. If we use only HES data to estimate the incidence rate of diagnosed PID, the estimate of cumulative incidence in women aged 35 is 4.6%, close to the Uppsala figure.

The population level results are primarily applicable to England in 2002 just before the introduction of the National Chlamydia Screening Programme (NCSP)[22] so the estimates can be used in conjunction with epidemiological studies of natural history. However, the model could easily be applied to other Countries or times provided the necessary data were available to fit it.

CONCLUSIONS

We estimate that in the England in 2002 33.6% of women age 35-44 have experienced at least one episode of PID (diagnosed or not) and 16.1% of them have experienced at least one

episode of salpingitis (diagnosed or not). Further work is required to assess the degree of overlap between routine data sources for PID and of PID history for women diagnosed with PID. Linkage of routine data-sources would enable tracking of referrals between settings, and ideally over time. Cross-sectional or retrospective studies of the proportion of PID that is diagnosed, and the proportion of PIDs that are salpingitis together with the severity distribution in different diagnostic settings would be valuable.

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Conflicts of interest PJH reports personal fees from Aquarius Population Health, grants, personal fees and non-financial support from Cepheid, personal fees from Crown Prosecution Service, personal fees from British Association for Sexual Health and HIV, grants from Mast Group Ltd, grants and personal fees from Hologic, outside the submitted work; in addition, PJH has a patent A sialidase spot test to diagnose bacterial vaginosis, issued to University of Bristol. The remaining authors report no conflicts of interest.

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Table 1. Distributions of numbers of PIDs after 8 years, posterior mean % in each category (95% Credible intervals), compared to the findings from the Lund study (see text).

	Model – All PID	Model – diagnosed PID	Lund study
Age 16-24			
1 PID	*66.3 (51.3,78.0)*	*85.4 (78.3,90.2)*	*77.7 (75.1,80.3)*
2 PID	23.6 (18.3,27.2)	12.8 (9.1,17.8)	16.0 (13.8,18.4)
3+ PID	10.1 (3.75,21.5)	1.8 (0.7, 3.9)	6.2 (4.8, 7.8)
Age 25-44			
1 PID	*75.2 (62.3,84.7)*	*90.0 (84.4,93.5)*	*87.0 (82.6,90.9)*
2 PID	19.3 (13.5,25.0)	9.3 (6.2,13.6)	11.0 (7.5,15.1)
3+ PID	5.5 (1.8,12.7)	0.9 (0.3, 2.0)	2.0 (0.6, 4.0)

Table 2. Predicted age-specific distributions of numbers of previous episodes from the Markov model. Posterior mean % in each category (95% credible intervals)

(a) PID

Age	0 PID Episodes	1 PID episodes	2 PID episodes	3+ PID episodes
All PID				
16-19	95.7 (94.2,96.9)	3.89 (2.90,5.09)	0.43 (0.19,0.81)	0.03 (0.01,0.10)
20-24	86.7 (82.5,90.2)	10.3 (7.94,12.9)	2.38 (1.25,3.91)	0.64 (0.16,1.69)
25-34	75.3 (67.9,81.6)	17.2 (13.7,21.0)	5.30 (3.10,7.95)	2.16 (0.64,5.25)
35-44	66.4 (56.9,74.6)	22.2 (18.2,26.3)	7.77 (4.83,11.1)	3.67 (1.21,8.49)

(b) Diagnosed PID

Age	0 PID Episodes	1 PID episodes	2 PID episodes	3+ PID Episodes
All PID				
16-19	98.4 (98.2,98.5)	1.58 (1.41,1.75)	0.06 (0.03,0.10)	0.00 (0.00,0.00)
20-24	94.6 (93.8,95.2)	4.97 (4.47,5.50)	0.44 (0.26,0.70)	0.03 (0.01,0.06)
25-34	89.3 (87.6,90.7)	9.44 (8.36,10.6)	1.15 (0.73,1.75)	0.09 (0.04,0.18)
35-44	84.7 (82.3,86.8)	13.0 (11.6,14.6)	1.81 (1.22,2.64)	0.49 (0.31,0.76)

(c) Salpingitis

Age	0 salpingitis Episodes	1 salpingitis episodes	2 salpingitis episodes	3+ salpingitis Episodes
All salpingitis				
16-19	98.1 (97.0,99.0)	1.85 (1.02,2.88)	0.04 (0.01,0.14)	0.00 (0.00,0.00)
20-24	94.1 (90.7,96.8)	5.56 (3.18,8.35)	0.34 (0.07,0.93)	0.02 (0.00,0.10)
25-34	88.6 (82.3,93.6)	10.4 (6.11,15.0)	0.99 (0.23,2.44)	0.10 (0.01,0.40)
35-44	83.9 (75.3,91.0)	14.2 (8.55,20.1)	1.71 (0.45,3.96)	0.20 (0.02,0.78)

(d) Salpingitis and subsequent PID

Age	0 salpingitis	1 salpingitis, 0 further PID episodes	1 salpingitis, 1 further PID episode	1 salpingitis, 2+ further PID Episodes
All cause				
16-19	98.1 (97.0,99.0)	1.69 (0.93,2.64)	0.19 (0.07,0.38)	0.01 (0.00,0.04)
20-24	94.1 (90.7,96.8)	4.59 (2.59,6.99)	1.06 (0.46,1.96)	0.28 (0.06,0.79)
25-34	88.6 (82.3,93.6)	8.03 (4.63,12.0)	2.44 (1.15,4.21)	0.98 (0.25,2.55)
35-44	83.9 (75.3,91.0)	10.7 (6.32,15.7)	3.66 (1.80,6.14)	1.69 (0.48,4.18)