The Epidemiology of Pelvic
Inflammatory Disease in England

This work is presented

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at the

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Abstract

Background  Pelvic inflammatory disease (PID) is considered to be a leading cause of morbidity in women but little is known of its epidemiology in England.

Aim  To investigate the epidemiology of PID and explore factors associated with PID.

Objectives  Four studies were undertaken: (1) to evaluate surveillance data available from health care settings; (2) to investigate the diagnosis, treatment and management of PID in general practice; (3) to use an available dataset to assess diagnostic accuracy based on clinical presentation; and (4) to investigate demographic and behavioural factors, serological parameters and causative agents associated with PID through an original case-control study.

Results  The highest burden of disease was seen in general practice where 1.7% of reproductive age women were diagnosed with PID, although management fell below acceptable standards. The most effective diagnostic criteria were the presence of lower abdominal pain and the exclusion of competing diagnoses. The case-control study showed that PID had the characteristics typical of a sexually transmitted disease. When compared against a tubal ligation control group increased risk of PID was associated with: age group <25 years; age at first sexual intercourse <20 years; non-White ethnic identity; having had children; a self reported history of an STD; and exposure to C. trachomatis. When compared against the general practice control group increased risk was associated with: age group <25 years; age at first sexual intercourse <15 years; lower socio-economic status; marital status other than being married; adverse pregnancy outcome; a self reported history of an STD; and exposure to C. trachomatis. Of the cases, 64% were not associated with any of the infectious agents measured in this study (idiopathic). Some idiopathic cases were associated with Mycoplasma genitalium.

Conclusions  Diagnostic methods and knowledge of disease aetiology need to be improved if further epidemiological investigations and surveillance initiatives are undertaken.
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Chapter 1  Introduction

Pelvic inflammatory disease (PID) can be defined as a clinical syndrome associated with upper genital tract infection in women. The definition of PID is discussed in more detail in sections 2.1 and 2.9. In England, a substantial proportion of cases are caused by Chlamydia trachomatis, a bacterial infection that is the commonest curable sexually transmitted infection. PID is a leading cause of reproductive ill health in women: it can cause ectopic pregnancy, tubal factor infertility and chronic abdominal pain and has been associated with ovarian cancer. A substantial burden of PID is thought to exist in reproductive age women but little is known of PID epidemiology in England and other established market economies (EME). The burden of disease and risk factors associated with PID are poorly understood but need to be investigated to inform public health action and clinical practice. Knowledge of PID epidemiology, that is the distribution and determinants of disease occurrence within populations, is essential to the understanding of reproductive morbidity in women. PID should be monitored as part of a chlamydial intervention programme and the Chief Medical Officers Expert Advisory Group on genital C. trachomatis infection recently highlighted the urgent need for information concerning PID epidemiology.

The epidemiology of PID is notoriously difficult to study, due to the low specificity of clinical diagnosis, and the variety of clinical specialities attended by women with PID. Many cases go unrecognised because they are atypical or asymptomatic. In addition, PID epidemiology changes over time in response to variations in microbial aetiology and medical intervention. Consequently interpretation of surveillance data and comparison between countries is difficult.
1.1 Thesis Scope

The thesis is limited to detectable PID, that is acute and chronic cases, not asymptomatic cases. The literature review is confined to studies and data from EMEs. This is because the epidemiology of PID in EMEs is different from that in developing countries. PID aetiology in developing countries is predominantly associated with *Neisseria gonorrhoeae* and *C. trachomatis*, and there is restricted access to diagnostic, treatment and management services. Sexual behaviour in developing countries is also different from EME: age at first sexual intercourse is probably younger in some developing countries than in EME, and polygamous marriages are common in many cultures, as are practices that are strongly associated with PID such as female genital mutilation (circumcision).^2^

1.2 Aim

1. To investigate the epidemiology of PID in England and explore factors associated with PID

1.3 Objectives

1. Evaluate surveillance data available from health care settings

2. Investigate the diagnosis, treatment and management of PID cases in general practice

3. Assess diagnostic accuracy based on clinical presentation

4. Investigate demographic and behavioural factors, serological parameters and aetiological agents associated with PID using a case-control study

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1.4 Thesis Layout

The thesis is in 9 parts: a background literature review including project rationale, general methods, 5 chapters that address an aspect of the aim and objectives, a general discussion and appendices. Chapter 4 is concerned with the interpretation of surveillance data, chapter 5 with how general practitioners diagnose and manage PID and chapter 6 with diagnostic accuracy based on clinical presentation. Chapters 7 and 8 describe an original case-control study designed and implemented by Ian Simms which investigated factors associated with PID. Methods specific to each chapter are given within those chapters. The appendices contain questionnaires, patient information sheets, standard operating procedures and published papers.

1.5 Statement of Authorship

The studies in chapters 4 to 7 were instigated, planned, conducted, analysed and interpreted by Ian Simms. The investigations in chapters 7 and 8 were supported by grants from the Department of Health (England) and the Public Health Laboratory Service. Ian Simms made the applications and was awarded both grants.

Other authors collected three datasets used in the thesis. The Morbidity Statistics from General Practice Fourth National Survey: 1991-1992 used in chapter 4 was collected by the Office of Population Census and Statistics (now the Office of National Statistics). The analysis of the data presented here was undertaken by Ian Simms and was an original interpretation of the published dataset: data relating to diagnoses of PID from this dataset had not been published previously. The Hospital Episodes Statistics data also used in chapter 4 were provided by the Department of Health and had not been published previously. Professor Lars Weströöm collected the data used in chapter 6, but the aims, objectives and analytical techniques used here were original.
Chapter 2  Background

'Pelvic inflammatory disease is a sexually transmitted disease with potentially serious sequelae usually managed badly by doctors with little interest in the condition'\textsuperscript{10}

It is over a decade since this bleak view of pelvic inflammatory disease (PID) management in the UK appeared in the \textit{British Medical Journal}. Since then a theme to emerge in sexually transmitted infection (STI) research has been increased awareness of genital chlamydial infection, which causes a substantial proportion of PID cases. In the UK, the Chief Medical Officer's (CMO) expert advisory group on genital chlamydial infection recognised PID as an important source of preventable reproductive morbidity in women\textsuperscript{4}. However, little is known of PID epidemiology in England. The burden of disease and factors associated with PID are poorly understood but need to be investigated to inform public health action and clinical practice\textsuperscript{5}.

2.1 Definition of PID

PID is the clinical syndrome caused by micro-organisms that ascend from the cervix or vagina to the upper genital tract and includes endometritis, salpingitis, tubo-ovarian abscess and pelvic peritonitis. Salpingitis is often used synonymously with PID. The PID diagnostic criteria suggested by Jacobson and Weström and later refined by Hager \textit{et al.} to include expert opinion were developed from data collected in the 1960s\textsuperscript{11,12}. This is the standard PID case definition used in genitourinary medicine (GUM) and Obstetrics and Gynaecology (O&G), and was used in this thesis (table 2.1)\textsuperscript{12}. PID diagnostic techniques are reviewed below (section 2.9).
Table 2.1  PID diagnostic criteria: Hager, et al. 1983\textsuperscript{12}

<table>
<thead>
<tr>
<th>All of the following*:</th>
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<tr>
<td>Abdominal direct tenderness, with or without rebound tenderness</td>
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<td>Tenderness with motion of cervix &amp; uterus</td>
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<tr>
<td>Adnexal tenderness</td>
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<th>plus 1 or more or the following:</th>
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<tbody>
<tr>
<td>Gram stain endocervix - positive for gram-negative, intracellular diplococci</td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
</tr>
<tr>
<td>Leukocytosis &gt;10 000</td>
</tr>
<tr>
<td>Purulent material (white blood cell count present) from peritoneal cavity by culdocentesis or laparoscopy</td>
</tr>
<tr>
<td>Pelvic abscess or inflammatory complex on bi-manual examination or sonography</td>
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</table>

* In the paper, Hager states that lower abdominal pain is the most frequent symptom seen in patients with laparoscopically confirmed acute salpingitis

2.2  HISTORICAL PERSPECTIVE

The origin of the term ‘pelvic inflammatory disease’ is unclear but it is thought to have been introduced by the World Health Organisation (WHO) after WWII in response to an increased awareness of the diverse presentation of salpingitis (RS Morton, personal communication). Prior to the nineteenth century, the ‘venereal poison’ was attributed to a wide range of conditions. However, the un-specific signs and symptoms that characterise PID, together with ineffective examination methods, the inaccessibility of the female upper genital tract and a general uninterest in women’s health meant that PID was not associated with venereal disease. During the mid-nineteenth century it was suggested that gonorrhoea could ascend to the upper genital tract and cause PID, but it was not until 1876 that Noeggerath produced evidence of an association between gonorrhoea, PID and infertility\textsuperscript{3-5}. Sulphonamides were used to treat PID in the 1930s and, during the late 1940s, the widespread use of antibiotics in the treatment of PID and other conditions reduced PID prevalence in Europe substantially\textsuperscript{16}. However, estimates of disease prevalence and the impact of treatment made at that time were probably inaccurate as many cases were attributed to other
diagnoses, such as appendicitis, either because of unspecific diagnostic techniques or an unwillingness to discuss sexual health with young women.

Laparoscopy, the examination of the abdominal structures within the peritoneum, was first described by Kelling in 1902. In the 1960s, Westrom used laparoscopy to systematically explore the clinical presentation of PID and revealed the wide range of clinical presentations of PID as well as its associations with ectopic pregnancy and tubal factor infertility (TFI). This work also established laparoscopy as the diagnostic 'gold standard' and a method of taking samples from the upper genital tract. Despite recent developments in microbiology, immunology and behavioural sciences, much remains to be learnt of the aetiology, pathogenesis, epidemiology and public health significance of PID.

2.3 Quality of Evidence

The literature was evaluated in comparison to the quality of evidence categories that were originally proposed by the Canadian Task Force on Periodic Health Examination and revised by the United States Agency for Health Care Policy and Research (table 2.2).

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<td>Ia</td>
<td>Evidence from meta-analysis of randomised controlled trials</td>
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<tr>
<td>Ib</td>
<td>Evidence from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence from at least one controlled trial without randomisation</td>
</tr>
<tr>
<td>IIb</td>
<td>Evidence from at least one other type of quasi-experimental study</td>
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<tr>
<td>III</td>
<td>Evidence from descriptive studies, such as comparative studies, correlation studies and case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence from expert committee reports or opinions, or clinical experience of respected authorities, or both</td>
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2.4 PID etiology

PID can be caused by genital mycoplasmas, endogenous vaginal flora (anaerobic and aerobic bacteria), aerobic streptococci, *Mycobacterium tuberculosis*, and STIs such as *C. trachomatis* and *N. gonorrhoeae*. It is difficult to establish the contribution of each of these etiological agents to PID epidemiology as their prevalence reflects current epidemics, and control and intervention strategies. In addition, most studies have been small-scale, cross sectional studies that did not use standard diagnostic or laboratory methods and investigated different organisms. Consequently the studies are difficult to evaluate and compare and the quality of evidence is low, restricted to evidence base level III.

*N. gonorrhoeae*, a Gram negative diplococcus, is seen as the 'classic' cause of PID because accurate diagnostic tests have been widely available for almost a century, and because *N. gonorrhoeae* was considered to be the dominant cause of PID when the first epidemiological investigations were undertaken in Europe during the 1950s and 1960s. Although Koch's postulate has never been fulfilled because animal models are difficult to establish, *N. gonorrhoeae* has been recovered from the cervix, endometrium, fallopian tubes and peritoneal fluid in women with PID. Between 10% and 19% of women with lower genital tract gonococcal infection have clinical signs of acute PID. Consequently in populations with high endemic rates of gonorrhea, a high proportion of PID cases are associated with gonorrhea. However, in the presence of pelvic pain, infection with *N. gonorrhoeae* is generally short lived in the upper genital tract either because the severity of symptoms rapidly leads to diagnosis and treatment, or because *N. gonorrhoeae* disappears in the presence of inflammation.

*C. trachomatis*, a non-motile Gram-negative bacterium, was first described in 1907. *C. trachomatis* exists in two forms (figure 2.1). The infectious non-
Figure 2.1  Life cycle of *Chlamydia trachomatis*
metabolically active elementary body (EB) is taken up by host cell into membrane bound inclusions. Within these inclusions the EBs change into reticulate bodies (RB), which then undergo mitosis. The RBs then change back into EBs and are released on lysis of the host cell. The process takes between 40 and 72 hours. *C. trachomatis* has been isolated from the cervix, endometrium and fallopian tubes of women with PID. *C. trachomatis* infects columnar epithelial cells. In childhood, the vagina is lined with columnar epithelium but at puberty the influence of oestrogen brings about a metaplastic change in which the columnar epithelium transforms into layers of squamous epithelium. This transformation is a gradual process and does not completely disappear until well into adulthood. By adolescence, the cervix still shows areas of exposed columnar epithelium, a condition known as ectopy which has been associated with increased risk of STI infection, such as *N. gonorrhoeae* and herpes simplex virus (HSV).

*C. trachomatis* has been detected in 14% to 65% of PID cases in different populations in different countries but, since these were small-scale studies, this does not reflect substantial variation over time and between countries (table 2.3). The studies also used a variety of diagnostic tests, such as culture and enzyme-linked immunoassays (EIA), which vary substantially in sensitivity and specificity. Some studies report a higher prevalence of *N. gonorrhoeae* than *C. trachomatis*, but again these were based on small sample sizes. Nevertheless, these data suggest that a substantial proportion of PID cases are caused by *C. trachomatis*. The largest UK study, based on only 147 women at one location, indicated that 39%, 95% confidence interval (CI) 29% to 49%, of PID cases were caused by *C. trachomatis* and 14% by *N. gonorrhoeae*.
Table 2.3  Prevalence of *C. trachomatis* in women with laparoscopically proven PID, selected studies, industrialised countries: 1980 to 2002

<table>
<thead>
<tr>
<th>Population</th>
<th>Country</th>
<th>Prevalence % (95% CI)</th>
<th>Sample size</th>
<th>Site of specimen collection</th>
<th>Author (year) reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>STD clinics</td>
<td>UK</td>
<td>40 (25 - 55)</td>
<td>17/43</td>
<td>Lower genital tract</td>
<td>Kinghorn (1986)</td>
</tr>
<tr>
<td></td>
<td>UK</td>
<td>43 (23 - 66)</td>
<td>10/23</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Stacey (1992)</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>30 (24 - 37)</td>
<td>69/228</td>
<td>Lower genital tract</td>
<td>Paavonen (1980)</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>42 (26 - 59)</td>
<td>15/36</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Heinonen (1989)</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>52 (29 - 63)</td>
<td>16/35</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Paavonen (1987)</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>33 (26 - 41)</td>
<td>52/156</td>
<td>Lower genital tract</td>
<td>Ripa (1980)</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>12 (7 - 17)</td>
<td>22/187</td>
<td>Upper genital tract</td>
<td>Brihmer (1987)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>15 (9 - 25)</td>
<td>13/84</td>
<td>Upper genital tract</td>
<td>Soper (1994)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>10 (2 - 27)</td>
<td>3/30</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Thompson (1980)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>5 (1 - 36)</td>
<td>2/20</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Sweet (1981)</td>
</tr>
<tr>
<td>Gynaecology outpatient</td>
<td>Canada</td>
<td>16 (7 - 29)</td>
<td>8/50</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Brunham (1988)</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>14 (5 - 26)</td>
<td>7/51</td>
<td>Upper genital tract</td>
<td>Cacciatore (1992)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>65 (43 - 84)</td>
<td>15/23</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Wöhnert-Hanssen (1988)</td>
</tr>
<tr>
<td>Accident &amp; Emergency</td>
<td>USA</td>
<td>61 (39 - 80)</td>
<td>14/23</td>
<td>Upper genital tract</td>
<td>Wasserheit (1986)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>38 (25 - 52)</td>
<td>21/55</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Kiviat (1986)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>30 (13 - 53)</td>
<td>7/23</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Livengood (1992)</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>17 (6 - 33)</td>
<td>6/36</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Soper (1992)</td>
</tr>
<tr>
<td>Primary care</td>
<td>Canada</td>
<td>25 (13 - 40)</td>
<td>11/44</td>
<td>Lower genital tract &amp; upper genital tract</td>
<td>Sellors (1991)</td>
</tr>
</tbody>
</table>
Estimates of the risk of PID after *C. trachomatis* infection are only available from two studies neither of which were designed to address this question. One study of antibiotic efficacy published nearly two decades ago suggested that between 10% and 40% of untreated *C. trachomatis* infections develop PID. An alternative estimate, made from the control arm of a randomised control trial aimed at reducing PID prevalence through chlamydial screening, suggested that 18% of untreated *C. trachomatis* infections develop PID within 1 year. The problems of interpreting the study are discussed further in section 2.13.

*Mycoplasma genitalium*, a fastidious slow growing bacterium, was first isolated in 1980. *M. genitalium* has been independently associated with acute non-gonococcal urethritis (NGU) in males. A causal relationship between *M. genitalium* and NGU is supported by the observation that *M. genitalium* causes acute polymorphonuclear leucocyte dominated inflammatory and antibody responses when inoculated into the urethra of male chimpanzees. Monkey models have shown that *M. genitalium* can also cause salpingitis. *M. genitalium* adheres to human fallopian tube epithelial cells and acute PID has been associated with elevated antibody titre to *M. genitalium* in the absence of gonococcal, chlamydial or *Mycoplasma hominis* infection. Studies have associated *M. genitalium* with non-gonococcal/non-chlamydial urethritis in men, and women with PID. An association between *M. genitalium* and PID in the absence of *N. gonorrhoeae*, *C. trachomatis* or *M. hominis* has been suggested in a serological study but not confirmed.

*Mycoplasma hominis* has been isolated from the endometrium and fallopian tubes of women with laparoscopically diagnosed PID. Animal models have shown that *M. hominis* can infect the upper genital tract and a cytopathic effect has been demonstrated after inoculation of *M. hominis* into human fallopian tube tissue culture.

Although *Ureaplasma urealyticum* has been isolated from fallopian tubes of women with PID, it is not considered to play a significant role in the aetiology of
PID. Detected prevalences are similar in healthy women and women with PID, and attempts to produce animal models have not been successful.

In addition to the above organisms, a number of aerobic and anaerobic bacteria are frequently isolated from the female upper genital tract in either the presence or absence of \textit{N. gonorrhoeae} or \textit{C. trachomatis}. Most are found in normal vaginal flora and include \textit{Prevotella bivius}, \textit{Peptostreptococcus} spp., \textit{Bacteroides} spp., staphylococci, group B to D streptococci, \textit{Campylobacter fetus}, clostridia, \textit{Escherichia coli} and \textit{Gardnerella vaginalis}. The presence of endogenous bacteria in the upper genital tract is more common in older women and may be associated with intrauterine device (IUD) use, chronic PID and the presence of other pathologies. Women with mild PID are generally less likely to have anaerobic bacteria in the upper genital tract. Bacterial vaginosis (BV) is a clinical syndrome which includes at least three of the following four criteria; thin, homogenous, uniformly adherent, white discharge; vaginal pH$>$4.5, fishy odour on addition of 10\% KOH; and 20\% clue cells on microscopic examination of vaginal smear. BV has been associated with PID in the absence of \textit{N. gonorrhoeae} and \textit{C. trachomatis}. Organisms associated with BV, \textit{G. vaginalis}, \textit{Mobiluncus} spp., \textit{Bacteroides} spp. and \textit{M. hominis}, are frequently isolated from the upper genital tract of women with acute PID. Respiratory pathogens, such as \textit{M. tuberculosis}, \textit{Haemophilus influenzae}, \textit{Streptococcus pneumoniae} and group A streptococci have also been isolated from the upper genital tract and probably reflect systemic infection. These pathogens could have been transmitted during oral sex but no studies have been undertaken to investigate this transmission route.

Acute PID is frequently associated with either \textit{N. gonorrhoeae} or \textit{C. trachomatis} in the lower genital tract or other bacterial infection in the fallopian tubes or peritoneum. The circumstances under which predominantly commensal vaginal organisms cause pathology in the upper genital tract are unclear but two scenarios have been suggested. An initial ascending gonococcal or chlamydial infection could be followed by a polymicrobial infection that eventually leads to
the formation of an abscess, or alternatively endogenous flora could ascend into the upper genital tract without an initial infection.

An aetiological role for viruses, such as HSV II and cytomegalovirus, has been suggested but not investigated thoroughly. There is no evidence to suggest that the human immunodeficiency virus (HIV) causes PID or that PID is more severe in women who also have HIV infection. There is no evidence that protozoa, such as *Trichomonas vaginalis*, cause PID.

In some studies, serological tests were used to allocate cases to a particular aetiology. Nevertheless, all studies that have evaluated PID aetiology have failed to find a causative organism in at least 20% of cases. However, many of the studies cited here were undertaken before molecular amplification techniques were available (section 2.6). It is likely that the use of more sensitive, versatile diagnostic techniques will reduce the percentage of idiopathic cases and improve knowledge of PID aetiology.

### 2.5 Pathogenesis and Disease Spectrum

PID sequelae include ectopic pregnancy, TFI and chronic pelvic pain, and PID has been associated with increased risk of ovarian cancer. The pathogenesis of PID is a complex interaction of genetic, immunological and bacterial virulence factors, and understanding of immunopathological pathways from infection to PID and tubal scarring is incomplete. Tubal deciliation, occlusion, and intraluminal and peritubal adhesions have been shown to occur in humans and animal models. The replacement of dead cells with in-growing fibroblasts causes tubal scarring and impairment of fallopian tube function. Pathogenesis also varies between micro-organisms. Organ culture studies have shown that *N. gonorrhoeae* can induce proinflammatory cytokine tumour necrosis factor-alpha (TNF-α) which can lead to inflammation and sloughing of ciliated cells in human fallopian tubes. This mechanism is thought to be important to the development of gonococcal salpingitis. Although serological tests have been developed to
detect antibodies to \textit{N. gonorrhoeae} the tests have sensitivities of around 70% and specificities of about 80%. These tests are thus not suitable for screening, case finding or diagnosis. \textit{C. trachomatis} stimulates both humoral (local and serum IgA, IgM and IgG antibodies) and cell mediated immune responses.

PID and tubal scarring associated with \textit{C. trachomatis} are thought to be caused either by a T-cell mediated cross reactive immune response or a delayed hypersensitivity reaction to chlamydial 60kDa heat shock protein (CHSP60)\textsuperscript{70-72}. \textit{C. trachomatis} can also induce cytokines such as TNF-\(\alpha\), interferon (IFN), interferon gamma (IFN-\(\gamma\)) and interleukins\textsuperscript{73,74}. Heat shock proteins (HSP) are conserved epitopes, homology varies from 40% to 90%, which are produced by prokaryotes, such as \textit{E. coli}, \textit{Mycobacterium} spp., and mammals, including humans. The cross reactive T-cell mediated response to CHSP60 is thought to involve an initial immune sensitisation to CHSP60 that is followed by reactivation of sensitised lymphocytes in response to human HSP, or a HSP from another organism, and can result in the release of inflammatory cytokines. The delayed hypersensitivity response is thought to consist of repeat or prolonged CHSP60 antigenic stimulus brought about by recurrent infection, which can lead to PID and tubal scarring. Animal models indicate that cell-mediated immune mechanisms are the dominant host response to chlamydial infection. This suggests that PID is an autoimmune disease and that severe inflammation can result from an immune response to CHSP60, although the role of heat shock proteins in the development of PID has recently been questioned\textsuperscript{75}.

Immunogenicity of HSP10 has been reported from \textit{Mycobacterium leprae} and \textit{M. tuberculosis} and have been shown to be prominent targets for T-cell antigens and serum antibody responses\textsuperscript{76,77}. HSP10 from both \textit{M. leprae} and \textit{M. tuberculosis} produce a strong human T-cell response, with the production of interleukin 2 and IFN-\(\gamma\), consistent with a delayed hypersensitivity response\textsuperscript{76,78}. The few studies that have looked at the human immune response to CHSP10 suggest that antibody to CHSP10 is associated with upper genital tract disease\textsuperscript{79,80}.
Incidence of PID sequelae in women with a history of PID is difficult to investigate because of diagnostic problems (section 2.9) and because large patient groups are difficult to follow up over long periods of time. The prevalence of infertility is particularly difficult to estimate as only those who wish to conceive seek medical advice. The largest prospective study of reproductive events after laparoscopically diagnosed PID was undertaken in Lund (Sweden) between 1960 and 1984. The study included 2501 women who underwent routine diagnostic laparoscopy because of a clinical suspicion of acute salpingitis. At index laparoscopy, none had any known previous episodes of PID, and were otherwise healthy with regular menstrual periods and no known fertility-reducing factors. Of the 2501 patients, 1844 were diagnosed as having salpingitis whereas 657 did not have any pathology. After index laparoscopy all patients were followed up for as long as possible. Data from the study indicate that women with a history of laparoscopically diagnosed PID were 6 times more likely to have had an ectopic pregnancy and 14 times more likely to experience TFI than those who had no evidence or history of PID. It also found that risk of developing sequelae was dependent on the number of PID episodes. The risk of ectopic pregnancy and TFI increased after one PID episode (odds ratio=6) and again after two episodes (OR=17). Animal models indicate that PID can develop within 5 days of *C. trachomatis* infection. In humans, failure to seek treatment within three days of the onset of lower abdominal pain can result in a three fold increase in the risk of PID and TFI. Early diagnosis and treatment are thus essential. In the UK, an 11-year record linkage cohort study showed that women with a history of PID were 6, 8, 10 and 10 times more likely to have diagnoses of endometritis, hysterectomy, abdominal pain and ectopic pregnancy respectively than controls.

Tubo-ovarian abscess, a late manifestation of PID, is not associated with either *N. gonorrhoeae* or *C. trachomatis*. Abscess formation is associated with infection by facultative and anaerobic bacteria. The clinical presentation and course of PID in women with symptomatic HIV disease and/or severe immune suppression may
be more aggressive than in HIV negative women\textsuperscript{83}. This also suggests that CD8 T-cells are important in the development of PID.

It has been suggested that severity of PID is related to the phase of the menstrual cycle\textsuperscript{84}. The cervix is a barrier to the ascent of micro-organisms but cervical mucus is more viscous in the progesterone (luteal) phase than the oestrogen (follicular) phase. In the luteal phase, cervical mucus inhibits the penetration of spermatozoa and micro-organisms whereas in the follicular phase, spermatozoa and micro-organisms can penetrate the endometrial cavity more easily. Gonorrhoea is diagnosed more often in the follicular phase and salpingitis is more likely to be diagnosed during or shortly after menses than in the luteal phase.

2.6 Microbiological investigations

Nucleic acid amplification tests for \textit{C. trachomatis} and \textit{M. genitalium}

Diagnosis of chlamydial infection relies entirely on laboratory techniques and consequently chlamydial research has been guided and determined by developments in diagnostic technology. Over the past decade molecular techniques have been applied to chlamydial diagnosis. Nucleic acid amplification tests (NAAT) can detect \textit{C. trachomatis} DNA at a level of a few organisms per sample and the use of these techniques has led to the development of tests that combine ease of collection and transport with high sensitivity and specificity. Self obtained vaginal and vulval swabs or urine can be used and collected in non-clinical settings and mailed to laboratories for testing. This has increased patient acceptability and allowed increased flexibility in study design, which has allowed the closer integration of microbiological and behavioural research within screening and epidemiological studies.

Nucleic acid amplification tests for \textit{M. genitalium} have been developed over the past decade and polymerase chain reaction (PCR) tests are available within specialist research laboratories only. However, few studies have used such
techniques and the optimum specimen which can be used to detect *M. genitalium* has yet to be defined.

**Chlamydial serological tests**

Over the past 21 years a variety of serological techniques have been developed including: complement fixation (CF); microimmunofluorescence (MIF); whole inclusion fluorescence (WIF); EIA tests that use elementary bodies (EBs) or reticulate bodies (RBs), infected cells or recombinant enzyme-linked immunosorbent assay (rELISA) to lipopolysaccharide (LPS); and enzyme-linked fluorescent assay (ELFA).

The 'gold standard' for measuring chlamydial antibodies is the MIF test which was published in 1970. It is the most specific serological test for chlamydial species and the only one that detects species and serovar specific responses. *C. trachomatis* has 15 serovars, that is serological variants arising from variation in the major outer membrane protein (MOMP), which is located in the cell outer membrane (figure 2.2).
Figure 2.2  Major outer membrane protein (MOMP) and lipopolysaccharide (LPS) within the cell membrane of *C. trachomatis* (adapted from: Christiansen G & Birkeland S.)

![Diagram showing Major outer membrane protein and Lipopolysaccharide (LPS) within the cell membrane of *C. trachomatis*](image)

Figure 2.3  Chlamydiaceae taxonomy (adapted from: Bush RM & Everett KDE. Molecular Evolution of Chlamydiaceae)

<table>
<thead>
<tr>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
<th>Typical host</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlamydiaceae</td>
<td>Chlamydophila</td>
<td><em>C. abortus</em></td>
<td>Mammals (humans)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. psittaci</em></td>
<td>Birds (humans)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. felis</em></td>
<td>Cats</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. caviae</em></td>
<td>Guinea pigs</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. pecorum</em></td>
<td>Mammals (humans)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. pneumoniae</em></td>
<td>Humans</td>
</tr>
<tr>
<td>Chlamydia</td>
<td></td>
<td><em>C. trachomatis</em></td>
<td>Humans</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. suis</em></td>
<td>Pigs</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>C. muridarum</em></td>
<td>Mice</td>
</tr>
</tbody>
</table>
These serovars were first described by the MIF test\textsuperscript{67} and were associated with three diseases: trachoma (serovars A, B, B\textsubscript{1} and C), lymphogranuloma venereum (L\textsubscript{1}, L\textsubscript{2} and L\textsubscript{3}) and genital infection (D to K). The species and serovar specificity of the MIF test is due to antibodies that react with species and serovar specific epitopes in chlamydial MOMP.

The WIF test, which is sometimes used in preference to MIF, detects every antigen expressed by \textit{C. trachomatis}, including MOMP, LPS which is located in the cell membrane (figure 2.3), EBs and RBs. Many of these antigens are expressed by several of the chlamydial species that infect humans (figure 2.3). In particular, LPS is highly conserved within the chlamydial species and consequently the WIF test is susceptible to cross reactivity. Elimination of genus cross reactivity is important as population based studies have shown that the prevalence of antibody to \textit{C. pneumoniae} may be as high as 75\% in women aged 15 to 19 years old\textsuperscript{69}.

The theoretical weaknesses of the MIF and WIF tests are clear when they are compared against a 'gold standard' consisting of the presence of plasmid DNA in endometrial biopsy tissue samples\textsuperscript{90}. In this comparison, WIF had a sensitivity of 100\% and a specificity of 81\%, whereas MIF had a high specificity (94\%) but low sensitivity (79\%). The low specificity of WIF reflects species cross reactivity, whereas the lower sensitivity of MIF is due to the small range of antigens included in the test. The MOMPs included in the MIF test vary between manufacturers and influence test sensitivity. In addition, the accuracy of the MIF test can vary between laboratories, as was shown in a recent comparison of \textit{C. pneumoniae} MIF testing performance\textsuperscript{91}. This emphasises the importance of using standardised methodologies and controls, together with internationally recognised reference laboratories.

IgM is an unreliable indicator of infection since the absence of IgM does not indicate that an infection has not occurred. IgM may be produced in response to
an initial infection with *C. trachomatis* and is less likely to be produced in response to subsequent infection⁹⁹.

HSP60 serology measures the antibody response to the 60kDa protein and has been used to measure antibody responses in patients with PID⁹²,⁹³. The specificity of the HSP60 test is high, as much as 100% in the detection of upper genital tract infection caused by *C. trachomatis*, whereas sensitivity can be as little as 43% and 31%⁹⁰,⁹³,⁹⁴. The low sensitivity and high specificity may be due to the selection of patients in these studies as most had recently acquired upper genital tract infections and may not have developed an antibody response. Few laboratories offer testing for CHSP60 and CHSP10, and commercial tests for CHSP10 are not available. Correlation between antibodies to CHSP60 and MIF has been detected in some, but not all studies⁹⁵,⁹⁶. These differences reflect the small sample size of these studies, a lack of standardised methodologies and variations in patient groups. For example, in one study 31 healthy blood donors were compared with 45 patients with acute *C. trachomatis* infection, patients that may not have developed an immunological response to *C. trachomatis*⁹⁶. This selection bias may account for absence of a correlation between the results of the MIF and HSP tests seen in this study.

Seroconversion may take up to two months and persist for long periods of time⁹⁹. Consequently serological tests cannot distinguish between lower and upper genital tract infection or current, past and treated infection. The titre detected depends on the duration of the infection: recent infection may have a low titre, whereas an established infection is likely to have a high titre⁹⁹. To distinguish the rising titre characteristic of recent infection two tests are needed: an initial test at the first clinic visit followed by a convalescent sample taken at least six weeks later.
0.7 FACTORS ASSOCIATED WITH PID

Information from studies that identify population subgroups at increased risk of PID can be used to initiate timely, effective intervention and inform the development of health education strategies. A case-control methodology, in which a population of women with PID are compared with a group of women who do not have PID, is the most efficient method of assessing risk factors in terms of the number of patients required to participate and financial cost. All such investigations undertaken to date have been case-control studies and most have been undertaken in North America. However, these studies have a number of weaknesses. Many have been based on small sample sizes and undertaken over several years, for example one San Francisco study spanned over eight years. Consequently, they are difficult to interpret as contraceptive practice, sexual behaviour and aetiology vary over time. In addition, the studies used a laparoscopic 'gold standard'. It is unclear from the publications whether laparoscopy diagnosis was routinely used on all patients with suspected PID. If it was not used routinely these studies may have included a biased sample of patients with PID. The small sample size of many studies means that they may not be able to demonstrate statistically significant relationships and that the studies may be unable to detect relationships within the data. The studies may also be unrepresentative of the populations from which they were recruited.

Sexual behaviour

Factors associated with the development of PID are closely associated with those of STI acquisition. Sexual behaviour is a key determinant in STI epidemiology. However, few studies have explored sexual behaviour in relation to PID, and the investigations that have been undertaken have not been standardised and have not been compared with other behavioural research. Where sexual behaviour has been evaluated, few questions have been asked; some studies have explored the number of sexual partners and frequency of sexual intercourse, whereas others
have looked at the number of lifetime partners and age at first sexual intercourse. In society, sexual behaviour changes over time. For example, in the UK between 1950 and 1990 median age at first heterosexual intercourse has fallen from 21 to 17 for women, and from 20 to 17 for men. Similarly the proportion of women reporting sexual intercourse before the age of 16 has increased. In 1990, less than 1% of those aged 55 and over had had sex before the age of 16 compared with nearly 20% of teenagers. Sexual behaviour also changes over an individual's lifetime; numbers of sexual partners and frequency of sexual intercourse decline with age, and sexual orientation may vary over time. Concurrency in sexual partnerships increases STI transmission and is most frequently reported in both sexes under 24 years of age. Partner concurrency was significantly associated with increased risk of genital chlamydial infection in the second National Survey of Sexual Attitudes and Lifestyles (Natsal 2000). Risk of PID may be associated with sexual behaviour over a substantial period of time and, since this is likely to be a confounder in any risk factor evaluation, it is important that data are collected on as many aspects of sexual behaviour as possible.

Age

Young people are behaviourally vulnerable to STI acquisition as they generally have higher numbers of sexual partners, higher numbers of concurrent partners and a higher frequency of partner change than older age groups. Young women may be at particular risk of infection because they do not have the skills and confidence to negotiate safer sex. High PID rates in women aged 16 to 24 years could reflect longer duration of infection or reduced clearance of chlamydial infection due to a lower concentration of protective chlamydial antibodies, larger cervical ectopy, or a greater permeability of cervical mucus compared with older age groups. Frequency of unprotected sexual intercourse is related to increased risk of PID among monogamous women as spermatozoa with attached C. trachomatis have been found in the upper genital tract of women with PID. Aspects of sexual behaviour, such as age at first
sexual intercourse, number of lifetime sexual partners, frequency of partner change and unsafe sex, are key determinants of STI transmission. In turn, age at first sexual intercourse and the number of lifetime sexual partners are known to vary with marital status, cohabitation and socio-economic group. The relationship between PID and socio-economic status is likely to reflect surrogate markers of sexual behaviour.

Contraception

Consistent, effective condom use reduces the risk of STD transmission and will prevent PID. However, inconsistent use of barrier contraception will not prevent PID, which is why barrier contraception is not always associated with a decreased risk of PID. It is thus important to gain information on contraceptive behaviour over a period of time and to know whether condoms were used to prevent pregnancy, infection or both. Spermicides have also been associated with a reduced risk of PID. The use of diaphragms also reduces the risk of PID although, as they are usually used with a spermicide, the reasons for this protective effect are unclear.

The association between PID and oral contraceptive (OC) use is incompletely understood. OCs are thought to prevent changes in the vaginal flora associated with BV, do not prevent gonococcal PID and have been associated with a 50% decrease in chlamydial PID. It is unclear whether OCs reduce the risk of chlamydial PID by altering the composition of cervical mucus or suppressing the immune response to chlamydial infection thereby promoting asymptomatic or silent PID. However, although OC may reduce the risk of infection, condoms are the only effective method of preventing the transmission of bacterial STIs during sexual intercourse.

Since their introduction in the 1960s, several types of OCs have been marketed: the first generation pill (high dose progesterone and œstrogen) of the 1960s, the second generation pill (low dose œstrogen and progesterone) and the third generation pill that became available in the 1990s. The use of OCs is likely to
have influenced the epidemiology of PID but its impact is difficult to assess. Risk factor investigations have been undertaken between 1970 and the 1990s during which a range of OCs have been used. These variations could have influenced risk factor studies; consequently comparability between studies is difficult.

In Britain, OC is used by 25% of reproductive age women but reliance on this contraceptive method varies with age and marital status. OC use declines steeply with age: 64% of women aged between 16 and 24 years used OC within the past year compared with 10% of those aged 35 to 44. Lower use in older women probably reflects guidelines on the use of combined pill in the over 40s. Over 50% of single and cohabiting women use OC compared to 20% of married women. OC is the contraceptive most commonly prescribed to teenage women and its use may coincide with first sexual intercourse or partner change, moments when women may be at increased risk of acquiring an STI.

**Smoking**

Cigarette smoking has been associated with increased risk of PID and is thought to either compromise the immune response to infection or oestrogen activity. It is also likely that smoking reflects poor health seeking behaviour in lower socio-economic groups and could reflect higher sexual risk.

**Douching**

Douching has been associated with increased risk of PID as it is thought to alter the microbiological environment of the vagina and flush bacteria into the uterus. In the USA douching is common amongst reproductive age women: a third of White women and two thirds of Black women douche regularly. However, less than 0.25% of UK women report this behaviour and thus it is unlikely to be an important factor associated with PID in the UK.

**Ethnicity**

US surveillance data from the National Disease and Therapeutic Index Survey (a measurement of consultations at private physician clinics, see section 2.10)
indicate that PID incidence amongst non-white women was 1.6 times that in white women\textsuperscript{120}. This probably underestimates the burden of PID within non-white women, as this group are less likely to consult a private physician than white women. In the US, ethnic groups (African-American, Hispanic, Asian/Pacific Islander, Native American) experience consistently higher rates of chlamydia and gonorrhoea than whites, but only two studies have reported increased risk of PID associated with African-American ethnicity\textsuperscript{24,99,121}. In the UK, increased risk of gonorrhoea and \textit{C. trachomatis} infection has been associated with black ethnic origin, but no investigations have explored the relationship between ethnicity and PID\textsuperscript{122-124}.

\textit{Socio-economic status}

Some sections of society are at higher risk of STDs than others but high risk groups can be difficult to define or identify as they may be marginalized in society\textsuperscript{125}. Lower socio-economic status has been associated with increased risk of STIs but despite the importance of socio-economic status to STI epidemiology, only two risk factor studies have taken socio-economic status into consideration and of those studies that explored the relationship between income and risk of PID, none found an independent relationship\textsuperscript{110,116}.

\textit{Iatrogenic PID}

IUD insertion, dilation and curettage, hysterosalpingography and termination of pregnancy (TOP) have been associated with iatrogenic PID, which occurs when instrumentation facilitates the introduction of vaginal and cervical microorganisms into the endometrial cavity\textsuperscript{126}. The contribution of iatrogenic PID to the burden of PID depends on the number of procedures and the use of antibiotic prophylaxis. In the UK, IUDs are used by only 3\% of reproductive aged women\textsuperscript{101}.

\textit{Problems of interpreting the evidence base}

Factors associated with PID in England and Wales have not been investigated. Findings from studies in other countries cannot be extrapolated as factors that
influence PID epidemiology, such as health care provision, health seeking behaviour, sexual behaviour, contraceptive practice and disease aetiology, vary between countries and over time. Evaluation of the evidence base indicates that it is essential that future studies are of adequate size and include a detailed evaluation of these determinants of incidence.

2.8 Treatment

A number of evidence based, broad spectrum antibiotic therapy regimes are recommended for the treatment of PID, and cover *N. gonorrhoeae, C. trachomatis* and anaerobic infection\textsuperscript{127,128}. All are given orally and treatment duration is around two weeks. No guidelines are available for the treatment of *M. genitalium*. In vitro antibiotic susceptibility of *M. genitalium* is similar to that of *C. trachomatis*, that is tetracycline, erythromycin, azithromycin and fluoroquinolones\textsuperscript{129}. Nevertheless, alternative treatment regimes need to be explored as antibiotics only suppress the growth of mycoplasmas, and antibiotic resistance in *M. genitalium* is theoretically possible but has not been described. Partner notification is an essential component of case management as it prevents reinfection and the spread of disease through sexual networks. Treatment failure can be due to reinfection, non-compliance with treatment or antibiotic resistance. Antibiotic resistance is an emerging issue in the management of bacterial infections as treatment failure can lead to an increased duration of infectiousness and an increased risk of the development of sequelae, such as PID. Antimicrobial resistance in *N. gonorrhoeae* is well documented and, in England and Wales in 2002, resistance to antibiotics used in first line therapy (penicillin and ciprofloxacin) accounted for 10\% of diagnoses\textsuperscript{123}. Few studies have explored the mechanisms and clinical significance of antimicrobial resistance in *C. trachomatis*\textsuperscript{130}. The widespread introduction of screening for *C. trachomatis* could potentially influence antimicrobial susceptibility. Three isolates of *C. trachomatis* which showed multidrug resistance to doxycycline, azithrocycline and ofloxacin have been reported, but antibiotic resistance is not a common clinical problem in
humans although tetracycline resistant *C. suis* has been reported in pigs in Nebraska\(^{130,131}\).

### 2.9 Current Approaches to Diagnosis

High diagnostic accuracy is essential to effective patient management. It determines the quality of surveillance and epidemiological studies, which in turn influences the efficiency of control and prevention strategies. The diagnosis of PID is notoriously difficult because clinical presentation can include a wide spectrum of unspecific signs and symptoms. This can delay management which, in turn, may contribute to the development of sequelae\(^{68}\). A variety of diagnostic techniques have been evaluated and were recently reviewed\(^{132}\). However, the quality of evidence is variable and confined to category III because studies are observational. They have also been small scale and some techniques have only been used at a single location.

Laparoscopy is considered the diagnostic ‘gold standard’ in patient management and academic papers. However, the risks associated with this invasive procedure outweigh the benefits. In the UK, few women with a clinical diagnosis of PID undergo laparoscopy as it is a costly procedure which is considered unethical if a competing diagnosis is not suspected and/or there is no need to alleviate symptoms, or where elements of the Hager definition are missing\(^2\).

Endometrial biopsy specimens can be taken under local anaesthesia and tested for the presence of intraepithelial polymorphonuclear leukocytes and/or plasma cells\(^{133}\). When compared to laparoscopy, endometrial biopsy is reported to have a sensitivity of 92% and a specificity of 87%\(^{134}\). The lower sensitivities and specificities reported by some studies may be due to the uneven distribution of endometrial inflammation. Fimbrial biopsy, removal of one of the fimbrial ends, and fimbrial mini biopsy, removal of a tissue sample from a fimbrial end, have been used in some studies but, since they have to be undertaken during laparoscopy, they have not been widely used. Laparoscopy has low sensitivity
(50%) and specificity (80%) for detecting PID when compared to fimbrial mini-biopsy and plasma cell endometritis\textsuperscript{87,134}. This is because laparoscopy may not identify mild intratubal inflammation and cannot detect endometritis. Evidence of endometritis may develop before infection reaches the fallopian tubes, although infection may reach the fallopian tubes via the parametrium, and thus endometrial biopsy may fail to detect some cases\textsuperscript{135}.

Inter-observer variation in the consistency of laparoscopic results has never been tested and thus comparability between studies is open to question. It has been suggested that a new ‘gold standard’ should include laparoscopy and endometrial biopsy, and that all cases diagnosed either histologically or laparoscopically should be considered true cases.

Culdocentesis, the aspiration of material from the Pouch of Douglas through the posterior fornix, has been used in North America. It has not been evaluated in women with mild or atypical disease, and no comparative studies have used culdocentesis with either laparoscopy or endometrial biopsy. There is a poor correlation between microbiological specimens obtained by culdocentesis and laparoscopy\textsuperscript{136}.

Pelvic imaging techniques, such as ultrasound, transvaginal colour and pulsed Doppler, computed tomography and magnetic resonance imaging, have been used as diagnostic tools, but there is insufficient evidence to assess the value of ultrasound particularly in the context of atypical presentation. Magnetic resonance imaging has also been used as a PID diagnostic tool and is considered more accurate than transvaginal ultrasonography\textsuperscript{137}. Both techniques require expensive equipment that is not generally available in primary care settings.

Tests for the presence of aetiological agents in the lower genital tract cannot be used as a PID diagnostic test because not all patients with PID have evidence of lower genital tract infection (section 2.4). However, the presence of lower genital tract infection has been included in diagnostic guidelines\textsuperscript{128}.
A range of laboratory tests have been suggested as non-invasive diagnostic tests including: examination of vaginal wet preparations for the presence of white blood cells\textsuperscript{138,139}, white blood cell count\textsuperscript{138,140}, erythrocyte sedimentation rate (ESR)\textsuperscript{138,139}, C-reactive protein\textsuperscript{141,142}, amylase\textsuperscript{143}, IFN-\(\gamma\)\textsuperscript{144} and CA-125\textsuperscript{145}. Increased vaginal white blood cells has been suggested as a sensitive indicator of upper genital tract infection and that combinations of results from various tests improve diagnostic accuracy, although these may be markers of other pathologies\textsuperscript{138}. However, the evidence base is limited and comparisons between studies are difficult to make because of differences in study design, sample size and the ‘gold standard’ used (some used laparoscopy whereas others use the presence of endometritis).

In the UK, despite the availability of a range of diagnostic tools, the standard method of diagnosis in primary care, GUM, and O&G clinics is based on the interpretation of clinical signs and symptoms, and exclusion of competing diagnoses, such as pregnancy, ectopic pregnancy and appendicitis. However, although signs and symptoms may be diagnostic markers, none is pathognomonic of PID. Seven studies have evaluated the accuracy with which signs and symptoms predict the presence of laparoscopically diagnosed PID and these were the subject of a review published over a decade ago\textsuperscript{11,139,141,142,146-148}. Hager et al. recognised that the diagnosis of PID was usually made on the basis of clinical criteria, which varied between institutions\textsuperscript{12}. The Hager definition was derived from an evaluation of data collected as part of the Lund study of reproductive events after laparoscopically diagnosed PID (section 2.5). Hager et al. recognised that lower abdominal pain was the most frequent symptom seen in patients with laparoscopically confirmed acute salpingitis (which is not surprising as this was the entrance requirement to the Lund study), and that high rates of adnexal tenderness, fever and abnormal vaginal discharge were seen in patients with acute salpingitis. The Hager definition and the Lund data have been used extensively in the formulation of diagnostic guidelines for PID but the definition is recognised as lacking sensitivity because laparoscopy only has a
sensitivity of 64% in predicting the presence of PID compared to a fimbrial histopathologic ‘gold standard’.

2.10 Incidence, Prevalence, Trends and Disease Burden

Although PID is not associated with high mortality, it is associated with high morbidity. The WHO estimates that PID accounts for 94% of morbidity associated with STIs in women (including HIV) in EMEs but the absence of validation studies and an explanation of how the estimates were derived make interpretation difficult. Nevertheless, the data indicate that a substantial burden of PID exists in many countries and, as such, PID represents an important health care issue.

There have been no population-based studies of PID and consequently much of our knowledge of the incidence and prevalence of PID relies on surveillance data. Surveillance ‘is the collection, collation and analysis of data to detect changes in trends or distribution to initiate investigative or control measures’. It plays a key role in epidemiological investigations by establishing an evidence base to identify risk groups, set priorities, monitor, audit and evaluate intervention and control programmes. The diverse and non-specific signs and symptoms associated with PID mean that women with PID may seek clinical management at a variety of clinical settings, such as general practice, family planning, GUM, accident and emergency, and O&G clinics. However, sources of surveillance data are limited and are only available for North America and a few European countries.

Sweden

Anecdotal observations and ad hoc studies are the only source of surveillance data prior to the 1950s. The burden of PID decreased substantially in Sweden after the introduction of chemotherapy: for example, the number of PID cases seen in Stockholm fell by 66% between 1932 and 1942. However, these data may be inaccurate as many PID cases were attributed to other diagnoses. Although national surveillance has never been undertaken in Sweden, data from four
Swedish counties, Göteborg, Lund, Örebro and Malmö give an insight into the factors that influence PID epidemiology. In Göteborg, between 1950 and 1959, the incidence of gonococcal salpingitis was relatively stable at 0.2 per 1000 population. The epidemic of *N. gonorrhoeae* experienced by industrialised countries in the 1960s peaked in Sweden in 1970. In Lund, this corresponded with an increase and subsequent decrease in PID incidence in the 15 to 24 year age group between the periods 1960 to 1964, and 1970 to 1974 (figure 2.4). The proportion of first episodes of PID increased until 1984 when almost all diagnoses were first episodes. Similarly, by 1985 to 1989 virtually all PID cases were related to *C. trachomatis* infection, and few were attributed to gonorrhoea or other aetiological agents. The Lund study also provides an insight into the influence of sexual behaviour on PID. Between 1970 and 1974, 50% of sexually active 15 year olds had four or more partners within the past year compared to 20% in 18 year olds. This is reflected in the sharp decrease in the incidence of first episodes of PID with increasing age: the risk of acquiring PID was 1:8, 1:10 and 1:80 among women aged 15, 16 and 24 respectively (figure 2.5). The public health response to the Swedish *N. gonorrhoeae* epidemic was centred on education, diagnosis, treatment and partner notification. Safe sex was promoted through sexual health awareness campaigns and increased availability of condoms. Condoms were commercially advertised and sales increased by 40% (35m to 50m) between 1970 and 1972. The decline in both *N. gonorrhoeae* and first and repeat PID episodes, together with a change in sexual behaviour brought about by primary prevention, suggest that the observed decrease in PID incidence was real.

The use of IUDs also influenced PID epidemiology and this can be seen in data from Örebro (figure 2.6). The incidence of acute gonococcal salpingitis decreased from 43% (54/126) in 1970 to 0% (0/63) in 1988 and the incidence of chlamydial salpingitis fell from 28% (27/96) in 1985 to 8% (2/25) in 1994. Despite these
Figure 2.4  Incidence of PID, Lund, Sweden: 1960 to 1994\textsuperscript{153,154}

Figure 2.5  Incidence of PID amongst sexually active women aged 15 to 24 years old, Lund Sweden: 1970 to 1974\textsuperscript{156}.
decreases hospital inpatient admissions for PID varied by less than 16% from year to year in the early 1970s and 1980s and increased by 75% in the mid-1970s, highest increases being seen in the 20 to 24 year age group. This peak in admissions coincided with an increased use of IUDs in nulliparous women, which rose from 3% in 1971 to 29% in 1974 \textsuperscript{154,158}. However, it is not possible to establish a causal association between IUD use and PID prevalence on the basis of these ecological data.

Data from Malmö show the relationship between \textit{N. gonorrhoeae}, PID and ectopic pregnancy (figure 2.7)\textsuperscript{152}. Cases of \textit{N. gonorrhoeae} peaked in 1970 and then fell by 98% between 1970 and 1988 after which cases plateaued. Salpingitis cases peaked in 1975 and then fell by 90% between 1974 and 1996. This sequence of events was mirrored in the rise in the number of ectopic pregnancies seen between 1985 and 1995. The increases in ectopic pregnancy may be related to the earlier peak in PID, but could also reflect an increase in genital chlamydial infection.

The Swedish regional surveillance data show a distinctive sequence of events. A primary epidemic of \textit{N. gonorrhoeae} was followed by a secondary PID epidemic that peaked at 11/1000 women aged 15 to 39 between 1970 and 1974, and then declined as a tertiary ectopic pregnancy epidemic emerged\textsuperscript{159}. However, it is not possible to establish a causal association between trends on the basis of ecological data. The studies also show that PID epidemiology is influenced by sexual behaviour, health policy (such as changes in contraception recommendations), intervention and control. All the studies potentially underestimate the true burden of PID as they are based on hospital inpatient data, that is acute cases, women experiencing recurrent chronic pain, and long term reproductive health problems associated with PID. Consequently the data are not representative of the true reservoir of PID in the general population.
Figure 2.6  Incidence of PID by age group, by five year time period, Örebro, Sweden: 1970 to 1994

Figure 2.7  Trends in *N. gonorrhoeae*, PID and ectopic pregnancy, Malmö, Sweden: 1969 to 1996
In 1970, the number of reproductive age women who reported ever having been treated for PID was similar in Sweden (15%) to that in the USA (10%) and the reported incidence of PID was also similar in these countries (14/1000 women aged 14 to 34)\(^{6,10}\). However, since 1970 the burden of STIs has varied between countries in response to variations in STI transmission patterns, contraceptive practice and intervention. Consequently the epidemiology of PID in the USA has followed a different course from that in Sweden. US surveillance data are derived from several sources: the National Hospital Discharge Survey (NHDS: which includes the number of inpatient attendances for PID, and includes repeat attendances), and National Disease and Therapeutic Index (NDTI: a sentinel survey of visits to private physicians offices).

These data indicated that PID incidence peaked in the early 1980s amongst women aged 20 to 24 (4.5/1000 person years) and 25 to 29 (12/1000 person years) in the NHDS and NDTI respectively\(^ {12}\). The NDTI contains variables on individual patients, such as ethnicity, but analysis of these data cannot be used to provide an accurate view of PID epidemiology as they do not include information on potential confounding factors such as socio-economic status, or sexual behaviour.

It is unclear whether the decreases seen in the NHDS and NDTI datsets reflect a true decrease as the data are influenced by changes in disease aetiology, diagnosis, management and referral practice (figures 2.8 and 2.9). An increasing proportion of chlamydial (subclinical) PID cases could account for this decrease in observed cases.
Figure 2.8  PID: hospitalisations (NHDS) of women aged 15 to 44, United States: 1980 to 1999

Figure 2.9  PID: initial visits to physicians offices (NDTI) by women aged 15 to 44, United States: 1980 to 2000
Similarly variations in diagnostic criteria, which vary between clinical settings and practitioners may have changed over time: those who were treated as inpatients during the 1980s may have been treated as outpatients in the 1990s. In addition, the NDTI excludes public clinics and thus those at increased risk of disease, such as some ethnic minority groups, refugees, commercial sex workers and those of low socio-economic status, could be excluded. This would substantially underestimate PID prevalence.

*Other industrialised countries*

Few countries have surveillance data that are consistently available over time. Data from Canada and Holland have been published\(^{161,162}\). Although these datasets are not complete over time, they indicate that there was a decline in inpatient episodes due to PID in the late 1980's, a fall that was also seen in the Swedish and USA data.

*England*

Few systematically collected PID surveillance data have been published for England, but information is available from four sources: the Oxford Record Linkage Study (ORLS), the hospital inpatient enquiry (hospital inpatient episodes statistics), the Royal College of General Practitioners (RCGP) Weekly Returns Service, and the National Survey of Sexual Attitudes and Lifestyles (Natsal 2000) undertaken for the UK\(^{26,103,163,164}\). The ORLS, conducted between 1970 and 1985, illustrated the long term consequences of PID. Hospital inpatient data indicate that highest prevalence and highest rates of increase are consistently seen in the 16 to 24 year age group, which reflects the substantial number of bacterial STIs seen in the 16 to 19 year age group (figure 2.10)\(^{165,166}\). Hospital inpatient data consist of acute cases, women experiencing recurrent chronic pain, and long term reproductive health problems associated with PID. As such, these data are unlikely to be representative of the true reservoir of PID in the general population. Data from the RCGP Weekly Returns Service are collected from 77 practices throughout England and Wales. The report includes a diagnostic
category called 'female pelvic inflammatory disease', although incidence in both females and males is published! This source of information is particularly difficult to interpret given the persistent incidence of PID in males, and non-reproductive age women (figure 2.11)\(^{163}\). Similarly, the high incidence in the 0 to 4 year age group indicates that the general practitioners who took part in the study did not use accurate diagnostic criteria. Nevertheless, the dataset does show the problems associated with using general morbidity surveillance data to look at specific diagnoses. The Natsal 2000 stratified probability sample survey found that 2.2% (95% CI 1.8 to 2.6) of women aged 16 to 44 reported having ever had PID and that 30% (95% CI 23 to 39) of those who reported having been diagnosed with PID had attended GUM services\(^{103}\). This represents the cumulative incidence of disease and indicates that PID is a substantial problem to the health of reproductive age women in the UK.

Figure 2.10 PID: hospital inpatient attendances by age group, England and Wales: 1966 to 1985\(^{164,165}\)
2.11 Problems of PID surveillance

The problems associated with surveillance stem from the fact that no single infection causes PID, no signs or symptoms are pathognomonic, and a cheap, simple, accurate diagnostic test does not exist. Consequently it is difficult to formulate a diagnostic ‘gold standard’. PID surveillance data are influenced by variations in case definitions between clinical settings, changes in disease chronicity associated with clinically mild chlamydial infection, variations in health seeking behaviour, variations in the use of IUDs and the increased management of PID in out patient settings\textsuperscript{167,168}.

Trends in reports of PID cannot be inferred from genital chlamydial infection surveillance data as these are heavily influenced by case ascertainment bias and unrepresentative of the true reservoir of genital chlamydial infection in the general population. In addition, short-term reductions in the prevalence of genital chlamydial infection may be associated with reduced duration of infection rather than reduced incidence. The prevalence of genital chlamydial infection cannot be inferred from that of gonorrhoea as the epidemiology of these
infections are different. The biases inherent in the surveillance of PID, related infections and sequelae make it difficult to assess trends in PID prevalence with certainty.

2.12 COSTS ASSOCIATED WITH PID

Both PID and its sequelae are expensive to individuals, health care systems and economies, costs that have increased substantially since the development of assisted reproduction techniques, such as in vitro fertilisation. In 1992, the cost of a subfertility service in one health district in England and Wales with a population of 46,000 women aged 20 to 44 years was estimated to be £0.88 million, giving a national total of £75 million. About 20% (£15 million) of this cost was likely to be associated with genital chlamydial infection and thus could have been prevented. The economic impact of PID has yet to be evaluated in the UK. In the USA, direct and indirect costs associated with PID and its sequelae were estimated at over $4.2 billion in 1990 and, assuming a constant incidence, was projected to exceed $10 billion by the year 2000. However, this study may have under estimated the economic burden associated with PID as the true incidence of PID is unknown.

2.13 PREVENTION AND POTENTIAL FOR HEALTH GAIN

Substantial health gains could be made from the prevention of PID. There are three approaches to effective control: education and behavioural change (primary prevention), screening for asymptomatic infection (secondary), and diagnosis and treatment of symptomatic disease (tertiary).

Primary prevention, based on education and behavioural change, is fundamental to disease control. Behavioural change, such as the increased use of barrier contraception and delayed sexual debut brought about by HIV and STI health campaigns, has been documented in European countries and has been associated with reduced incidence of symptomatic PID. However, in the UK low
awareness of PID amongst health care professionals and the public is an obstacle to primary prevention. Vaccination is potentially the most effective long-term method of controlling *C. trachomatis* infection and could be less costly than screening. Computer modelling has shown that vaccination would rapidly reduce the prevalence of *C. trachomatis* but the candidate vaccines developed to date have not been effective because the conferred immunity is short lived and serovar specific.\(^{171}\)

Since a substantial proportion of PID cases are chlamydial in origin, the prevention of costs associated with PID and related sequelae is a key benefit that is anticipated from screening for genital chlamydial infection. The high level of asymptomatic genital chlamydial infection emphasises the role of screening for this infection to the prevention of pelvic infection. Secondary prevention, or the diagnosis and treatment of asymptomatic genital chlamydial infection, has been shown to be successful in reducing both the prevalence of genital chlamydial infection and associated PID. The only randomised controlled trial (RCT) to have assessed the effectiveness of chlamydial screening was undertaken in Puget Sound, Washington State, USA between 1990 and 1992.\(^{49}\) The study was based on women aged 18 to 34 years of age who were identified as being at increased risk of PID using a questionnaire. Women were randomly assigned to undergo testing for *C. trachomatis* (n=1009) or receive usual care (n=1598) and both groups were followed for one year. The study showed that a decrease in the prevalence of genital chlamydial infection was associated with a significant reduction in PID prevalence: relative risk (RR)=0.44 (95% CI 0.20 to 0.90). However, at the time of publication, concerns were raised about problems in the study methodology. Firstly, subjects were not randomised before they had been assigned to either the intervention or control arms of the study. Women were recruited more aggressively to the intervention arm and this led to the recruitment of 20% more women to this arm of the study, which is a potential source of bias.\(^{172}\) Secondly, there was different service usage between the screening and control groups. The screening arm was subject to intensive contact with health care services, which
may have been seen as health education by those taking part. Consequently, education, rather than screening could have been responsible for the observed differences: the study could have measured change in sexual behaviour as much as change in PID incidence bought about by screening\textsuperscript{173}. Thirdly, 364 subjects were excluded from the 1009 assigned to the screening and treatment arm of the study. These women were not screened, received no intervention and thus did not differ from the control group. In the paper, the women were included in the screening and intervention arm and the study produced a significant result. However, if they had been were included in the control group, the RR of PID in the screening group would have been 0.60 (95% CI 0.22 to 1.3, p=0.22). In contrast, if the subjects had been excluded from the analysis, the RR would have been 0.52 (95% CI 0.19 to 1.2, p=0.11)\textsuperscript{174}. Fourthly, it is unclear as to how the PID cases were diagnosed. It appears that most diagnoses were based on a combination of clinical presentation, diagnosis reported by subjects, or as recorded in the patient's medical notes. Only three were likely to have been diagnosed using laparoscopy. As discussed in section 2.9, as a basis for the diagnosis of PID clinical presentation lacks sensitivity and specificity, and it is likely that some of the subjects diagnosed with PID did not have PID. This, together with the misclassification of a large proportion of subjects may have resulted in a biased study and the detection of a false positive result. Evidence for the effectiveness of chlamydial screening from this RCT is thus unconvincing and further studies are needed.

In Wisconsin, USA, intervention based on screening for genital chlamydial infection reduced the incidence of PID and ectopic pregnancy by 33% and 20% respectively over a five year period\textsuperscript{175}. Ecological evidence from a Swedish intervention programme also suggests that screening for genital chlamydial infection can rapidly reduce the incidence of ectopic pregnancy amongst 20 to 24 year olds, but no evidence to support these associations is available from RCTs\textsuperscript{176}. No study has demonstrated that genital chlamydial screening can reduce the prevalence of TFI.
Theoretical studies have attempted to quantify the cost-effectiveness of a genital chlamydial screening programme. Based on various assumptions, the threshold prevalence of genital chlamydial infection at which screening becomes cost-effective has been estimated to be between 3.9% and 6% (using NAATs and azithromycin treatment)\(^{177}\). However, threshold prevalences as high as 14% have also been suggested\(^{177}\). One reason for this wide variation is that many studies only take the burden of symptomatic PID into account. Sensitivity analysis indicates that a key determinant in the assessment of chlamydial screening cost-effectiveness is the prevalence of PID\(^{177}\). If studies are extended to include subclinical or undiagnosed PID, the threshold prevalence at which screening is cost-effective may be at least as low as 3.9%\(^{177}\). This emphasises the importance of accurately estimating the prevalence and incidence of PID.

Tertiary prevention, the prompt recognition and treatment of symptomatic PID, is also required to reduce repeat episodes and further sequelae. Although antibiotic prophylaxis prior to either IUD insertion or TOP is considered to both reduce the risk of iatrogenic PID and be cost-effective, this evidence is not based on double blinded, RCTs\(^{178,179}\).

Prevention of re-exposure to infection through partner notification is an integral part of PID management. Health care professionals need to recognise disease symptoms, promote timely self-referral to treatment centres and encourage therapy compliance amongst both women and their partners. In the UK, PID management guidelines have been published by a variety of professional bodies but their impact is difficult to assess\(^{128,180}\). This represents a missed opportunity for control and prevention. Professional and public education is required to improve knowledge, attitudes and skills to ensure effective case management.

2.14 Study rationale

Epidemiological and surveillance data are crucial to effective disease control as they provide an evidence base for public health action: to define those at risk, set
priorities, plan interventions and allocate resources. The CMOs Expert Advisory Group on C. trachomatis highlighted the urgent need for information concerning PID epidemiology, particularly the assessment of intervention programmes aimed at genital chlamydial infection\(^4\). It is only by using PID as an end point measure in such a study that the true reproductive health impact of intervention can be measured\(^5\). Lack of knowledge of PID epidemiology also represents a gap in our knowledge of STI epidemiology. It prevents a true realisation of the burden of reproductive morbidity amongst women and the development of an evidence based approach to the provision of health services. From this literature review a number of key epidemiological research priorities can be identified (table 2.4). Priorities 1 to 4 are addressed within the aims and objectives of this thesis. Points 5, 6 and 7, which build on work included in the thesis, are discussed in the further work suggested within chapters 4 to 8 and the general discussion (chapter 9).

**Table 2.4 Key epidemiological research priorities**

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<td>1</td>
<td>Develop a case definition for use in epidemiological research</td>
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<td>2</td>
<td>Establish social, behavioural and demographic factors associated with PID</td>
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<td>3</td>
<td>Estimate disease prevalence/incidence</td>
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<td>4</td>
<td>Estimate the proportion of PID cases associated with C. trachomatis</td>
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<td>5</td>
<td>Improve surveillance in a range of primary care settings</td>
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<td>6</td>
<td>Investigate disease aetiology and establish diagnostic &amp; management guidelines for use in patient management systems</td>
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<td>7</td>
<td>Implement validated, representative, active sentinel surveillance</td>
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New methods of monitoring PID are urgently required, but a number of methodological issues need to be addressed before epidemiological studies can be undertaken. These problems are not new, many, such as the lack of a simple, specific diagnostic method, variations in reporting practice and reliance on small-scale studies, were described by Weström in 1980\(^6\). The fundamental research problem is concerned with case definition and diagnostic accuracy, but in the quest to solve these problems, tests are becoming increasingly invasive. Such
techniques may improve individual patient case management but will not improve knowledge of PID epidemiology as the use of invasive techniques has resulted in predominantly small-scale, unrepresentative studies that have inherent selection and participation biases. PID epidemiological studies have to move away from a reliance on invasive diagnostic techniques towards a syndromic diagnosis that can be used in a variety of clinical settings, including primary care. Whilst this may not offer a perfect solution in terms of diagnosis, as it would compromise diagnostic accuracy, it would allow representative studies to be undertaken. Syndromic diagnosis could be incorporated within established management guidelines but this is controversial as the use of such methods in the control of STIs in developing countries has been disappointing. A diagnostic algorithm would also be difficult to validate in terms of sensitivity and specificity. There is no perfect solution to these problems but epidemiological data are needed and consequently compromises in case definition have to be made.

2.15 CONCLUSIONS

PID is a key issue facing women’s reproductive health in England but little is known about its epidemiology and there are a number of methodological problems that prevent epidemiological studies from being carried out effectively. The aim of this thesis is to explore the epidemiology of PID in England. It will evaluate available surveillance data, develop a case definition for use in epidemiological research, assess current diagnostic and management practice in primary care, and investigate social, behavioural and demographic factors associated with PID.
Chapter 3 General methods

3.1 LITERATURE SEARCH METHODOLOGY

Literature searches were carried out on Medline (PubMed) using the key words 'pelvic inflammatory disease', 'endometritis', 'salpingitis', 'laparoscopy', 'endometrial biopsy', 'Chlamydia trachomatis', 'Mycoplasma genitalium', and the names of authors known to have published studies concerned with PID and C. trachomatis. The searches showed that the literature is widely dispersed through the Medline journals and many key epidemiological sources were not quoted on Medline. Much of the literature review was undertaken by requesting references quoted in papers through inter-library loan services, or searching for them in through the World Wide Web (Internet). I also contacted experts in the field for permission to use unpublished literature and data sources.

3.2 PEER REVIEW AND ETHICAL APPROVAL

All investigations undertaken in chapters 4 to 8 were peer reviewed by the Communicable Disease Surveillance Centre (CDSC) Project Review team and the Public Health Laboratory Service (PHLS) Research and Development review. For the case-control study (chapters 7 and 8), ethical approval was sought from and given by the Public Health Laboratory Service (PHLS), Wirral Health Authority (HA), Liverpool HA, South Sefton HA, Wandsworth HA and the Multi-Centre Research Ethics Committee (Northern).

3.3 CONFIDENTIALITY OF PATIENT IDENTIFIABLE INFORMATION

All data capture, storage, handling and retrieval procedures were audited by the CDSC Caldicot Committee and complied with established PHLS policy for handling patient identifiable information. Permission to use the electronic version of the Hospital Episodes Statistics (HES) dataset was given by NHS Security and Confidentiality Committee.
3.4 Statistical methods

Apart from the discriminant analysis given in chapter 6 which used SPSS for Windows, all analyses were performed using STATA 6[^1][^2]. Sample size calculations were made using SAMPLE, a GLIM4 based statistical system[^3].
Chapter 4 Evaluation of surveillance data derived from health care settings

4.1 INTRODUCTION

PID is characterised by a wide spectrum of clinical presentation: patients with PID may access a variety of clinical services, such as general practice, family planning, GUM, Accident and Emergency and O&G. The aim of this study was to critically evaluate the available surveillance data in different clinical settings (objective 1 section 1.3). Data from the investigation are presented in papers 1 and 2 (appendix 5)\textsuperscript{185,186}.

4.2 METHODS

*Systematic review of surveillance datasets*

A systematic review of national and local sexual health surveillance data sources was undertaken (appendix 1)\textsuperscript{187}. Several datasets are available from a range of health care settings but most are limited in coverage and scope, and many settings do not record diagnostic information as part of data collection. Only 5 datasets included a diagnosis of PID.

*Reports from GUM clinics on form KC60 (Körner code 60)*

GUM clinics have a statutory obligation to report to CDSC (which collects data on behalf of the Department of Health) on form KC60. Coverage approaches 100\%\textsuperscript{1}. The KC60 form collects data on diagnosis, including diagnoses of uncomplicated gonorrhoea and genital chlamydial infection, and workload and has been used since the second quarter of 1988. Clinics complete returns to standard diagnostic guidelines. Although the KC60 dataset does not include PID as a separate diagnosis, it may be recorded in one of the following categories: B5 (gonococcal complications), C4B (complicated chlamydial infection) and C5 (complicated non-gonococcal/non-specific infection). Not all diagnoses within these categories are PID as these codes may refer to other conditions, such as
reactive arthritis. The aggregate KC60 dataset contains a limited range of parameters: clinic, condition, sex, number of male cases homosexually acquired (selected conditions only), and age group (selected conditions only). Factors such as ethnic group, socio-economic status and sexual behaviour are not collected.

The previous data collection form, the SBH60 return, was used by the Department of Health between 1971 and the first quarter of 1988. The codes used in the SBH60 return were more restricted than in the KC60 return and there was no specific code for PID. The only code that PID could have been recorded under was B1.4 (new cases of gonorrhoea – upper genital tract complications). Prior to 1971, data from GUM clinics were collected under the Veneral Disease Regulations. These data did not include a category under which PID could be recorded. Factors such as ethnic group, socio-economic status and sexual behaviour were not collected as part of either the SBH60 return or the Veneral Disease Regulations.

Hospital Episode Statistics & Hospital In-patient Enquiry

Between 1964 and 1985, the Hospital Inpatient Enquiry (HIPE), a national 10% sample of hospital admissions, was used to estimate total hospital inpatient admissions. The Hospital Episodes Statistics (HES), which has been collected since 1987, included hospital inpatient attendances based on a 25% extract sample of finished consultant episodes. Diagnostic coverage has varied over time and increased from 70% in 1988/9 to 94% in 1992/3. The Department of Health estimated the total burden of diagnoses in each year based on the distribution of cases in the original sample. The first year of HES, 1987/8, was not included here as coverage was incomplete.

The coding of PID in the hospital inpatient data also changed over time. Up to 1977, the 8th International Classification of Disease (ICD) coding system was used (PID: codes 612, 613, 614, 616), between 1978 and 1995 the 9th ICD coding system was used (PID: 614, 615), and from 1995 quarter 2 to the present the ICD10 coding system was used (PID: N70-4, N80).
Population-based studies & primary care datasets

Four general practice surveillance data sources are available. The General Practice Research Database (GPRD) and MediPlus® UK Primary Care Database are based on attendances at general practices and are representative of the general population in terms of age, sex and regional distribution. Substantial costs are associated with using these datasets. The RCGP’s General Practice Research Unit undertakes sentinel surveillance in 77 practices covering 600,000 people in England and Wales, and collects a limited range of demographic and diagnostic data. Here, the *Morbidity Statistics from General Practice Fourth National Survey: 1991-1992* (MSGP4) was used to investigate the burden of PID in general practice. Previous *Morbidity Statistics from General Practice* surveys were undertaken in 1962, 1972 and 1982. Although not a random sample, the Office of National Statistics (ONS) consider that the MSGP4 is representative of the general population with respect to age, sex, marital status, socio-economic status, smoking behaviour and burden of disease. The dataset was derived from attendances over a 1 year period 1991/92 at 60 general practice (GP) clinics in England and Wales and represented a 1% sample of the population. Diagnoses made by collaborating general practitioners (ICD9 coding), age, ethnic background, socio-economic status, current smoking habit, length of time the person was registered at the practice during the year and marital status (a combination variable including marital and cohabitation status) were collected for each patient. ONS did not provide collaborating centres with guidelines for the diagnosis of PID in the MSGP4. Similarly, the ICD9 coding system only gives a description of the condition, not diagnostic guidelines. One record per person was included in the analysis, and records were only included where complete data were recorded. Technically the data were derived from consultations rather than the total age/sex register. However, since 78% of those on the age/sex register of the practices included in the study consulted their general practitioner at least once during 1991/92, this was a close estimate of the burden of diagnosed
disease in the study population, referred to here as the diagnostic rate (number of 
PID diagnoses per persons years at risk). The classification of ethnic group was 
simplified to: White, Black (Black Caribbean, Black African, Black other) and 
Asian (Indian, Pakistani, Bangladeshi). The analysis included 73 810 women aged 
16 to 46. The length of time patients were registered with their general 
practitioner varied from a day to a year. The denominator was thus calculated as 
person years at risk by dividing the number of days each person was included in 
the survey by 366 (1992 was a leap year) giving a total of 70 791 person years at 
risk. Single and multivariable analyses were undertaken using a poisson 
regression model. The outcome variable was a diagnosis of PID made during the 
study period (ICD9 code 614). No distinction was made between whether these 
were new diagnoses or a consultation for an episode first diagnosed outside the 
study period. The analysis thus gives a prevalence estimate. Interactions were 
investigated and a main effects model was used to describe the data. Unadjusted 
and adjusted rate ratios (RRs) were calculated.

4.3 RESULTS

The KC60 data indicate that there was a rise in diagnoses of gonorrhoea in 
women during the 1950s and 60s, which was followed by a fall during the 1970s, 
80s and 90s (figure 4.1). Diagnoses of PID rose steadily from 1957 and plateaued 
in the mid 1980s, whereas ectopic pregnancies have gradually risen since the mid 
1980s. Age group data indicate that highest diagnostic rates in the hospital 
inpatient data are consistently seen in the 16 to 24 year age group (figure 4.2).

The analysis of the MSGP4 dataset indicates that the rate of PID diagnoses in 
women aged 16 to 46 attending general practice was 167/10 000 person years at 
risk (1189/70 791), or 1.7%. The number of diagnoses and the rate per 10 000 
person years at risk were calculated. RRs adjusted for other variables in the 
regression analysis were calculated together with 95% confidence intervals (CI) 
(table 4.1). The data were re-coded to avoid problems with sparse data in some 
categories (see section 4.2). All two-way interactions were investigated but none
was significant at the 5% level. There was a significant difference between age groups, with women aged 35 to 39 at half the risk of having a diagnosis of PID (p<0.0001, adjusted RR=0.54; 95% CI 0.40 to 0.72) and those aged 40 to 46 were at a quarter of the risk (adjusted RR=0.26 95% CI 0.19 to 0.36) compared to the 16 to 19 year age group. Smokers were at higher risk of PID than non-smokers (p<0.0001, adjusted RR=1.85; 95% CI 1.65 to 2.09). Patients in socio-economic groups III to V were all at higher risk of PID than those in socio-economic group I/II (p<0.0001). Compared to patients who were married, increased risk of PID was also associated with those patients who were widowed, separated or divorced and not cohabiting (adjusted RR=1.62; CI 1.35 to 1.97), and with those who were unmarried but cohabiting (adjusted RR=1.32; 95% CI 1.11 to 1.56). The difference in the risk of PID between ethnic groups was not statistically significant (p=0.0994), but there was evidence of increased risk in both Black (adjusted RR=1.65; 95% CI 0.97 to 2.79) and Asian patients (adjusted RR=1.53; 95% CI 0.84 to 2.78) compared to White patients.

**Figure 4.1** Gonorrhoea, PID and ectopic pregnancy, England and Wales: 1957 to 1997

† Diagnoses made at GUM clinics
Figure 4.2  PID hospital inpatient attendances by age group, England and Wales: 1966 to 1993/4 (see figure 2.10)\textsuperscript{164,165}
<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence (cases/10 000 persons years at risk)</th>
<th>Adjusted RR (95% CI)</th>
<th>p value (adjusted RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 to 19</td>
<td>223 (91/4072)</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>20 to 24</td>
<td>251 (289/11 520)</td>
<td>1.07 (0.84 - 1.36)</td>
<td></td>
</tr>
<tr>
<td>25 to 29</td>
<td>220 (308/13 977)</td>
<td>0.94 (0.72 - 1.21)</td>
<td></td>
</tr>
<tr>
<td>30 to 34</td>
<td>188 (249/13 221)</td>
<td>0.80 (0.61 - 1.05)</td>
<td></td>
</tr>
<tr>
<td>35 to 39</td>
<td>127 (149/11 666)</td>
<td>0.54 (0.40 - 0.72)</td>
<td></td>
</tr>
<tr>
<td>40 to 46</td>
<td>63 (103/16 334)</td>
<td>0.26 (0.19 - 0.36)</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>167 (1164/69 692)</td>
<td>1.00</td>
<td>0.0994</td>
</tr>
<tr>
<td>Black</td>
<td>264 (14/529)</td>
<td>1.65 (0.97 - 2.79)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>193 (11/569)</td>
<td>1.53 (0.84 - 2.78)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>131 (540/41 123)</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cohabiting</td>
<td>262 (196/7462)</td>
<td>1.32 (1.11 - 1.56)</td>
<td></td>
</tr>
<tr>
<td>Widowed/separated/divorced not cohabiting</td>
<td>236 (138/5840)</td>
<td>1.62 (1.35 - 1.97)</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>192 (315/16 365)</td>
<td>0.88 (0.75 - 1.05)</td>
<td></td>
</tr>
<tr>
<td><strong>Social class</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>114 (223/19554)</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>III non-manual</td>
<td>157 (443/28260)</td>
<td>1.22 (1.04 - 1.43)</td>
<td></td>
</tr>
<tr>
<td>III manual</td>
<td>223 (131/5867)</td>
<td>1.59 (1.28 - 1.97)</td>
<td></td>
</tr>
<tr>
<td>IV partly skilled</td>
<td>239 (314/13121)</td>
<td>1.65 (1.38 - 1.97)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>196 (78/3989)</td>
<td>1.52 (1.17 - 1.98)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>122 (591/48294)</td>
<td>1.00</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>266 (598/22497)</td>
<td>1.85 (1.65 - 2.09)</td>
<td></td>
</tr>
</tbody>
</table>
4.4 DISCUSSION

Few surveillance data were available and most are limited in coverage and scope, even in settings that specialise in sexual health. Data quality varies substantially between clinical settings, HA and NHS regions, and datasets cannot be compared or combined because of differences in collection methods. In particular, the severity of clinical presentation varies between clinical settings: patients attending primary care will generally have low chronicity, whereas attenders at inpatient services will be women experiencing acute and chronic pain and long-term reproductive health problems associated with PID.\(^{44,165}\)

Over the past five decades in England and Wales, variations in numbers of cases of gonorrhoea, hospital inpatient episodes of PID and ectopic pregnancy have followed a similar pattern to that seen in Sweden (section 2.10). Interpretation of the long-term trends in gonorrhoea, PID and ectopic pregnancy are difficult because ecological analyses cannot be used to establish a causal association between the conditions. There are several gaps in reporting due either to changes in collection methods or absence of data. Another concern is that the steep increase in gonorrhoea seen after World War II is not reflected in a rise in inpatient attendances for PID. This questions the representativeness and accuracy of the PID inpatient data collected during the 1950s. In addition, the decline in inpatient episodes seen in Sweden, Holland, Canada and the USA in the mid to late 1980s was not seen in the English data (section 2.10).

There is a substantial reservoir of undiagnosed PID in the general population. The 1.7% prevalence of PID diagnosis seen in the analysis of the MSGP4 dataset suggests that, in 1992, 165 000 cases of PID would have been diagnosed in general practice among reproductive age women. This contrasts with only 21 168 and 5735 cases seen as hospital inpatients and attenders at GUM clinics respectively in the same year.\(^{160,161}\) This finding indicates that general practice provides an important focus for the diagnosis and treatment of PID. The 41% increase in PID
diagnoses seen in attendances in general practice between 1982 and 1992 suggests that PID may be increasingly managed in this setting, although this rise may also reflect increased case ascertainment. Natsal 2000 showed that only 30% of those who had been diagnosed with PID had attended GUM services, indicating that the majority of PID cases seen in clinical settings are seen in settings outside GUM.

Although age specific hospital inpatient data suggest that highest diagnostic rates and highest rates of increase are consistently seen in the 16 to 24 year age group, the multivariable analysis of the MSGP4 dataset indicated that women between 16 and 34 years are at equal risk. Consequently, whereas rates of genital chlamydial infection peak in teenage women, associated morbidity affects the reproductive health of women over a substantial age range.

The analysis of the MSGP4 dataset supports previous observations that women who smoke are at significantly higher risk of PID (section 2.7). A relationship between risk of PID and divorced marital status has also been reported in studies in England and Wales. This association, and that between PID and socio-economic group, are probably surrogate markers of sexual behaviour. For example, age at first sexual intercourse and number of lifetime sexual partners are known to vary with marital status, cohabiting and socio-economic group. Unfortunately measures of sexual behaviour were not included in the MSGP4 dataset, and this severely limits interpretation, as facets of sexual behaviour could be potential confounders in observed relationships.

Recent studies have speculated on whether Black ethnic groups have a high burden of reproductive morbidity, and some evidence of increased risk in Blacks and Asians was seen in the analysis. Black and Asian ethnic groups are under represented, accounting for only 1.6% of the MSGP4 sample, compared to 5% reported in the 1991 census. After adjusting for socio-economic status, these groups were not found to be at higher risk of PID than Whites. However, the presence of RRs higher than 1 together with lower confidence limits that only
just encompass 1 for both the Black and Asian categories, indicates that risk of PID was approaching significance for these categories. These data suggest that the burden of PID in different ethnic groups needs to be explored further.

The analysis of the MSGP4 was the first study to be undertaken in a primary care setting and no international comparisons are available. The analysis gives an insight into the epidemiology of PID but has a number of limitations. Firstly, the dataset is intended for general disease surveillance and does not include information on factors that are either known to be associated with PID, or are potential confounders. Secondly, clinical samples were not collected so the aetiology of the PID cases is unknown. Thirdly, the findings of the study are limited to the time of data collection, that is 1992. PID epidemiology changes over time (section 2.10) and so the results of the study cannot be used as an evidence base other than for the time period studied.

The available surveillance data do not provide an accurate view of PID epidemiology. They are biased because: some are collected infrequently (MSGP); they are prospective studies designed for general surveillance (GPRD, MediPlus® UK Primary Care); little or no behavioural, demographic and reproductive health data are collected; standard diagnostic criteria are not used; the methodologies cannot be modified; and diagnostic samples cannot be collected. Nevertheless, although PID diagnosis in general practice is likely to have a lower specificity and sensitivity than that diagnosed in hospital, the surveillance data indicate that information from general practice is likely to provide a more complete view of PID epidemiology. Nationally representative, prospective data are required to produce the timely, accurate insight into PID epidemiology needed to guide control and prevention strategies. Two areas of further work need to be addressed: a new, tailor made surveillance system and a PID surveillance case definition.
4.5 OUTLINE OF AN ENHANCED SURVEILLANCE METHOD

Ideally, population-based studies provide the best method of assessing the epidemiology of STDs, such as PID, that are not confined to core groups, but such studies are rare. In the UK, the only investigation undertaken to date was the C. trachomatis study included in Natsal 2000\textsuperscript{103}. The complex, costly methodology of Natsal 2000 makes it unfeasible as a basis of routine data collection. Whilst not as accurate as population-based studies, surveillance within primary care could provide timely, representative estimates of the burden of morbidity within a group that closely corresponds to the general population. Almost 80\% of the UK population consult a general practitioner at least once a year, and other primary care settings, such as family planning, are regularly attended by young people\textsuperscript{7}.

The aims of the surveillance programme would be to estimate prevalence, and change in prevalence over time. The need for the timely collection of detailed data together with a clinical sample suggests that a methodology based on a substantial population sample is inappropriate. A point prevalence sampling technique would increase efficiency. A random sample of about 4000 females would give a representative view of disease prevalence over the range 1\% to 2.5\% (table 4.2). The methodology and sample size calculations would have to be evaluated in a pilot study and the sampling strategy tailored to surveillance priorities, such as geographic variation in prevalence. Patients could be invited to participate at clinic visits or by post. Measuring change in prevalence is an important method of evaluating intervention, but changes are difficult to predict and may be small\textsuperscript{694}. Again, a sample of 4000 would allow year on year trends to be detected accurately.
Table 4.2  Number of females required to detect difference in prevalence*

<table>
<thead>
<tr>
<th>Difference between populations (%)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>-3</td>
<td>-</td>
</tr>
<tr>
<td>-2</td>
<td>-</td>
</tr>
<tr>
<td>-1</td>
<td>969</td>
</tr>
<tr>
<td>+1</td>
<td>2514</td>
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<tr>
<td>+2</td>
<td>865</td>
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<td>+3</td>
<td>488</td>
</tr>
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<td></td>
<td>1.5</td>
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<td>-3</td>
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<td>-</td>
</tr>
<tr>
<td>-1</td>
<td>1747</td>
</tr>
<tr>
<td>+1</td>
<td>3273</td>
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<tr>
<td>+2</td>
<td>1053</td>
</tr>
<tr>
<td>+3</td>
<td>571</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>-3</td>
<td>-</td>
</tr>
<tr>
<td>-2</td>
<td>482</td>
</tr>
<tr>
<td>-1</td>
<td>2514</td>
</tr>
<tr>
<td>+1</td>
<td>4023</td>
</tr>
<tr>
<td>+2</td>
<td>1239</td>
</tr>
<tr>
<td>+3</td>
<td>653</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
</tr>
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<td>-3</td>
<td>-</td>
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<td>675</td>
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<td>4765</td>
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<tr>
<td>+2</td>
<td>1423</td>
</tr>
<tr>
<td>+3</td>
<td>734</td>
</tr>
</tbody>
</table>

* Calculations assumed a random sample, 5% two sided significance level and 80% power

Potentially there are problems associated with such an enhanced surveillance strategy, the main concern being the comparability between the general practice age/sex register and the general population. For females between the ages of 15 and 44 attending general practice the median contact days remain relatively constant over time at 9.8/100 persons per week. This enhanced surveillance initiative would have to be adapted to specific situations as it may be unfeasible or inappropriate to collect detailed data in some situations. In addition, the focus on general practitioners may make such a study difficult to implement at a time of increasing demands, although primary care research networks could be used as the framework for such an initiative. This system could also be used as the basis of a harmonized surveillance system that would allow a rapid evaluation of STI epidemiology and sexual health within and between countries.

PID incidence is associated with a number of factors (section 2.7), and ideally this information would be collected using self-administered patient questionnaires that could be scanned into a computer database. This would allow the diagnosis to be placed within the context of the patients' reproductive and contraceptive history, sexual behaviour, demographic characteristics and health seeking behaviour. Points of reference would be included that would allow comparisons to be made with related UK studies, such as Natsal 2000. This would allow a database to be constructed and 'cleaned' within a few days. Information could
thus be collected, interpreted and disseminated quickly. This would allow an
efficient assessment of PID epidemiology and health service access behaviour but
would need to be evaluated by a pilot study.

4.6 CONCLUSIONS

Of all the surveillance datasets evaluated here, the MSGP4 analysis provided the
closest estimate of disease prevalence available. The findings of this study need
to be validated using a specifically designed study that includes a standardised,
evidence based diagnostic algorithm. Problems of diagnostic accuracy lie at the
heart of PID surveillance. However, since the associations found in the MSGP4
analysis were broadly similar to those seen in other studies it is likely that
diagnostic criteria were generally applied consistently. Nevertheless, if
surveillance and intervention are to be undertaken effectively, the accuracy of
diagnostic criteria used in general practice needs to be investigated and a
standard evidence-based case definition developed. This was the focus of the
investigations in chapters 5 and 6.
Chapter 5  How is PID diagnosed, treated and managed in general practice?

5.1  INTRODUCTION

The study in chapter 4 showed that the majority of PID cases seen in clinical settings are diagnosed in general practice. Diagnostic accuracy influences both case management and the quality of surveillance data but little is known of the way in which cases are diagnosed. This study investigated current diagnosis and management in general practice (objective 2, section 1.3). The study is presented in paper 3 (appendix 5).

5.2  METHODS

The study was conducted in collaboration with the Medical Research Council (MRC) General Practice Research Framework (GPRF). The framework is coordinated by the MRC Epidemiology and Medical Care Unit and was the first UK primary care network, set up in 1970. It includes practices that are interested and experienced in research, and undertakes projects appropriate to general practice. The framework was used in this study because of its experience of working in this field and the wide network of motivated, experienced clinics that it includes. The 781 practices in the MRC GPRF in England and Wales were invited to take part in the study by the GPRF co-ordinating centre. All practices that did not return the questionnaire within three weeks were sent an additional questionnaire; if this copy was not returned a reminder was made by telephone. The GPRF is a non-random sample of general practices that covers 11% of the population of England and Wales. It includes practices with a broad range of Carstairs indices. The Carstairs index is a measure of deprivation based on the UK 1991 Census derived from the number of persons per household, rate of male unemployment, social class and number of overcrowded households. A structured questionnaire (appendix 2) was used for the study which covered practice characteristics (part A) and diagnosis, treatment and referral policy of the
physician completing the questionnaire (part B). Part C explored the management of the last case seen by the general practitioner. This critical incidence technique was used as a method of reducing recall bias.

A ‘gold standard’ definition of diagnosis, treatment and management was derived from the literature and consultation with a panel of experts. Ian Simms convened and chaired a meeting of experts drawn from general practice, GUM, O&G, and microbiology to discuss the management of PID and suggest what they considered to be the most effective method of diagnosis, treatment and management based on their knowledge of the literature and clinical practice. Five categories were suggested that covered symptoms, signs, microbiological investigation, antibiotic therapy and partner notification (table 5.1). Responses from the general practices were compared against this ‘gold standard’.
Table 5.1  ‘Gold standard’ definition

<table>
<thead>
<tr>
<th>Question</th>
<th>‘Gold standard’ definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Which symptoms?</td>
<td><em>Two or more or the following:</em></td>
</tr>
<tr>
<td></td>
<td>Irregular menstrual bleeding, lower abdominal pain</td>
</tr>
<tr>
<td></td>
<td>(particularly where related to dyspareunia), vaginal discharge, dysuria, deep dyspareunia</td>
</tr>
<tr>
<td>Which signs?</td>
<td><em>Two or more of the following:</em></td>
</tr>
<tr>
<td></td>
<td>Lower abdominal pain, cervical motion tenderness, cervical discharge, pyrexia &gt;38%, rebound</td>
</tr>
<tr>
<td></td>
<td>tenderness, adnexal mass</td>
</tr>
<tr>
<td>Do you undertake microbiological investigation?</td>
<td>Usually</td>
</tr>
<tr>
<td>Antibiotic therapy</td>
<td><em>One of the following treatment regimes:</em></td>
</tr>
<tr>
<td></td>
<td>1 Tetracycline, doxycycline or erythromycin if doxycycline not tolerated, &amp; metronidazole</td>
</tr>
<tr>
<td></td>
<td>2 Ofloxacin &amp; metronidazole</td>
</tr>
<tr>
<td></td>
<td>3 Ampicillin/sulbactam &amp; (doxycycline, tetracycline or erythromycin)</td>
</tr>
<tr>
<td></td>
<td>4 Ciprofloxacin &amp; (doxycycline, tetracycline or erythromycin) &amp; metronidazole</td>
</tr>
<tr>
<td>Are partners of PID cases treated?</td>
<td>Usually</td>
</tr>
</tbody>
</table>

A sample size calculation that estimated the confidence intervals associated with the proportion of GPs who gave the same response as the ‘gold standard’ showed that the 297 practices included in the study should have given a reasonably precise estimate of the percentage of respondents giving the ‘gold standard’ answer (table 5.2).
Table 5.2 Sample size calculation: 95% CIs associated with percentage of respondents giving the same answer to one question

<table>
<thead>
<tr>
<th>Proportion of GPs giving same answer as the 'gold standard' (%)</th>
<th>Sample size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>2.65 - 8.48</td>
</tr>
<tr>
<td>10</td>
<td>6.58 - 14.41</td>
</tr>
<tr>
<td>20</td>
<td>15.22 - 25.50</td>
</tr>
<tr>
<td>30</td>
<td>24.34 - 36.09</td>
</tr>
</tbody>
</table>

Responding and non-responding practices were compared in terms of size and Carstairs index using the Wilcoxon rank sum (Mann-Whitney) test. The \( \chi^2 \) test was used to compare the sex of the physician responsible for completing the questionnaire.

Responses were compared against the 'gold standard'. For each answer that reached the 'gold standard' '1' was added to a total field. Practices with total scores above 2 were satisfactory (diagnostic and management quality code=1); those with 2 or less were coded as unsatisfactory (diagnostic and management quality code=0).

Single and multivariable analyses were undertaken using logistic regression. The outcome measure was diagnostic quality. The explanatory variables included in the analyses were: the sex of the practitioner responsible for completing the questionnaire, the number of patients per practitioner, whether or not the practice was computerised, cervical cytology coverage, immunisation coverage, practice location and Carstairs index.
5.3 RESULTS

Of the 781 questionnaires sent out, 297 (38%) were returned. There was no statistically significant difference between responders and non-responders in terms of practice size (p=0.47), Carstairs index (p=0.55) and the sex of the contact physician (p=0.33). Of the male physicians, 40% (243/619) responded compared with 33% (51/154) of female physicians. The sex of 1% of responding physicians was unknown.

Of those practices that did respond, 95% were computerised, 66% were based in urban areas/small towns, 13% in rural areas and 21% in mixed urban/rural areas. Immunisation coverage of 90% or more was achieved by 86% of the practices and a cervical cytology target of 80% was achieved by 87% of practices. Seventy two percent of practices said they would refer patients to O&G and 68% said they would refer to GUM clinics.

Comparison of current practice against the ‘gold standard’ indicated that 100 (34%) named at least 2 signs and 2 symptoms, 160 (54%) named the correct antibiotic therapy, 64 (22%) usually treated the partner, and 252 (85%) usually undertook microbiological investigation (91% took an endocervical swab). Only 21 (7%) answered all sections of the ‘gold standard’ correctly. Unfortunately, only 11% (34/297) of respondents completed part C of the questionnaire and so these data were excluded from the analysis.

Adjusting for other variables strengthened the effects seen in the single variable analysis (table 5.3). Significantly lower management quality (p<0.01) was associated with practices without computerisation compared with those that were computerised (OR 0.07: 95% CI 0.005 to 0.96). Quality was significantly higher (p=0.05) when the clinician was female compared to male (OR 2.34: 95% CI 1.19 to 4.63) and quality increased by 12% (95% CI 5% to 21%) with each unit increase in the Carstairs index, that is quality increased with deprivation. No statistically significant interactions were found between the variables.
Table 5.3 Comparison of reported practice against ‘gold standard’

<table>
<thead>
<tr>
<th></th>
<th>Number of practices</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
<th>p value (adjusted OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex of contact practitioner</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>243</td>
<td>1.00</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Female</td>
<td>51</td>
<td>2.26 (1.19 - 4.28)</td>
<td>2.34 (1.19 - 4.63)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>0.99 (0.16 - 19.67)</td>
<td>1.73 (0.14 - 21.57)</td>
<td></td>
</tr>
<tr>
<td><strong>Patients per practitioner</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>22</td>
<td>1.00</td>
<td>1.00</td>
<td>0.21</td>
</tr>
<tr>
<td>1000 - 1999</td>
<td>214</td>
<td>1.32 (0.47 - 3.75)</td>
<td>1.70 (0.49 - 5.89)</td>
<td></td>
</tr>
<tr>
<td>&gt;=2000</td>
<td>61</td>
<td>0.67 (0.20 - 2.23)</td>
<td>0.91 (0.22 - 3.72)</td>
<td></td>
</tr>
<tr>
<td><strong>Cervical cytology coverage (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80%</td>
<td>38</td>
<td>1.00</td>
<td>1.00</td>
<td>0.87</td>
</tr>
<tr>
<td>&gt;=80%</td>
<td>259</td>
<td>0.94 (0.43 - 2.04)</td>
<td>0.92 (0.32 - 2.60)</td>
<td></td>
</tr>
<tr>
<td><strong>Immunisation coverage (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90%</td>
<td>43</td>
<td>1.00</td>
<td>1.00</td>
<td>0.92</td>
</tr>
<tr>
<td>&gt;=90%</td>
<td>254</td>
<td>0.85 (0.41 - 1.76)</td>
<td>0.95 (0.35 - 2.56)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinic location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>115</td>
<td>1.00</td>
<td>1.00</td>
<td>0.50</td>
</tr>
<tr>
<td>Urban/small town</td>
<td>81</td>
<td>1.01 (0.53 - 1.92)</td>
<td>1.74 (0.86 - 3.68)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>40</td>
<td>0.68 (0.28 - 1.63)</td>
<td>1.26 (0.46 - 3.47)</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>61</td>
<td>0.81 (0.39 - 1.67)</td>
<td>1.09 (0.49 - 2.43)</td>
<td></td>
</tr>
<tr>
<td><strong>Was the practice computerised?</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>284</td>
<td>1.00</td>
<td>1.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No</td>
<td>13</td>
<td>0.19 (0.02 - 1.44)</td>
<td>0.07 (0.005 - 0.96)</td>
<td></td>
</tr>
<tr>
<td><strong>Carstairs index, 1991</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuous variable</td>
<td>N/A</td>
<td>1.08 (1.02 - 1.14)</td>
<td>1.13 (1.05 - 1.21)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
5.4 DISCUSSION

This was the first evaluation of PID diagnosis in general practice and the first national study of PID management to be undertaken in England and Wales. Consistent, accurate diagnosis is vital to effective patient management and disease surveillance, but sub-optimal diagnosis and management is common. The Royal College of Obstetricians and Gynaecologists recommend that women with a clinical diagnosis of PID should be tested for *C. trachomatis* and *N. gonorrhoeae*, receive appropriate antibiotic treatment and partner notification\(^{180}\). Diagnostic and management guidelines are used in GUM clinics and Accident and Emergency Departments. A previous study indicated that 91% of GPs consider they manage PID effectively, but this study suggests that diagnostic practice falls well below expectation\(^ {194}\). Only 7% of practices reached the most effective level of case management and only 34% named the 'gold standard' diagnostic criteria. This is consistent with low disease awareness and sub-optimal management reported from settings outside GUM clinics in the UK, Scandinavia and the USA\(^ {200-202}\). Low awareness may be related to the number of cases seen by individual GPs. Evidence to support this is the association between the quality of diagnosis, treatment and management, and increased social deprivation. This may reflect increased familiarity with PID in more deprived areas where prevalence is highest, as was seen in chapter 4 and reported in previous studies (section 2.7). Low quality was also significantly related to the absence of a computerised patient record system in the practice, although only fifteen practices were not computerised.

Female practitioners managed PID cases more effectively than their male colleagues. Many female patients prefer to consult a female practitioner as they are perceived to have greater empathy, and to be more knowledgeable and experienced in gynaecological problems\(^ {203}\). Female practitioners have also been shown to have lower referral rates to gynaecology, manage women's urinary
incontinence more effectively than their male colleagues, and achieve higher uptake rates for cervical cytology than their male colleagues\textsuperscript{204,205}.

The CMOs expert advisory group on genital chlamydial infection recommended that women at risk of PID should be encouraged to undergo an STI investigation, based on effective treatment of both patient and partner\textsuperscript{4}. Most GPs undertook a microbiological investigation, and would have taken a sample capable of detecting genital chlamydial infection, that is an endocervical swab. However, although the majority of GPs named the correct broad spectrum antibiotic treatment regimen, few said they would usually treat the partner of the case. Current case management would thus not prevent re-infection from the case's sexual partner. Referral to GUM clinics is important to allow partner notification to be undertaken.

The MRC GPRF is recognised as a well organised network of motivated GPs who regularly take part in research projects, and has been used by organisations such as the Department of Health and the National Institute of Clinical Excellence to undertake definitive research studies. Recent GPRF studies of acute lower back pain and 'glue' ear achieved response rates of over 80\%.\textsuperscript{206,207} The unusually poor response rate to a GPRF study reflects low disease awareness and sub-optimal management and highlights a fundamental obstacle to effective intervention and surveillance. Early recognition is essential to reduce this source of reproductive morbidity and the main opportunity for PID control lies in general practice. The results of this study have been disseminated to the GPs who took part in the study. A further evaluation will be required to close the audit loop and assess whether practice has changed as a result of the study. Low awareness of PID represents an obstacle to effective disease diagnosis, intervention and surveillance. Initiatives have been made in recent years to improve effective diagnosis and management of PID but this study clearly indicates that further medical education is urgently required\textsuperscript{180}.
5.5 CONCLUSIONS

The studies in chapter 4 found that the majority of PID cases seen by clinical services attend general practice. The systematic collection of timely, representative surveillance data from primary care is needed if future prevention needs are to be addressed. However, this study showed that diagnostic accuracy is low. Epidemiological studies and intervention initiatives will only be effective if diagnostic accuracy is improved and standardised. The next investigation explored the accuracy of PID diagnosis based on clinical presentation.
Chapter 6  How accurate is the diagnosis of PID? – an investigation using an available dataset

6.1  INTRODUCTION

Diagnosis of PID in primary care, GUM, and O&G clinics is focused on syndromic diagnosis and the exclusion of competing diagnoses. Recommended diagnostic criteria are based on the definition proposed by Hager et al., which is focused on clinical presentation (section 2.1)\(^{12}\). The accuracy with which signs and symptoms predict the presence of PID has been evaluated using a laparoscopic ‘gold standard’ (section 2.9). However, interpretation of the evidence base has been flawed and needs to be re-evaluated so that new diagnostic criteria can be formulated objectively. Here I critically evaluate the evidence base, discuss problems of interpretation and suggest the most effective diagnostic criteria (objective 3, section 1.3). Results of this investigation were presented at the 2003 ISSTDR Congress (Ottawa) and have been accepted for publication in *Sexually Transmitted Infections*.

6.2  ASSESSMENT OF EVIDENCE BASE

Seven studies were found where laparoscopy had been used as the ‘gold standard’, most of which had been reviewed previously\(^{11,44,139,141,142,146-148}\). The limited evidence base is not surprising as such studies are difficult to undertake due to the high cost, associated risks and infrequent use of laparoscopy. Weaknesses can be seen if the studies are compared against a sample size calculation. Assuming a 5% level of significance, 80% power and a minimum detectable difference of 5%, the number of positive and negative patients required at the following sensitivities would be: 70% (323 each of positives and negatives, total = 646), 80% (246 each, total = 492), 90% (138 each, total = 276). Consequently, most of the published studies are too small to accurately detect real differences.
Table 6.1 Summary of studies that have examined the relationship between clinical and laparoscopic findings in suspected PID cases

<table>
<thead>
<tr>
<th>Clinic population</th>
<th>Country</th>
<th>Sample size</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetrics &amp; Gynaecology</td>
<td>Sweden</td>
<td>716 (532/184)</td>
<td>Jacobson* 1969</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynaecology</td>
<td>Finland</td>
<td>35 (26/9)</td>
<td>Lehtinen 1986</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynaecology</td>
<td>Sweden</td>
<td>552 (414/138)</td>
<td>Hadgu* 1986</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynaecology/USA</td>
<td>36 (22/14)</td>
<td>Wasserheit 1986</td>
<td></td>
</tr>
<tr>
<td>Accident &amp; Emergency/Sexually</td>
<td>Finland</td>
<td>41 (31/10)</td>
<td>Paavonen 1989</td>
</tr>
<tr>
<td>Transmitted Disease</td>
<td>USA</td>
<td>176 (134/42)</td>
<td>Morcos 1993</td>
</tr>
<tr>
<td>Obstetrics &amp; Gynaecology/Czech</td>
<td>141 (43/98)</td>
<td>Cibula 2001</td>
<td></td>
</tr>
<tr>
<td>Republic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Both studies used data collected by Lund University

within the data (a type II statistical error) (table 6.1). The insufficient sample size is reflected in the wide confidence intervals that surround estimates of specificity and sensitivity derived from these data. For example, in a study of 36 women with clinically and laparoscopically diagnosed PID, erythrocyte sedimentation rate (ESR) had a sensitivity of 83% (95% CI 52% to 98%) and a specificity of 45% (95% CI 24% to 68%)\(^{14}\). Meta-analysis would be problematic because of difficulties in accessing data, reconciling selection criteria, intra-observer error and diagnostic methodologies. Nevertheless, it is unlikely that large-scale studies will be undertaken for the foreseeable future and this emphasizes the importance of the existing evidence base. Previous analyses have been undertaken using the Lund dataset but the investigation described here is new because it takes the study entry criteria into consideration. Three analytical techniques were used to compare the accuracy with which clinical presentation predicted the presence of laparoscopically diagnosed PID.
6.3 FINDING THE DATA

From the literature review undertaken for chapter 2, it was clear that the Centers for Disease Control (CDC), Atlanta, USA had created an electronic version of the Lund dataset in the mid-1980s. Gaining access to the dataset proved difficult. Professor Lars Weström readily gave me permission to use the dataset, provided a copy of the data dictionary and a copy of his Doctor of Philosophy thesis. I worked out the coding structures and exclusion criteria from these sources and the published literature. However, I had to wait a further 8 months for CDC to release the data. The case-control study described in chapters 7 and 8 had started by the time CDC had released the Lund dataset and so the findings from the analysis in this chapter could not be used in the design of the case-control study.

6.4 METHODS

The anonymised dataset included women who attended the Department of O&G, Lund University Hospital, with suspected PID between 1960 and 1984\textsuperscript{208}. This analysis was confined to first episodes of suspected PID collected between 1960 and 1969, the period for which the largest number of clinical variables was available. All patients included in the study had an initial clinical diagnosis based on clinical presentation (signs and symptoms), the criteria were lower quadrant bilateral abdominal or pelvic pain of less than 3 weeks duration, together with 2 or more of the following: abnormal vaginal discharge, fever \(>38\,^\circ\text{C}\), vomiting, menstrual irregularity, ongoing bleeding, symptoms of urethritis, rectal temperature \(>38\,^\circ\text{C}\), marked tenderness of pelvic organs on bimanual examination, adnexal mass and ESR \(\geq15\text{mm per hour}\). Laparoscopy was used to verify the clinical diagnosis, the criteria used were pronounced hyperemia of the tubal surface, oedema of the tubal wall, and exudate on the tubal surface and fimbriated ends, if patent\textsuperscript{208}. 

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For the purposes of this analysis, the data were divided in two: (1) laparoscopically diagnosed PID, and (2) women who did not have PID on laparoscopy. These groups were compared in terms of age using the $t$ test, whereas the number of births before index laparoscopy, and whether an IUD had ever been used were compared using the $\chi^2$ test.

Three methods were used to explore the relationships between clinical presentation and presence of laparoscopically diagnosed PID. Firstly, the specificity and sensitivity of individual variables were assessed together with 95% confidence intervals. Secondly, likelihood ratios were used to assess whether the presence of individual variables altered the index of suspicion based on the pre-test probability. Thirdly, forward step wise discriminant analysis (a method of finding the combination of variables that most effectively separates populations) was used to determine which variable best predicted the presence of laparoscopically proven PID. Discriminant analysis was used because it performs two functions. Firstly, it identifies those variables that are significantly associated with a diagnosis of PID (as would multivariable logistic regression). Secondly, it uses the variables significantly associated with a diagnosis of PID to classify the patients into two categories, those in which PID is likely to be present or likely to be absent.
6.5 RESULTS

A total of 623 patients were included in the analysis, 494 patients were laparoscopically confirmed as having PID and 129 were not. There was no statistically significant difference between these groups in terms of: age (p=0.649), number of pregnancies (p=0.447), births (p=0.375), and whether an IUD had been either used (p=0.675) or inserted within six weeks of the index laparoscopy (p=0.100).

None of the variables had both high specificity and sensitivity (table 6.2). Some achieved high sensitivity (tenderness of pelvic organs on bimanual examination and ESR) or high specificity (proctitis symptoms and vomiting) but most had low specificity and sensitivity.

The pre-test probability of having laparoscopically confirmed PID was 79% (494/623), 95% CI 76% to 82%. All the likelihood ratios were positive and there was little variation between the variables in terms of either the likelihood ratios or the post-test probabilities (table 6.2). For example, the lowest likelihood ratio (0.98) produced a post-test probability of 79% (95% CI 74% to 81%), whereas the highest likelihood ratio (1.73) had a post-test probability of 84% (95% CI 81% to 87%). Consequently, for all the variables studied, the post-test probability was not significantly different from the pre-test probability.

The discriminant analysis indicated that three variables significantly influenced the predicted presence of PID: ESR (correlation value=0.669; p<0.0001), fever (CV=0.584; p<0.0001) and adnexal tenderness (CV=0.540; p<0.0001). These variables correctly classified 65% of patients with laparoscopically diagnosed PID (95% CI 61% to 69%) (table 6.3). The other variables did not reach significance, that is the presence of these variables did not increase the probability that a patient had PID.
Table 6.2  Prediction of laparoscopically diagnosed PID: sensitivity and specificity of signs and symptoms, likelihood ratios and post-test probabilities*

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
<th>Sensitivity % (95% CI)</th>
<th>Specificity % (95% CI)</th>
<th>Laparoscopically diagnosed PID</th>
<th>Likelihood ratio†</th>
<th>Post-test probability</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n=494) Number (%)</td>
<td>Absent (n=129) Number (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>74 (69.99 - 77.90) 24 (16.95 - 32.34)</td>
<td>366 (74) 98 (76)</td>
<td>0.98</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>47 (42.49 - 51.47) 64 (55.43 - 72.58)</td>
<td>234 (47) 47 (36)</td>
<td>1.30</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (11.03 - 17.34) 88 (81.55 - 93.34)</td>
<td>68 (14) 16 (12)</td>
<td>1.11</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td>45 (40.49 - 49.45) 57 (48.36 - 66.03)</td>
<td>223 (45) 56 (43)</td>
<td>1.04</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Ongoing bleeding</td>
<td>25 (21.34 - 29.17) 77 (68.49 - 83.73)</td>
<td>124 (25) 29 (22)</td>
<td>1.12</td>
<td>0.81</td>
<td></td>
</tr>
<tr>
<td>Urinary symptoms</td>
<td>35 (30.81 - 39.41) 64 (55.43 - 72.58)</td>
<td>173 (35) 46 (36)</td>
<td>0.98</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Proctitis symptoms</td>
<td>10 (7.43 - 12.90) 92 (86.21 - 96.22)</td>
<td>50 (10) 10 (8)</td>
<td>1.31</td>
<td>0.83</td>
<td></td>
</tr>
<tr>
<td>Tenderness of pelvic organs on bimanual examination</td>
<td>99 (97.65 - 99.67) 0.007 (&lt;0.01 - 2.84)</td>
<td>489 (99) 128 (99)</td>
<td>1.00</td>
<td>0.79</td>
<td></td>
</tr>
<tr>
<td>Palpable adnexal mass or swelling</td>
<td>52 (47.52 - 56.51) 70 (61.06 - 77.54)</td>
<td>258 (52) 39 (30)</td>
<td>1.73</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate≥15mm/h</td>
<td>81 (77.23 - 84.34) 33 (25.28 - 42.17)</td>
<td>402 (81) 86 (66)</td>
<td>1.22</td>
<td>0.82</td>
<td></td>
</tr>
</tbody>
</table>

* Pre-test probability = 79%

† Likelihood ratio interpretation. >10 and <0.1 (large difference between pre & post test probability), 5 to 10 and 0.1 to 0.2 (moderate difference), 2 to 5 and 0.5 to 0.2 (small), 1 to 2 and 0.05 to 1 (small & rarely important difference)
Table 6.3 Classification of results from forward stepwise discriminant analysis

<table>
<thead>
<tr>
<th>Predicted group membership*</th>
<th>Absent</th>
<th>Present</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laparoscopically diagnosed PID</td>
<td>Absent</td>
<td>85</td>
<td>44</td>
</tr>
<tr>
<td>Present</td>
<td>174</td>
<td>320</td>
<td>494</td>
</tr>
<tr>
<td>Total</td>
<td>258</td>
<td>366</td>
<td>623</td>
</tr>
</tbody>
</table>

* Patients with ESR, adnexal tenderness and fever

6.6 DISCUSSION

High diagnostic accuracy is essential to effective patient management and disease control. It determines the quality of surveillance and epidemiological studies which, in turn, influence the efficiency of control and prevention strategies. ‘Lower abdominal pain plus 2 or more symptoms and signs’ or ‘lower abdominal pain, adnexal tenderness and cervical motion tenderness’ are widely recommended diagnostic criteria, but are not supported by the evidence base$^{27,180}$. The Lund dataset is the only investigation of sufficient size to act as an evidence base, and has been used as the primary source of data for the formulation of PID diagnostic guidelines. A variety of diagnostic guidelines have emerged because they were developed by expert panels which drew on personal experience and knowledge of local disease aetiology as well as evidence from the Lund dataset: a combination of quality of evidence categories III and IV (section 2.3).

A number of problems are associated with the use of the Lund dataset. Firstly, there is a temporal bias as the data were collected in Sweden between 1960 and 1967. At that time the dominant cause of PID was *N. gonorrhoeae*. It is thought that gonococcal PID is more symptomatic than chlamydial PID. Consequently, where the prevalence of *C. trachomatis* is high and that of *N. gonorrhoeae* low, as it is in most industrialized countries today, the specificity and sensitivity of clinical parameters are likely to be lower than in the Lund dataset. Secondly, laparoscopy may lack sensitivity and specificity when compared to fimbrial biopsy and plasma cell endometritis as it may not identify mild intratubal
inflammation and cannot detect endometriosis (section 2.9). And thirdly, data were based on women with acute PID attending an O&G clinic, whereas most cases are diagnosed in primary care where cases have mild/unspecific symptoms. At the time of the study there would have been women in Lund who had PID who did not qualify for hospital admission because they did not have pain, or their symptoms were too mild to require referral to hospital. Nevertheless, women who develop TFI can have mild symptoms that are never diagnosed as PID. The Lund study is thus biased towards women with clinically apparent disease. Cases of mild disease need to be included in studies of PID diagnosis so that a case definition can be developed that will include all cases that have an adverse long-term outcome.

Analysis of the Lund data showed that, after exclusion of competing diagnoses, women with lower abdominal pain had a high pre-test probability of having laparoscopically diagnosed PID. Analyses of the other clinical variables showed that specificity and sensitivity were inappropriate measures because of the wide confidence intervals. In addition, the calculation of specificity and sensitivity are unable to take the other variables into consideration, that is they could not determine whether a variable was influenced by one or more of the variables for which information was collected. This is a particular concern here as many of the variables are closely associated. The use of likelihood ratios showed that the post-test probability was not significantly different from the pre-test probability. In contrast, the discriminant analysis, which took all the variables into consideration, clearly showed that only the presence of ESR, fever and adnexal tenderness influenced pre-test probability. These findings emphasise the limitations of the Lund dataset for the formulation of diagnostic guidelines as today few clinics use ESR in the diagnosis of PID and few cases present with fever. This indicates that the most effective diagnostic criteria are based on the presence of lower abdominal pain and exclusion of competing diagnosis, and justifies the high index of suspicion considered acceptable on the grounds that early intervention can prevent sequelae. However, early antibiotic therapy may
also be associated with elevated risk of increased antibiotic resistance, potential side effects such as candidosis, and unnecessary patient anxiety caused by the diagnosis of a condition that is largely associated with STIs.

A variety of diagnostic techniques have been explored and these were reviewed earlier in the thesis (section 2.9). A recent study of the association between clinical presentation and PID diagnosis used histologic endometritis as a 'gold standard'. The study may have lacked sensitivity but, in view of the costs and ethical issue surrounding the use of laparoscopy, such techniques will probably be used increasingly as a 'gold standard' in future studies. The diagnostic problem presented by PID will only be resolved by the development of a simple diagnostic laboratory test.

6.7 FUTURE WORK

There is insufficient evidence to support existing diagnostic guidelines. A new evidence base is urgently needed which will allow effective diagnosis based on standardised criteria. This would investigate the association between clinical presentation and PID diagnosed using a variety of techniques, including laparoscopy and endometrial biopsy. It would also establish the accuracy of a number of diagnostic strategies. This would allow researchers to use clearly recognised case definitions whether they are undertaking epidemiological studies in primary care or projects in settings where more invasive techniques are available. Such a study, which would be undertaken in primary care, GUM and O&G, would be expensive and would rely on women with mild, moderate and severe PID consenting to laparoscopy and other invasive procedures that are not part of standard case management. Recruitment, particularly amongst women with mild PID attending primary care, would be low. As indicated by the sample size calculation in section 6.2, the study would need to include at least 646 patients (323 cases and 323 controls), although the exact sample size would have to be based on the findings of a feasibility study. Selection bias would be a problem to such a study and the investigators would need to document and
regularly evaluate the characteristics of both participants and non-participants. Although inter-observer error would be an important consideration in a multi-centre study, the large number of patients needed indicates that it could not be undertaken at a single location. A European study that includes experts with established reputations in the field would be a way of minimising this source of bias and establishing the study as the new primary evidence base for the diagnosis of PID. Nevertheless, such a study could be difficult to co-ordinate as professional specialties vary between European countries: for example, the UK has a genitourinary medicine specialty whereas STDs are pre-dominantly managed by dermatovenereologists in other European countries. Inter-observer error could be reduced by limiting the collaborating sites to those with established reputations in the field. Standard operating guidelines would be developed and agreed by all the collaborators, and all the staff taking part in the study would be trained to agreed standards. In addition, each centre would be regularly audited to assess performance during the course of the investigation.

6.8 CONCLUSIONS

High diagnostic accuracy is essential to effective patient management. The evaluation of the evidence base shows that the most effective diagnostic criteria are the presence of lower abdominal pain and the exclusion of competing diagnoses. The simplicity of these diagnostic criteria makes it suitable as a surveillance case definition but unfortunately it lacks specificity and sensitivity. The results of this investigation will be useful in guiding a re-evaluation of PID diagnostic criteria and the formulation of a new surveillance case definition.
Chapter 7  Who's at risk? A case-control study

7.1  INTRODUCTION

Results of studies that identify population subgroups at increased risk of PID can be used to initiate timely, effective intervention and inform the development of health education strategies. The study in chapter 4 showed that increased risk of PID was associated with age less than 34 years of age, smoking and lower socio-economic status. However, as discussed in section 4.4, the MSGP4 dataset cannot be used to accurately explore factors associated with PID. The study described in this chapter was specifically designed to explore factors associated with PID. The aims were: firstly, to investigate demographic and behavioural factors, serological parameters and aetiological agents associated with PID and, secondly, to estimate the number of PID cases associated with \textit{C. trachomatis} infection (objective 4, section 1.3). Results of this investigation were presented at the 18\textsuperscript{th} Congress of the International Union of Sexually Transmitted Infections (IUSTI Europe) (paper 4, appendix 5).\textsuperscript{210}

7.2  METHODS

A case-control methodology was used. The Hager definition was used to diagnose PID cases in both GUM and O&G clinics but did not require the presence of either fever or leukocytosis\textsuperscript{12}. PID diagnosis, based on either clinical presentation (figure 7.1; pathways A&B) or laparoscopic evidence (figure 7.1; pathways C&D), was the outcome measure.

A case-control methodology is usually a retrospective study. Here cases of PID were identified at diagnosis and information collected during the consultation was used to investigate determinants of incidence. It is difficult to establish causality using a case-control methodology so significant relationships between
variables and outcome measures are referred to here as associations not risk factors.

In the design of a case-control study controls should be derived from the same population as the cases but should not have the disease under investigation, in this case PID. The number of cases included in the control groups should be kept to a minimum. Laparoscopy is carried out on women attending for tubal ligation and thus any cases of PID seen in this group can be excluded from the study. Control group 1 was thus a group of sexually active fertile women undergoing bilateral tubal ligation in O&G clinics. However, this is a potentially biased control group as these women are likely to have higher parity and be older than the cases. This could bias the odds ratios (OR) associated with variables in the analysis, such as parity, contraception and measures of sexual behaviour. Consequently a second control group (control group 2) was used which consisted of women attending general practice.

Inclusion criteria

Women between 16 and 46 years of age were included in the study. The inclusion criteria used for cases and controls are described in the appropriate sections below.

Exclusion criteria

Patients were excluded from the study if they had a competing diagnosis such as pregnancy, ectopic pregnancy, appendicitis, urinary tract infection or gastroenteritis. Patients with evidence of PID were excluded from both control groups.

Patient consent, confidentiality and management

Informed consent was sought from all patients. Before taking part patients were verbally introduced to the study by the attending health care professional, given background information and, if they wanted to take part, were asked to sign a consent form (appendix 3). No named data were collected and all questionnaires,
microbiological and serological results were matched at CDSC using either a hospital or clinic number. Where infection was detected, patients were managed according to standard clinical guidelines\textsuperscript{127}.

Questionnaires

Three questionnaires were used: a patient questionnaire used for the cases and both control groups, and two clinical questionnaires, one for the cases, the other for control group 1 which were completed by the physician and/or clinic records staff (appendix 3). Data from previous studies indicated that the following factors are likely to be associated with significantly higher risk of PID: presence of genital chlamydial infection, current gonococcal infection, history of TOP or other instrumentation of the cervix, history of smoking, lower socio-economic status, age at first intercourse less than 18 years of age and more than one sexual partner\textsuperscript{24,100,116}. These factors were included in the questionnaire together with questions on contraceptive history, demography and reproductive history. Wherever possible questions were worded to accord with the Natsal 2000 to allow comparison between the studies\textsuperscript{102}.

Sample size calculation

To ensure that the study avoided a type II error, that is the probability of failing to detect a real difference, it was designed so that it was likely that the aims of the investigation would be answered. To do this a sample size calculation was used to estimate the number of cases and controls needed to address the aims of the investigation. The number of cases and controls required by the study is dependent on the OR that the study could detect. The higher the OR, the smaller the sample size required. It is important to estimate the number of samples that are needed so that the study is designed efficiently. Published studies give an indication of the size of the OR that would be associated with variables in a PID case-control study (table 7.1). A history of smoking, presence of gonococcal infection, age at first sexual intercourse less than 18 years of age, and more than one sexual partner were taken from a US study because no data for England were
The estimates of *C. trachomatis* prevalence were taken from UK studies\(^{32,110,211}\). These estimates were not an ideal information source on which to base the sample size calculation for the reasons discussed in section 2.7, but they provided a starting point for estimating the size of the study. It was anticipated that ORs detected in this study would be different from the estimates in the original sample size calculation and that the sample size calculation would need to be revised during the study.

### Table 7.1 ORs associated with factors used in first sample size calculation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Observed prevalence (%)</th>
<th>OR</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genital chlamydial infection</td>
<td>Case 40, Control 4</td>
<td>10</td>
<td>Bevan(^{22}), Grun(^{211})</td>
</tr>
<tr>
<td>Smoker (current)</td>
<td>Case 43, Control 23</td>
<td>2</td>
<td>Scholes(^{110})</td>
</tr>
<tr>
<td>Gonorrhoea</td>
<td>Case 15, Control 5</td>
<td>3</td>
<td>Scholes(^{110})</td>
</tr>
<tr>
<td>1 lifetime partner</td>
<td>Case 12, Control 29</td>
<td>0.5</td>
<td>Scholes(^{110})</td>
</tr>
<tr>
<td>2-4 lifetime partners</td>
<td>Case 42, Control 33</td>
<td>1.6</td>
<td>Scholes(^{110})</td>
</tr>
<tr>
<td>Age at first sexual intercourse &lt;18</td>
<td>Case 68, Control 31</td>
<td>2.8</td>
<td>Scholes(^{110})</td>
</tr>
</tbody>
</table>

The sample size calculation assumed a case/control ratio of 1:2, 5% significance level and 80% power. For factors where the proportion of control exposed is between 10% and 50% (such as that in specific age ranges), a sample of 200 cases and 400 controls would detect a minimum OR of 1.65 (for 50% exposed) and 2.1 (for 10% exposed): sufficient to demonstrate significant effects where a variable has a true OR of 2 or more. It was anticipated that, with a prevalence of 1.7% (estimate from chapter 4), few cases would be included in the control groups, so it was not likely that this would be a source of bias in the study.

Further sample size calculations were made after the project had been running for two years. This was a longer period than that anticipated at the start of the study and was leading to recruitment fatigue amongst the collaborators, particularly in control group 1. In the interests of efficiency and the ethical basis of the project, it was decided that the study should finish when it could be demonstrated that it had sufficient statistical power to answer the aims of the
investigation. To do this, an estimate of the study's statistical power was made using ORs from a multivariable analysis undertaken on the available dataset. Statistical power was calculated for samples of 100, 120 and 140 using the adjusted ORs derived from an interim analysis and the percentage of controls exposed. It assumed a case/control ratio of 1:1 and 5% significance (tables 7.2 and 7.3). Where a variable contained more than two categories, more than one OR was calculated only if the adjusted ORs within the variable were substantially different from each other. The sample size calculations indicated that the statistical power for most variables was over 80% if more than 100 patients were recruited for the case and both control groups. Consequently it was decided that the study should end when 140 cases, 100 tubal ligation controls and 140 general practice controls had been recruited.
Table 7.2  Cases & control group 1: variation in statistical power (%) in relation to the adjusted ORs & percentage of controls exposed at sample sizes of 100, 120 & 140*

<table>
<thead>
<tr>
<th>Variable†</th>
<th>Adjusted OR (%)</th>
<th>Statistical power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(% controls exposed)</td>
<td>100</td>
</tr>
<tr>
<td>Age group</td>
<td>4.65 (14)</td>
<td>100</td>
</tr>
<tr>
<td>Age at first sexual intercourse</td>
<td>0.03 (16)</td>
<td>97</td>
</tr>
<tr>
<td>Contraception (oral)</td>
<td>2.40 (41)</td>
<td>83</td>
</tr>
<tr>
<td>Contraception (other)</td>
<td>6.77 (32)</td>
<td>100</td>
</tr>
<tr>
<td>Marital status (single)</td>
<td>3.09 (37)</td>
<td>97</td>
</tr>
<tr>
<td>Smoker</td>
<td>0.87 (47)</td>
<td>4</td>
</tr>
<tr>
<td>Adverse pregnancy outcome</td>
<td>1.30 (43)</td>
<td>12</td>
</tr>
<tr>
<td>History of a STI</td>
<td>0.06 (90)</td>
<td>100</td>
</tr>
<tr>
<td>Exposure to C. trachomatis</td>
<td>0.13 (93)</td>
<td>100</td>
</tr>
</tbody>
</table>

* Assumes a 5% level of significance
† Lifetime sexual partners & children are not shown because the numbers of cases seen in each category within these variables were equal

Table 7.3  Cases & control group 2: variation in statistical power (%) in relation to the adjusted ORs & percentage of controls exposed at sample sizes of 100, 120 & 140*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted OR (%)</th>
<th>Statistical power (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(% controls exposed)</td>
<td>100</td>
</tr>
<tr>
<td>Age group</td>
<td>6.78 (29)</td>
<td>100</td>
</tr>
<tr>
<td>Age at first sexual intercourse</td>
<td>2.77 (16)</td>
<td>90</td>
</tr>
<tr>
<td>Lifetime sexual partners</td>
<td>2.34 (33)</td>
<td>78</td>
</tr>
<tr>
<td>Children</td>
<td>0.41 (50)</td>
<td>85</td>
</tr>
<tr>
<td>Contraception (oral)</td>
<td>1.21 (40)</td>
<td>7</td>
</tr>
<tr>
<td>Marital status (single)</td>
<td>2.82 (55)</td>
<td>90</td>
</tr>
<tr>
<td>Smoker</td>
<td>1.21 (54)</td>
<td>7</td>
</tr>
<tr>
<td>Adverse pregnancy outcome</td>
<td>0.69 (69)</td>
<td>18</td>
</tr>
<tr>
<td>History of a STI</td>
<td>0.07 (89)</td>
<td>100</td>
</tr>
<tr>
<td>Exposure to C. trachomatis</td>
<td>0.40 (91)</td>
<td>51</td>
</tr>
</tbody>
</table>

* Assumes a 5% level of significance
Selection and recruitment of centres

Ian Simms recruited all the centres, visited them once a month and gave presentations on the project to their research meetings. The study was funded by the Department of Health (England) as part of the Chlamydia Screening Pilot that was conducted on The Wirral and in Portsmouth. The Wirral and Merseyside were selected as centres to take part in this case-control study because there were GUM, O&G and general practice clinics in these areas that were willing to take part. Case load at the participating clinics was evaluated before and during the pilot phase of this case-control study. An initial evaluation suggested that sufficient cases and controls could be recruited from the Merseyside clinics and recruitment started in January 2000. However, at the end of the first 3 months of the study, it was clear that the Merseyside clinics would not be able to recruit sufficient patients to the study and it was decided to extend the study to another English city. Ian Simms approached the British Cooperative Clinical Group to help identify interested GUM clinics but recruitment proved difficult. This was because GUM, O&G and primary care clinics were need at each location. After negotiations with several clinics a further centre based around St George’s Hospital (South London) was recruited. Although the Department of O&G at St George’s Hospital was keen to participate they did not recruit any tubal ligation controls. This was because of a change in clinical priorities that occurred during the study. Women requesting tubal ligation within the Wandsworth HA were being offered IUD insertion and the theatre time saved was used for other purposes. A similar pattern was seen throughout London. The study ended in March 2002. The majority of patients in the cases and control group 1, were recruited from the Liverpool centre, whereas the St George’s centre recruited the majority of patients for control group 2 (table 7.4).
Table 7.4 Number of patients recruited by centre*

<table>
<thead>
<tr>
<th>Centre</th>
<th>Cases (n)</th>
<th>Control Group 1</th>
<th>Control Group 2</th>
<th>Total recruited</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liverpool</td>
<td>61</td>
<td>67</td>
<td>46</td>
<td>174</td>
</tr>
<tr>
<td>The Wirral</td>
<td>55</td>
<td>38</td>
<td>38</td>
<td>131</td>
</tr>
<tr>
<td>St George's</td>
<td>24</td>
<td>0</td>
<td>52</td>
<td>76</td>
</tr>
</tbody>
</table>

* Data collected started in Liverpool and the Wirral at the beginning of 2000 whereas the St George's centre did not start recruitment until 2001

Procedure

Standard Operating Procedures (SOPs)

Ian Simms produced standard operating procedures in consultation with the clinicians and microbiologists who were to take part in the study. These SOPs were distributed to all the centres that participated in the study (appendix 4).

Both the case and control groups were self-selected. No records were kept of those patients who refused to take part.

Cases

Woman aged 16 to 46 with a clinical diagnosis of PID who had not previously taken part in the study were recruited (figure 7.1 and 7.2). Patients were told about the study and given the information sheet to read. If they wanted to take part, patients were asked to sign the consent form (see SOPs appendix 4) and complete the patient questionnaire (appendix 3). The clinician signed the consent form (which was held in the O&G clinic) and gave a copy to the patient. The patient then sealed the questionnaire in an envelope and this was sent to CDSC. The physician completed the clinical questionnaire and this was also sent to CDSC.

Three swabs were be taken by the physician, one high vaginal swab and two endocervical swabs (one each for *C. trachomatis* and *N. gonorrhoeae*). A study label was attached to each sample and they were sent to Liverpool Public Health Laboratory to be tested. The blood sample was taken by the phlebotomist and the patient was recalled six weeks later to have a further blood test. Liverpool
PHL returned the test results to the O&G clinic and sent the results to CDSC. The patient was advised of the test result either by letter if the result was negative, or 'phone if positive. Appropriate counselling, treatment and partner notification were given where necessary. The test result and questionnaire were linked at CDSC using the patient’s hospital number.
Figure 7.1  Summary of PID diagnosis in Obstetrics & Gynaecology and Genitourinary Medicine clinics

Clinical history taken

All competing diagnoses excluded

A: Clinical presentation meets Hager definition
   - Treated with antibiotics
     - Sent home

B: Clinical presentation meets Hager definition
   - More ill than A - admitted
     - Responds to antibiotic treatment
       - Sent home

C: PID suspected but may be pregnant
   - Pregnant
     - Yes
       - Given laparoscopy to resolve diagnosis
         - Sent home
     - No
       - Likely to have laparoscopy to resolve diagnosis
         - Sent home

D: PID suspected but missing some elements of Hager definition
   - Given laparoscopy to resolve diagnosis
     - Sent home
Figure 7.2  Procedure summary, PID cases: Obstetrics & Gynaecology and Genitourinary Medicine clinics

PID Case
Confirmed PID diagnosis using Hager definition No competing diagnosis

Patient fulfils inclusion criteria is given information sheet & invited to take part in study

Patient agrees to take part in the study

Yes

Patient & clinician sign consent form & patient completes patient questionnaire

1st blood sample taken
Endocervical & high vaginal swabs taken

Samples sent to laboratory for testing

Clinical questionnaire completed by physician & sent to CDSC

Laboratory test results sent to CDSC

Patient advised of results of laboratory tests, with appropriate counselling, treatment and partner notification

Test results & questionnaires linked on patient clinic number at CDSC

2nd blood sample taken 6 weeks later and tested at laboratory
Control group 1 - laparoscopic sterilisation

The procedure used for the selection and recruitment of control group 1 (laparoscopic sterilisation) is summarised in figure 7.3. Patients were invited to take part in the study if they were: aged 16 to 46; had no history of PID or tubal damage; no chronic lower abdominal pain (mild pain of more than 2 weeks duration), or moderate or severe lower abdominal pain; and had not already taken part in the study. Patients attended for pre-operative assessment between 3 months and 1 day before their operation. During the consultation, patients were told about the study and given the information sheet to read. Patients were allowed at least 24 hours to consider whether they wanted to take part in the study. If they wanted to take part, the patient was asked to sign the consent form (see SOPs appendix 4) and complete the patient questionnaire (appendix 3). The patient then sealed the questionnaire in an envelope, which was then sent to CDSC. A record stating that the patient had agreed to take part in the study was made in their notes so they could be identified when they re-attend for laparoscopic sterilisation.

A blood sample was taken as part of routine case management at the pre-operative clinic (figure 7.3) and part of the sample was sent to Liverpool PHL for testing. Laparoscopic sterilisation was then carried out. The physician completed the clinical questionnaire (appendix 3) after the surgical procedure and this was returned to CDSC. If evidence of PID was found on laparoscopy, the patient was excluded from the study and the rest of the procedures were not carried out. If no evidence of PID was found high vaginal and endocervical swabs were taken from each patient during laparoscopic sterilisation and the samples sent for microbiological testing. The laboratory sent the test results to the O&G clinic. The patient was advised of the laboratory test results by letter if negative, or 'phone if positive. Where appropriate counselling, treatment and partner
notification were provided. The test results and questionnaires were linked at CDSC using the patient’s hospital number.

Figure 7.3 Procedure summary, controls: women requesting bilateral tubal ligation (control group 1)
**Control group 2 - general practice**

Women were invited to take part if they were: aged 16 to 46; had no history of PID or tubal damage; no chronic lower abdominal pain (mild pain of more than 2 weeks duration), or moderate or severe lower abdominal pain; were going to have a blood sample taken as part of routine management; and had not already taken part in the study (figure 7.4). Patients were told about the study during the consultation and given the information sheet to read. If they wanted to take part, the patient was asked to sign the consent form (see SOPs appendix 4) and complete the patient questionnaire (appendix 3). The clinician signed the consent form (to be held in the O&G clinic) and gave a copy to the patient. The patient then sealed the questionnaire in an envelope which was then sent to CDSC.

The blood sample was be taken by the phlebotomist and the patient gave a urine sample. Part of the blood sample (approximately 5ml) was sent to Liverpool PHL. Liverpool PHL returned the test results to the general practice. The patient was advised of the laboratory test results either by letter if the result was negative or 'phone if positive. Appropriate counselling, treatment and partner notification was given where necessary. The test results and questionnaire were linked at CDSC using the patient’s NHS number.

The general practices that took part in the Wirral arm of the study also participated in the Department of Health Chlamydia Screening Pilot and were given standard operating procedures for the management of genital chlamydial infection and PID. Chlamydia information leaflets were distributed to attenders at these practices, consequently there was a higher level of awareness of chlamydial infection and PID amongst women attending these practices.
Figure 7.4 Summary of procedure, controls: general practice

**Patient fulfils all three inclusion criteria:**

- Woman aged 16 to 46 with no history of PID, tubal damage or chronic lower abdominal pain
- Blood sample to be taken as part of routine management
- Not previously included in the study

Patient fulfils inclusion criteria, is given information sheet and invited to take part in study by the GP

Patient agrees to take part in the study

Yes

Patient given consent form & questionnaire

Patient and clinician sign consent form & patient completes patient questionnaire

Blood sample taken by phlebotomist.

Patient gives urine sample

Samples sent to Liverpool PHL for testing

Laboratory test results returned to GP from Liverpool PHL

Patient advised of laboratory test results, with appropriate counselling, treatment and partner notification

No

Patient and clinical questionnaires sent to CDSC by GP receptionist

Laboratory test results sent to CDSC by Liverpool PHL

Test results and questionnaire linked on patient NHS number at CDSC
Laboratory methods

Microbiological investigations were undertaken on cases and controls. For cases and tubal ligation controls, samples were collected that were tested for the presence of: *C. trachomatis*, *N. gonorrhoeae*, bacterial vaginosis, Candida spp. and *Streptococcus B*. Two endocervical swabs were taken: one to detect the presence of *C. trachomatis* and the other to detect the presence of *N. gonorrhoeae*. A high vaginal swab (HVS) was tested by culture and microscopy for the other conditions. A ligase chain reaction (LCR) test (Abbott LCx *Chlamydia trachomatis* assay, Abbott Laboratories) was used to detect the presence of *C. trachomatis*. The bacteriology tests undertaken on the HVS complied with PHLS standard operating procedures. For the general practice control group (control group 2), a urine sample was taken to detect the presence of *C. trachomatis* using the Abbott LCx test. Although different samples were taken from different sites to test for the presence of *C. trachomatis* using the LCR test, the results are comparable because there is little difference in the performance of the LCR test between urine and endocervical samples.

Serological testing for anti-*C. trachomatis* antibody was undertaken on cases and controls using MIF (Medical Research Laboratories) and heat shock protein-60 enzyme immunoassay (HSP-60 EIA) using serovars D and L2. The MIF testing was carried out at Liverpool PHL and the National Center for Sexually Transmitted Diseases (NCSTD), Winnipeg, Canada acted as the reference laboratory. The HSP-60 testing was undertaken by the NCSTD, Canada. The results of the MIF test were interpreted as follows: *C. trachomatis* IgG titre <16 no evidence of infection; *C. trachomatis* IgG titre ≥16 evidence of infection; titre of *C. trachomatis* IgG ≥ titre of *C. pneumoniae*, cross reaction unlikely; titre of *C. pneumoniae* > titre of *C. trachomatis*, indeterminant result.

Diagnosis of *M. genitalium* was not included in the original protocol because the test was not available. However, during the study a PCR test for *M. genitalium*
became available that could use the samples taken for the *C. trachomatis* LCR test. This *M. genitalium* PCR test was included in the methodology. Additional ethical approval for this part of the project was given by the MREC. The clinicians involved in the project did not vary the treatment regime beyond the existing management protocol\(^2\). The results of the *M. genitalium* investigation are given in chapter 8.

**Data analysis**

Cases were compared against the control groups in terms of age and age at first sexual intercourse, using the \(\chi^2\) test. Reasons for using condoms between cases and controls were also compared using the \(\chi^2\) test. Data were also analysed using logistic regression: ORs were calculated for the aetiological, behavioural, serological and demographic parameters measured in the study. Some continuous variables were converted to categorical variables to increase the effectiveness of the analysis. The partitioned \(\chi^2\) test was used to transform continuous variables into categorical variables and amalgamate categories where there were a number of categories with a small number of numbers, such as the socio-economic variable. Cases were compared against control groups 1 and 2 separately using single and multivariable analyses.

The marital status and cohabiting variables were recoded into a single variable hierarchy: (1) married, (2) cohabiting, (3) widowed/separated/divorced, and (4) single. Similarly since many women used more than one method of contraception the data were converted into a hierarchy: (1) condom, (2) pill, (3) other and (4) none. The patient’s current occupation was used to allocate social class using the Standard Occupational Classification (SOC) 2000 classification used in the 2001 ONS census\(^2\). The categories used in the SOC 2000 major group occupational classification were as follows: (1) managers and senior officials, (2) professional, (3) associate professional and technical, (4) administrative and secretarial, (5)
skilled trades, (6) personal service, (7) sales and customer service, (8) process, plant and machine operatives, and (9) elementary. An unknown category (10) was introduced which included students and the unemployed. The 10 categories within this hierarchy were reduced to 5 by amalgamating adjacent codes, that is 1 to 3, 4 and 5, 6 and 7, 8 and 9. The unknown code remained separate from the other groups. Centre, Merseyside (1), The Wirral (2) and St George’s (3), was included as a cluster variable. The ethnicity variable was reduced to two categories, white and other, because only 27 (7%) of the patients included in the study were in the non-white categories. The adverse pregnancy outcome variable was created from the questions concerned with miscarriage, ectopic pregnancy and still birth. In an initial evaluation of the data these variables had similar ORs and were thus combined into one variable. Exposure to C. trachomatis was defined as ever (yes) or none (no) which were defined as follows: ever (LCR positive and/or MIF positive and/or CHSP60 positive); none (LCR negative and MIF negative and CHSP60 negative).

Baselines were allocated separately for each variable. Where the variables had a yes/no answer and were known to be associated with an increased risk of PID (smoker, TOP, adverse pregnancy outcome, a self reported history of a STD, and exposure to C. trachomatis) the baseline was taken as no. Increased risk of PID was thus shown as an OR significantly higher than 1. For the children variable, the baseline was again set at 1 so that increased risk would be shown as an OR significantly higher than 1. In the case of contraception, condom use (barrier contraception) was taken as the baseline because this is the contraceptive method that is most effective in preventing PID. For marital status, the married category was used as the baseline because this is the most stable sexual partnership in terms of the number of sexual partners and concurrent partners. The baseline in the age group category was set at the 25 to 34 category because this was the category which held the majority of the data for the case and control groups. For
age at first sexual intercourse, the baseline was the 15 to 19 year age group because it is within these ages that the majority of the population has intercourse for the first time. Similarly, the baseline in the lifetime sexual partners category was taken as the 1 to 4 group because the mean number of partners lies within this category. The baseline of the socio-economic variable was taken as category 1 as the MSGP4 analysis (chapter 4) showed that this was at lower risk than the manual occupations. The baseline for the ethnicity variable was taken as white as this category included the majority of the patients.

Single and multi-variable analyses were undertaken to investigate associations between the variables in the case and control groups. Interactions were investigated and a main effects model was used to describe the data. The centre variable, which reflects patient recruitment at the different sites rather than any difference in disease presentation between the geographic locations, was included as a variable in the initial analyses but was not included in the final presentation as it was not associated with any confounding.

Although bacteriology results were available for the cases, results were only available for 37 patients in control group 1 (no bacteriology samples were collected for control group 2). Physicians appeared to forget to take the samples during tubal ligation. This is probably a reflection of study fatigue at the centres. Consequently there were insufficient bacteriology samples to be included in this analysis, although results were included in the study described in chapter 8.
7.3 Results

The data were collected over the period January 2000 to March 2002. A total of 384 patients were recruited: 140 cases, and 105 and 136 controls in groups 1 and 2 respectively (3 patients were excluded because serological samples were not available) (table 7.5). The median age of the cases was 23 (range 16 to 43), whereas that of the control group 1 was 33 (range 21 to 46) and control group 2 was 28 (range 16 to 46). There was a significant difference between the cases and control groups in terms of age (p<0.001) and age at first sexual intercourse (p<0.001).

<table>
<thead>
<tr>
<th>Table 7.5 Summary of results</th>
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<tr>
<td></td>
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<tr>
<td>Total</td>
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<tr>
<td>Median age (range)</td>
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<tr>
<td>Mean age at first sexual intercourse</td>
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<tr>
<td>C. trachomatis &amp; serology)</td>
</tr>
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</table>

Seventeen percent of cases, 23% of tubal ligation controls and 19% general practice controls had not used contraception within the 6 months prior to taking part in the study despite being sexually active. There was a significant difference between cases and both control groups in terms of the reasons for using condoms (p<0.001). Under half the women included in the case and control groups had used condoms as a contraceptive method within the past 6 months. The main reason for using condoms was to prevent pregnancy in both the cases (33/35) and tubal ligation control group (34/40). In contrast, the main reasons for women in the general practice control group for using a condom were either to prevent infection (25/53), or to prevent infection and pregnancy (22/53).
Evidence of ever having had *C. trachomatis* infection (LCR and serology) was found in 42 (30%; 95% CI 23% to 38%) of cases (17 cases LCR positive, 25 cases serology positive), whereas *N. gonorrhoeae*, *Streptococcus B* and bacterial vaginosis were seen in 2, 10 and 13 cases respectively. *C. trachomatis* was seen in 8% (8/105) of the tubal ligation group (none LCR positive, 8 serology positive) and 8% (11/136) of the general practice control group (1 LCR positive, 11 serology positive) (table 7.5). No aetiological agent was found in 64% of the PID cases. There was good comparability between the serological test results produced by Liverpool PHL and the reference laboratory (NCSTD, Canada). The titres given by the NCSTD were generally slightly lower than those found by Liverpool PHL but gave a comparable result in all but 2 cases. In both these cases the result from the Liverpool investigation was used in the analysis. Serological evidence of *C. trachomatis* infection was found in 43 patients. Positive test results in both the MIF and HSP-60 EIA test were only seen in 6 patients.

In the single variable analyses, PID was associated with: age < 25 years (control group 1 p<0.0001; control group 2 p<0.0001); having ≥5 lifetime sexual partners (CG1 p=0.0136; CG2 p=0.0063); age at first sexual intercourse ≤14 years of age (CG1 p<0.0001; CG2 p<0.0001); lower socio-economic status (CG1 p=0.0016; CG2 p<0.0001); single, cohabiting, and widowed/separated/divorced marital status (CG1 p<0.0001; CG2 p<0.0001); having a self-reported history of a STD (CG1 p<0.0001; CG2 p<0.0001); and ever having been exposed to *C. trachomatis* (CG1 p<0.0001; CG2 p<0.0001) (tables 7.6 and 7.7). Cases had significantly fewer children than control group 1 (p<0.0001), smoking was associated with a significant risk of PID when cases were compared against control group 2 (p=0.0026), and non-white ethnic identity was significantly associated with increased risk of PID when compared to control group 1 (p<0.0007).

In the multi-variable analysis, increased risk of PID was significantly associated with: age at first sexual intercourse less than 20 years (CG1 p=0.0126; CG2
p=0.0093); non-white ethnic identity (CG1 p=0.0297); lower socio-economic status (CG2 p=0.0048); not having had children (CG1 p=<0.0001); single, and widowed/-separated/divorced marital status (CG2 p=0.0044); having had an adverse pregnancy outcome (CG2 p=0.0270); having a self reported history of a STD (CG1 p<0.0001: CG2 p<0.0001); and having been exposed to C. trachomatis (CG1 p<0.0001: CG2 p=0.0246) (tables 7.6 and 7.7). All two-way interactions were investigated but none were found to be significant at the 5% level.
<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>Unadjusted OR (95% CI)</th>
<th>p value</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
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<td>p value</td>
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* coil, cap, injection (Depo-Provera®)
† still birth, miscarriage, ectopic pregnancy
‡ Combined results of nucleic acid amplification, serological & CHSP60 test results (see section 7.2)
Table 7.7  Cases & control group 2 (general practice): unadjusted ORs, adjusted ORs & 95% CIs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
<th>Unadjusted OR (95% CI)</th>
<th>p value</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
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<td>Controls</td>
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<td>p value</td>
<td>Adjusted OR (95% CI)</td>
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<td>125</td>
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* coil, cap, injection (Depo-Provera®)
† still birth, miscarriage, ectopic pregnancy
‡ Combined results of nucleic acid amplification, serological & CHSP60 test results (see section 7.2)
7.4 DISCUSSION

This is the first case-control study to investigate factors associated with PID in England, and the first of its kind to be undertaken in Europe. It was also the first case-control study to use a case definition based on clinical presentation and thus it reflects the epidemiology of the condition that GUM and O&G clinicians call PID. The large sample size was justified, as was the revision of the sample size that ensured that the number of patients recruited by the study was kept to the minimum required to answer the aim and objectives of the investigation.

The selection of the control groups, recruitment of patients and the case definition were potential sources of bias in the study. The control groups gave profiles of women in the general population but there were significant differences between cases and control groups 1 and 2 in terms of age, and between the cases and control group 1 in terms of reproductive history. A tubal ligation control group was used here because it was considered important to the study design that one of the control groups should be laparoscoped to ensure that all women with the 'gold standard' diagnosis of PID were excluded (section 7.2). Of the women who seek tubal ligation the majority do so because they have completed their families, although they may also seek tubal ligation because they are unable to find an alternative suitable method of contraception (J Hopwood, personal communication). This accounts for the reason why control group 1 was significantly older than the cases and control group 2, and had significantly more children than the cases. If the 35 or over age group is excluded from the comparison of cases against control group 1, the relationships within the data are unchanged although the odds ratio change and the confidence intervals widen. This indicates that the difference in age between the cases and control group 1 was not a source of bias within the study.
The comparison of cases against control group 1 was not likely to have been influenced by an age cohort effect in terms of sexual behaviour because there was no significant difference in the median age at first sexual intercourse between the cases and both control groups. Natsal 2000 showed that age at first sexual intercourse and number of lifetime sexual partners does not vary over the age ranges 16 to 29 years old\textsuperscript{102}. Other age cohort effects that could have been seen include number of births and smoking. It is unlikely that these potential sources of bias influenced the analysis because no significant interactions were detected in the multivariable analysis. Interactions would have been seen if the relationship between cases and controls had been influenced by other, unmeasured factors.

Recruitment was a potential source of bias as the patients included in the study were a self-selected, non-random sample. Unfortunately no information was recorded on those patients that did not take part so the characteristics of participants could not be compared with non-participants. If sufficiently detailed data, including sexual behaviour, socio-economic status and ethnicity, had been collected from non-participants it would have allowed an objective assessment of whether selection bias had influenced the study and allowed the analysis to be adjusted accordingly. However, ethical considerations that prevent data from being collected from patients who do not wish to take part research studies, would not have allowed this type of investigation to have been carried out. Although there is little evidence to suggest that the patients were not representative of the populations from which they were recruited, the inability to recruit patients to control group 1 from St George's hospital resulted in problems in the investigation of increased risk of PID associated with ethnic groups.

Case definition was another potential source of bias. As shown in chapter 6, a case definition based on clinical presentation lacks sensitivity and specificity: consequently some cases included in this study may not have had PID. This is a
problem common to all studies of PID irrespective of diagnostic criteria. Reviewers criticised the project grant proposal for its use of a case definition based on clinical criteria and suggested that an invasive technique should be used. This advice was inconsistent with the published literature as a clinical case definition was used as the outcome variable in the RCT that is widely considered to be the primary evidence base to support the introduction of chlamydial screening. The consistent findings seen in this study suggest that case definition was not a major source of bias.

The collection of a wide range of demographic, aetiological, behavioural, and reproductive health variables allowed a detailed exploration of factors associated with PID. But like Natsal 2000, this information was based on reported experience and behaviour, and so it is susceptible to biases associated with recall, accuracy and truthfulness. In control group 1, behavioural variables such as the number of sexual partners could have increased during the 3 months between recruitment and the taking of microbiological samples during tubal ligation.

In the single variable analysis increased risk of PID was associated with ethnicity, marital status other than married, lower socio-economic status, younger age, having had more than four lifetime sexual partners, having had first sexual intercourse at less than 15 years of age, having a self reported history of a STD, ever having been exposed to C. trachomatis, and a history of smoking: many of the associations that were observed in the analysis described in chapter 4. However, the multi-variable analysis showed that increased risk of PID was associated with a more limited range of variables. When cases were compared against both control groups, increased risk of PID was associated with age less than 25 years old. This relationship may reflect behavioural and biological factors as discussed in section 2.7. These behavioural factors may have influenced the low use of condoms amongst the cases and could account for the lack of an association seen between PID and barrier contraception. Age at first sexual intercourse was also
significantly associated with PID when cases were compared against both control
groups, and this may also reflect behavioural factors. Natsal 2000 showed that
early sexual intercourse was not associated with reported experience of a STI,
but, since a high proportion of PID cases are asymptomatic, those people
included in Natsal 2000 may not have been aware that they had had a STI.

No association was seen between increased risk of PID and TOP. This may be
because of the widespread use of antibiotic prophylaxis in the management of
women undergoing TOP. An association was seen between increased risk of PID
and adverse pregnancy outcome (miscarriage, ectopic pregnancy and still birth)
when cases were compared against control group 2. The relationship between
PID and ectopic pregnancy is well documented (section 2.5).

The association seen in the comparison between cases and control group 1
supported the observation made in chapter 4 that ethnic minorities are at
increased risk of PID. However, the relationship seen in this study could equally
be the result of a bias in the selection of control group 1. Only one patient who
was of non-White ethnicity was recruited to the tubal ligation control group and
this reflects the fact that the proportion of the Merseyside population that has a
non-White ethnic identity is below the national average. When cases were
compared against control group 2, which was recruited from all the centres, no
relationship was seen between increased risk of PID and ethnicity. Socio-
economic status is a well documented confounder of the relationship between
disease occurrence and ethnicity, and increased risk of PID was associated with
the personal service, sales and customer service categories when cases were
compared against control group 2. However, interpretation of these data is
difficult because of the high number of women for whom occupation was
unknown. The reason for this is that the SOC 2000 classification is used to define
the working population and is based exclusively on current occupation.
Consequently there is no category for students, and the occupation of those who
are unemployed is based on previous employment. Current occupation was collected in the case-control study but this was probably an insensitive measure of socio-economic status given the high number of students and housewives included in the study. The problems associated with this measure of socio-economic status may have influenced the assessment of risk in ethnic groups, as many of the women from ethnic minorities were students.

The study was undertaken at a time when there were substantial increases in diagnoses of bacterial STIs seen in GUM clinics throughout the UK. Diagnoses of *N. gonorrhoeae* and *C. trachomatis* seen at local GUM clinics increased during the study period, as did the prevalence of antibiotic resistant gonorrhoea in Merseyside. Treatment regimes used at the Merseyside GUM clinics were adjusted in response to these developments and local public health information campaigns were undertaken. Only two cases of gonorrhoea were seen in the study, and this suggests that GUM management strategies were effective in treating cases effectively and preventing infection from progressing to PID.

The study found that genital *C. trachomatis* infection was important to the aetiology of PID whereas little evidence of infection was seen in both control groups. When confidence limits are taken into consideration, the cumulative incidence of genital chlamydial infection seen in the cases was not significantly different from the 40% (95% CI 29% to 49%) reported in another English study of PID aetiology (section 2.4). However, 64% of cases were idiopathic which confirms the findings of other studies (section 2.4). Two reasons could account for the high number of idiopathic cases. Firstly, some cases may not have had PID, and secondly the laboratory tests could only find those organisms for which they tested. In a recent study of idiopathic cases of salpingitis, *Prevotella* spp., *Peptostreptococcus*, *Streptococcus pyogenes* and *Leptotricha* spp. were identified in fallopian tube specimens using NAAT, whereas no rDNA amplicons were
detected amongst a tubal ligation control group. Other aetiological agents may thus play a role in the development of PID.

Interpretation of the aetiological investigation is difficult as no samples were taken from the upper genital tract, and consequently there is no direct evidence of association between the aetiological agents and the site of disease. A serological response was used as a potential indicator of previous infection, but again this does not necessarily mean that infection was present in the upper genital tract. Although it has been suggested that the height of a WIF titre may indicate tubal damage, comparative studies using the MIF test have not been undertaken. Unfortunately, despite efforts to recall patients, only two reattended to give a second blood sample. This limited the interpretation of the serological results where patients either had a low titre on the first test and short duration of symptoms (characteristic of recent infection), or where patients had a low titre and no organism were isolated from the endocervix.

The results of the CHSP60 EIA test provided another source of serological evidence of exposure to chlamydial infection. However, the results of the MIF and HSP60 tests did not correlate, a discrepancy that may have reflected patients being in the early stages of infection (section 2.6).

The associations found in this study, expressed as odds ratios, are specific to the population studied and cannot be compared with those reported elsewhere. However, consistent findings between studies indicate general relationships between variables and a diagnosis of PID. In the case of this study, comparisons are difficult to find as the literature is confined to US studies and there are a number of problems associated with comparing studies from these countries (section 2.7). However, the findings of this case-control study are broadly similar to the US studies that used a laparoscopic diagnostic ‘gold standard’. In both countries PID was associated with younger age, aspects of sexual behaviour and
exposure to STIs. This supports the findings of this study and the use of a case definition based on clinical presentation.

7.5 FURTHER WORK

This analysis highlighted a number of areas for further research. The relationship between ethnicity, socio-economic status and increased risk of PID should be investigated with a specific study focused on ethnic minorities. This study should include a more comprehensive measure of socio-economic status, including questions relating to occupation and salary. More detailed questions could be used to explore sexual behaviour, such as the number of concurrent partners, reproductive history and contraception. The use of alcohol and recreational drugs in sexual relationships, particularly at first sexual intercourse, could also be investigated.

The aetiology of PID needs to be investigated in more detail, particularly the aetiology of idiopathic cases, and a further investigation is described in chapter 8. This study also highlighted the problems of using available serological tests to investigate disease aetiology. The requirement for two samples makes the MIF test difficult to use in epidemiological studies and new methods need to be developed. Serological diagnostic techniques need to be developed to answer specific questions. Here the problem encountered was the inability of serological tests to detect recent infection. An avidity technique could be used to distinguish recent from established infection as has been done for HIV infection. The technique cannot be applied to all infections as the specificity and sensitivity of the test depend on the expression of target antigens and the speed at which the host response develops to these antigens. However, if the technique was feasible, it could be used to screen serum banks for genital chlamydial infection, and allow the prevalence of genital chlamydial infection to be estimated in different
populations. This could be a potentially important method of evaluating the impact of a future genital chlamydial screening programme.
7.6 CONCLUSIONS

The associations seen in the study correspond with those that would be expected to be associated with a syndrome that is predominantly associated with STIs. Whilst the study confirms the importance of genital *C. trachomatis* infection to the aetiology of PID in England, it shows that other aetiological agents may play an important role in PID pathogenesis. The study in chapter 8 investigates the relationship between *M. genitalium*, *C. trachomatis* and PID using a subset of the data collected for this investigation.
Chapter 8  Associations between *Mycoplasma genitalium*, *Chlamydia trachomatis* and pelvic inflammatory disease

8.1  INTRODUCTION

There is growing evidence that *M. genitalium* is a cause of non-gonococcal, non-chlamydial urethritis and mucopurulent cervicitis (section 2.4), but the relationship between *M. genitalium* and sequelae such as PID remains unclear. Serological evidence has associated *M. genitalium* with PID and a recent Kenyan study suggested an association between *M. genitalium* and acute endometritis. This study is one of the first to evaluate the relationship between *M. genitalium*, *C. trachomatis* and PID. Results of the investigation were presented at the 18th Congress of the International Union of Sexually Transmitted Infections (IUSTI Europe) (paper 5, appendix 5), have been published in *Sexually Transmitted Infections* (paper 6, appendix 5) and accepted for publication in the *Journal of Clinical Pathology*.

8.2  METHODS

The patients included in this study were a subset of the case-control study described in chapter 7. A PCR test for *M. genitalium* that had been developed by Dr Kirstine Eastick at Bristol Public Health Laboratory became available half way through the case-control study, and was added to the protocol. All patients who had a *M. genitalium* test were included in this subgroup analysis. Cases were only compared against the tubal ligation control group because this was the only control group for which appropriate samples were collected. Results of the MIF, gonorrhoea, bacteriology and LCR tests were available for all the patients included in this sub-analysis. Although a detailed dataset containing information on sexual behaviour, demographic factors and reproductive health was collected as part of the PID case-control study described in chapter 7, it could not be used
in the analysis here because of the small number of *M. genitalium* cases detected and the small sample size. To reduce the risk of deductive disclosure patient data are shown as totals.

The *M. genitalium* PCR test used the following protocol. Two hundred microlitres of swab eluate was processed using the QIAamp DNA mini kit (Qiagen Ltd.) blood and body fluid protocol according to the manufacturer’s instructions. For swabs in LCx medium or transport medium, 1µg calf thymus DNA was added as a carrier prior to extraction. Swabs transported to the laboratory dry were incubated at room temperature in 500µL phosphate-buffered saline for 1 hour and vortex-mixed. Two hundred microlitres of expressed fluid was processed using the QIAamp DNA mini kit swab protocol without carrier DNA. Nucleic acid was eluted from QIAamp columns using 50µL of buffer AE (as supplied by the manufacturer) and was incubated on the column for 5 minutes. The same buffer was then used to elute nucleic acid from the column a second time. Amplification was performed by in-house PCR using the LightCycler instrument.

The following primers were used to target the 16S rRNA gene of *M. genitalium*: 16SFG2: 5’ CCT TAT CGT TAG TTA CAT TGT TTA A 3’ and 16SRG: 5’ TGA CAT GCG CTT CCA ATA AA 3’. Reactions were set up for the LightCycler consisting of (final concentrations in 10µL reactions): 500nM each primer, 200µM each dNTP, 50mM TRIS-HCl pH 8.3, 5mM MgCl2 and 0.65 U Platinum *Taq* polymerase (prediluted in 1µL 2.5mg/mL BSA to prevent denaturation). This mix was dispensed and made up to 10µL using the QIAamp extracts. The LightCycler instrument (Roche Diagnostics) was programmed as follows: after initial denaturation of 1 minute at 95°C, 50 cycles were performed consisting of 0 seconds at 95°C, 0 seconds at 55°C and 15 seconds at 72°C (program type: melting curves). After each cycle a single fluorescence reading was taken. The results were ascertained using a melt cycle at 0.2°C per second with continuous
fluorescence readings. A positive specimen was judged to have a Tm within ± 1°C of the positive control. This was approximately 88.5°C. Positive results were confirmed using a hemi-nested block-based PCR.

Statistical analysis was undertaken using the Fisher’s exact test. Cases and controls were compared in terms of age using the Wilcoxon rank sum (Mann-Whitney) test.

8.3 Results

A total of 82 women were included in the study, 45 cases of PID and 37 patients undergoing tubal ligation (table 8.1). Cases were significantly younger than controls (p<0.001). The median age of the cases was 25 (range 16 to 43), whereas that of the controls was 34 (range 21 to 45).

Evidence of M. genitalium infection was found in 13% (6/45) of the cases compared with none of the controls. Of the cases, 27% (12/45) had C. trachomatis infection (LCR with or without serology) compared to none of the controls, and 16% (7/45) of the cases had serological evidence only of C. trachomatis infection compared to 5% (2/37) of controls (table 8.1). BV was not detected in any of the cases or controls. Two cases had co-infections: one with C. trachomatis and N. gonorrhoeae, the other between M. genitalium and C. trachomatis (the patient was LCR positive and had a raised MIF titre). The remaining 5 M. genitalium infected patients had no serological evidence of C. trachomatis infection. Of the 6 patients with M. genitalium infection, half were over 30 years old, none had children, none had experienced either a TOP, miscarriage, still birth or ectopic pregnancy, 2 had had sexual intercourse under the age of 16 years, and 2 had had over 10 sexual partners. Cases were more likely to present with M. genitalium and/or C. trachomatis than controls (p<0.001).
Table 8.1 Evidence of \textit{M. genitalium} and \textit{C. trachomatis} in cases and controls

<table>
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<tr>
<th></th>
<th>Cases (n = 45)</th>
<th>Controls (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{M. genitalium}</td>
<td>6*</td>
<td>0</td>
</tr>
<tr>
<td>\textit{N. gonorrhoeae} only</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>\textit{C. trachomatis} (ligase chain reaction with or without serological evidence)</td>
<td>12††</td>
<td>0</td>
</tr>
<tr>
<td>\textit{C. trachomatis} (serology only)</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Rest</td>
<td>19</td>
<td>35</td>
</tr>
</tbody>
</table>

* Includes 1 co-infection with \textit{C. trachomatis}
†† Includes 1 co-infection with \textit{N. gonorrhoeae}
‡‡ 7 had serological evidence of \textit{C. trachomatis} infection

8.4 DISCUSSION

This is the first case-control study of PID to test for \textit{M. genitalium}. The results suggest that there is an association between \textit{M. genitalium} and PID, and that \textit{M. genitalium} is not merely a commensal organism detected at the site of an STI infection. This finding is similar to those from studies of \textit{M. genitalium} in men with non-gonococcal urethritis\textsuperscript{57,224}. The results of this study suggest that \textit{M. genitalium} may be associated with PID.

In addition to the biases discussed in section 7.4, two sources of biases could have influenced the investigation described in this chapter. Firstly, the significant difference in age between cases and controls is a potential source of bias but since half the patients with \textit{M. genitalium} were over 30 years of age, it is unlikely to have influenced the study results. Secondly, there is no standard methodology for sampling the female genital tract for \textit{M. genitalium}. Here, the endocervix was sampled because it was thought to be the site from which \textit{M. genitalium} migrates to the upper genital tract. The performance of the LightCycler PCR assay was similar to that of the block-based assay using the same primers, but detected 5-fold less DNA (equivalent to 10 genome copies) of \textit{M. genitalium} in a dilution series\textsuperscript{222}. In tests using 28 common micro-organisms, none produced a product with the T\textsubscript{m} typical of that from \textit{M. genitalium}. However, the testing methodology may have lacked sensitivity because many of the specimens had previously been
tested for *C. trachomatis* using the LCR test, which includes an incubation step at 95°C in a high-magnesium buffer and mycoplasma DNA may be susceptible to degradation, perhaps due to a relatively low guanine and cytosine content. The inclusion of a serological test would have provided evidence of previous exposure to *M. genitalium* but was not carried out because this specialist technique was not available at the laboratory.

Both this study and that described by Cohen *et al.* were based on small opportunistic cohorts that were not specifically designed to examine the relationship between *M. genitalium* and PID. A structured programme of research is required to evaluate the public health importance of PID. The pathological basis of the relationship between *M. genitalium* and PID needs to be investigated further. Specifically designed epidemiological investigations need to determine the prevalence, incidence and factors associated with *M. genitalium*. It is not until these questions have been answered that the public health response to *M. genitalium* can be formulated. The first step in assessing the epidemiology of *M. genitalium* would be to investigate the prevalence of infection.

### 8.5 Further work: design of a prevalence study

The sample size of a prevalence study is difficult to estimate because published investigations have been confined to small opportunistic cohorts within clinical settings. Experts working in the field consider that the prevalence may be 1% (P. Totten, personal communication), but it could be higher or lower. If a 1% prevalence is assumed, a sample size of 1000 would have a 95% CI of 0.48% to 1.83%, whereas a sample of 3000 (95% CI 0.67% to 1.42%) and 6000 (95% CI 0.76% to 1.28%) would give more accurate estimates. Ideally both males and females would be included which would double these sample size estimates. A specifically designed study would include the collection of a clinical sample and patient questionnaire similar to that used in chapter 7. A non-invasive clinical
sample, such as a urine test, would be used to increase patient acceptability together with a NAAT such as that used in this chapter. However, a quicker, more cost-effective solution would be to use an available cohort. The urine samples collected for Natsal 2000 would allow the prevalence in both males and females to be investigated, together with the factors associated with increased risk of *M. genitalium*. Natsal 2000 was a stratified probability sample of 11,161 males and females aged 16 to 44 years in Britain, half of all the sexually experienced respondents aged 18 to 44 were invited to provide a urine sample for LCR testing for *C. trachomatis*. A total of 3529 participants gave a urine sample, 1474 males and 2055 females. These sample sizes are adequate to give an accurate estimation of prevalence based on the calculations given above. All participants in Natsal 2000 who gave a urine sample consented to these samples being tested for other organisms in the future and in 2003 the samples will be tested for HSV types I and II. A PCR test for *M. genitalium* could also be included in the protocol. However, before the samples can be tested for *M. genitalium* the PCR testing strategy has to be optimised and clear guidelines are needed on whether urine samples from females can be used to detect *M. genitalium*.
Chapter 9  General discussion

The aim and objectives set out in sections 1.2 and 1.3 were met by the original studies conducted within the thesis. These evaluated and analysed the available surveillance data (chapter 4), investigated how PID is diagnosed, treated and managed in general practice (chapter 5) and assessed the accuracy of PID diagnosis based on clinical presentation (chapter 6). Finally the demographic and behavioural factors, serological parameters and causative agents associated with PID were explored (chapters 7 and 8).

9.1  KEY FINDINGS

The study in chapter 4 was the first to critically evaluate the available PID surveillance data in England. In clinical settings, the highest burden of disease was seen in general practice where 1.7% of reproductive age women were diagnosed with PID. When diagnosed, PID was generally not managed to agreed standards by general practitioners. Diagnosis in general practice, GUM and O&G is predominantly based on clinical presentation. The methodological problems associated with the use of a diagnostic technique based on clinical presentation were addressed in the thesis, although an original comparative assessment of diagnostic techniques was not attempted. An analysis of the largest available evidence base showed that the most effective diagnostic criteria are the presence of lower abdominal pain and the exclusion of competing diagnoses. The simplicity of these criteria makes it attractive as a surveillance case definition but unfortunately it lacks specificity and sensitivity.

The investigation of demographic and behavioural factors, serological parameters and aetiological agents in the case-control study was the first to be undertaken in Europe, and the first to use a case definition based purely on clinical presentation. This case definition allowed the investigation of the
condition GUM and O&G physicians call PID, as opposed to the characteristics of the minority of women with PID who have a laparoscopic investigation, as has been the case in previous case-control studies (section 2.7). The case-control study showed that PID had the characteristics that would be expected of a STD, and that these associations were generally consistent between the two control groups used in the study. When compared against a tubal ligation control group, increased risk of PID was associated with: age group less than 25 years; age at first sexual intercourse less than 20 years; having a non-White ethnic identity; not having had children; having a self reported history of an STD; and having been exposed to infection with *C. trachomatis*. When compared against the general practice control group, increased risk of PID was associated with: age group less than 25 years; age at first sexual intercourse less than 15 years; having lower socio-economic status; having a marital status of cohabiting, single, and widowed/separated/divorced; having a self reported risk of PID; having experienced an adverse pregnancy outcome; a history of an STD; and having been exposed to infection with *C. trachomatis*.

Although increased risk of PID was associated with exposure to infection with *C. trachomatis* and a self reported previous history of an STD, 64% of the PID cases were idiopathic. The investigation in chapter 8 showed an association between *M. genitalium*, *C. trachomatis* and PID, and suggested that some idiopathic cases may be associated with STIs.

### 9.2 Influence on Clinical Practice and Disease Control

Clinicians working in primary care, GUM and O&G clinics diagnose and manage PID syndromically, although this is not recognised in official management guidelines\(^{127}\). This has limited the development of a standard case definition for clinical diagnosis, disease surveillance and epidemiological studies. A variety of diagnostic guidelines have emerged because they were developed by expert
panels that drew on personal experience and knowledge of local disease aetiology as well as evidence from the Lund dataset (the primary evidence base). The Lund dataset is over 30 years old and may not reflect the presentation of PID seen in clinical settings today. However, this evidence base supports the recommendation that a high index of suspicion for PID should be used when diagnosing a woman with lower abdominal pain and no competing diagnoses. Nevertheless, the diagnostic problem presented by PID will only be resolved by the development of a simple diagnostic laboratory test. A recent study of the association between clinical presentation and PID diagnosis used histologic endometritis as a 'gold standard'. The study may have lacked sensitivity but, in view of the costs and ethical issues surrounding the use of laparoscopy, such techniques will probably be used increasingly as a 'gold standard' in future studies.

'The National Strategy for Sexual Health and HIV' emphasised the need for primary care to play a central role in the management of STIs and highlighted the need for further training of general practitioners. The study in chapter 5 showed that general practitioners need to be more aware of PID diagnostic criteria and manage cases to standard guidelines: essentially 'think PID' when they see a young woman with lower abdominal pain. The findings of the studies described in chapters 5 and 6 have been published in peer review journals and presented at primary care conferences. The information was also used in the formulation of the PRODIGY (Practical Support for Clinical Governance) guidelines that provides decision support guidance for general practitioners, and is also used by nurses, medical students and Primary Care Trusts. These studies are part of the growing evidence of the problems of managing PID and will aid the implementation of future studies of PID epidemiology.

The multifactorial aetiology of PID is well established and was seen in the case-control study in chapter 7. This supports the recommendation that broad
spectrum antibiotic treatment should be used to manage women with PID. In view of the high number of idiopathic cases, it is unlikely that the results of current diagnostic tests will add to case management beyond the information already available to the clinician. This questions the use of diagnostic tests, particularly as the case-control study showed that it cannot be assumed that a case of PID is not associated with an STI if neither *N. gonorrhoeae* nor *C. trachomatis* are detected in the lower genital tract. Idiopathic cases may be associated with organisms for which tests are not widely available and management guidelines have not been formulated. This indicates that suspected cases should be treated with a broad spectrum antibiotic regime and managed as if they were sexually transmitted, which includes the use of partner notification. The combination of a high level of diagnostic suspicion and broad spectrum antibiotic treatment could lead to over diagnosis and over treatment but this is considered to be acceptable as it ensures effective antibiotic therapy that will prevent future reproductive morbidity.

These studies were undertaken at a time of increasing STI diagnoses in the UK, which is a symptom of changing sexual behaviour. Behavioural change is a key factor in the primary prevention of PID and the case-control study showed that increased risk of PID was associated with younger age and having had first sexual intercourse at less than 15 years of age. The study also showed that few cases used barrier contraception despite being sexually active. These associations represent potential modifiable risk factors, determinants of incidence that could be targeted through educational campaigns to reduce the probability of disease occurrence.

To date the emphasis of PID control has largely centred on the control of genital chlamydial infection and *The National Strategy for Sexual Health and HIV* emphasized the need to screen young women for genital chlamydial infection. Although this is a welcomed public health initiative, the evidence base to support
the success of genital chlamydial screening as a method of preventing PID is limited (section 2.13), a problem highlighted by the emergence of other potential aetiological agents. In chapter 8, infection with *M. genitalium* was shown to be largely independent of *C. trachomatis* and the epidemiology of these infections may be different. Patients with *M. genitalium* may not be identified in a screening programme aimed at genital chlamydial infection and the antibiotics used to treat genital chlamydial infection may be less effective in the treatment of *M. genitalium*\(^\text{52}\). This suggests that PID control strategies need to be re-evaluated with a view to preventing all cases of PID, not just those that are associated with *C. trachomatis*.

9.3 **WHAT IS TO BE DONE?**

Effective surveillance and intervention relies on knowledge of the aetiology, diagnosis and epidemiology of PID. These issues were explored in this thesis and the findings have been widely disseminated through conference presentations, publications in peer reviewed journals and peer reviewed management guidelines. Further studies were suggested that would add to these investigations and these fall into four categories: developing surveillance; diagnosis; aetiology; and risk factors and awareness to PID.

**Developing surveillance**

Disease surveillance provides information for action and the recent publication *'Getting ahead of the curve, a strategy for combating infectious diseases'* emphasised the importance of detailed surveillance data\(^\text{227}\). The need to improve surveillance was shown in the key priorities given in table 2.4 and this thesis has highlighted the limited range of datasets available, together with the problems associated with interpretation. Laboratory surveillance is highlighted in *'Getting ahead of the curve'* as a method of improving surveillance but is of little help to the surveillance of PID (chapter 4). The available surveillance data do not provide an
accurate view of PID epidemiology but they indicate that information from general practice is likely to provide surveillance data that are most representative of the burden of disease in the population. Nationally representative, prospective data are required to produce the timely, accurate insight into PID epidemiology that is needed to guide control and prevention strategies, and to monitor their effectiveness. Surveillance could be improved in two ways. Firstly, the available primary care surveillance datasets could be improved by standardising diagnostic criteria, and undertaking studies of determinants of incidence within the existing sampling frames. Secondly, a specifically designed study could assess the burden of disease within the population using a point prevalence sampling technique such as that described in section 4.5 to validate the findings of the analysis of the MSGP4 dataset made in chapter 4. A standardised diagnosis would be used, and a clinical sample would be collected, together with a detailed dataset, including information on patients' reproductive and contraceptive history, sexual behaviour, demographic characteristics and health seeking behaviour.

Both initiatives would provide a much needed insight into the epidemiology of PID, and provide resources for assessing the impact of screening for genital chlamydial infection. However, at a time of increasing demands on primary care services, the focus on general practitioners may make such studies difficult to implement. Future surveillance initiatives will need to be preceded by a feasibility study to assess the use of routine and enhanced surveillance strategies.

**Diagnosis**

If surveillance and clinical management are to be undertaken effectively, the accuracy of diagnostic criteria needs to be investigated further and a standard evidence-based case definition developed. Problems of diagnostic management are fundamental to the accuracy and success of PID surveillance and were clearly seen in this thesis: with the exception of chapter 6, there was no independent
confirmation in chapters 4 to 8 that the condition under investigation was PID. The development of internationally recognised standard diagnostic criteria would end the controversy that surround PID studies and would allow surveillance and epidemiological investigations to be more easily instigated and peer reviewed. Such a set of standard diagnostic criteria could be developed through a study of the associations between clinical presentation and PID diagnosed using a variety of techniques (section 6.2). This would establish the accuracy of a number of diagnostic strategies and give clear guidance to researchers undertaking studies in O&G, or primary care. Such a study would be expensive and would rely on women consenting to invasive procedures that are not part of standard case management. In addition, it could not be undertaken at a single location because of the large number of cases and controls that would need to be recruited. A European study that includes experts with established reputations in the field would reduce intra-observer error and establish the study as the new primary evidence base for PID diagnosis. Nevertheless, such a study could be difficult to co-ordinate as professional specialties vary between European countries: for example, the UK has a genitourinary medicine specialty whereas STDs are pre-dominantly managed by dermatovenereologists in other European countries. Inter-observer error could be reduced by limiting the collaborating sites to those with established reputations in the field. Standard operating guidelines would be developed, and agreed by all the collaborators and all the staff taking part in the study would be trained to agreed standards. In addition, each centre would be regularly audited to assess performance during the course of the investigation.

Ætiology

The ætiology of PID needs more detailed investigation, particularly the ætiology of the large number of idiopathic cases. The case-control study highlighted the problems of using available serological tests to investigate disease ætiology. The
requirement for two samples makes the MIF test difficult to use in epidemiological studies and new serological diagnostic techniques need to be developed to answer specific questions. Here the main problem was the inability to detect recent infection. An avidity technique could be used to distinguish recent from established infection and, if feasible, it could be used to screen serum banks for *C. trachomatis*. This could allow the prevalence of genital chlamydial infection to be estimated in different populations and would be a useful method of evaluating the impact of a future genital chlamydial screening programme.

Whilst the case-control study confirmed the importance of genital *C. trachomatis* infection to the aetiology of PID, it indicated that other aetiological agents play an important role in PID pathogenesis. Further identification and classification of novel organisms associated with PID is needed. This will increase our understanding of the aetiology and pathogenesis of PID and allow an evaluation of the public health response to the control of these aetiological agents. The results of the investigation in Chapter 8 indicated that *M. genitalium* could play a role in the pathogenesis of PID. As a preliminary investigation into the epidemiology of *M. genitalium*, a prevalence study could be undertaken (section 8.5). A specifically designed study would include the collection of a clinical sample and patient questionnaire similar to that used in chapter 7 together with a non-invasive clinical sample, such as urine. However, a quicker and more cost-effective solution would be to use an available cohort such as the urine samples collected for Natsal 2000. This would allow the prevalence in both males and females to be investigated, together with the factors associated with increased risk of *M. genitalium*. In 2003 the samples from Natsal 2000 will be tested for HSV types I and II. A PCR test for *M. genitalium* could be included in the protocol but before testing can begin the PCR testing strategy has to be optimised.
Risk factors and awareness to pelvic inflammatory disease

Both the analysis in chapter 4 and the case-control study showed that ethnic minorities and lower socio-economic groups were at increased risk of PID but neither study was large enough to provide conclusive evidence of an association. The relationship between ethnicity, socio-economic status and increased risk of PID should be investigated with a specific study focused on ethnic minorities. The study should include a more comprehensive measure of socio-economic status, including questions relating to occupation and salary. More detailed questions could be used to explore sexual behaviour, such as the number of concurrent partners, reproductive history and contraception. The use of alcohol and recreational drugs in sexual relationships, particularly at first sexual intercourse, could also be investigated.

Low awareness of PID represents an obstacle to effective diagnosis, management and surveillance. Young women need to be more aware of PID and the symptoms associated with condition, and health care professionals need to ‘think PID’ more often. Initiatives have been made in recent years to improve the effectiveness of PID diagnosis and management but, as the study in Chapter 5 showed, further medical education is urgently required.

9.4 CONCLUSIONS

PID is a key issue facing women’s reproductive health. This thesis is an original assessment of PID surveillance and epidemiology in England. The findings strongly support the hypothesis that PID is primarily caused by STIs but the precise aetiology of many cases is unclear. Diagnostic methods and knowledge of disease aetiology need to be improved if further epidemiological investigations and surveillance initiatives are undertaken.
Appendix 1 Sexual Health in England

Authors: Simms, I, Nicoll, A. Sexual Health in England: a guide to national and local surveillance and monitoring data. London: Health Education Authority, 2000

Sexual Health in England: a guide to national and local surveillance and monitoring data

This briefing is a short, critical guide to the local and national quantitative data that are generally available and can be used when planning and monitoring sexual health services and health promotion/education activities. It is not concerned with the important role of qualitative data in this process. Its intended audience is those working in public health, planning, commissioning or managing sexual health interventions within the statutory or voluntary sectors.

Introduction

Sexual health is a key health issue that concerns the majority of the population. For example, almost all women will experience some form of sexual activity in their lifetime, and 6 per cent of women and 4 per cent of men aged 16–24 have attended a genito-urinary medicine (GUM) clinic. Moreover sexual ill health is a particular health issue in England; which has the highest teenage pregnancy rate in Western Europe (44,000 in 2000 among aged 15–17), an incidence of gonorrhoea that increased by 32 per cent between 1994 and 1998, and significant rates of female and male sexually transmitted infections.

A definition of sexual health

- Treatment of sexual infections/injuries
- Prevention and promotion of reproductive health
- Menstrual and reproductive anomalies
- Menstrual and reproductive anomalies
- Prevention and promotion of reproductive health


The Government is committed to a national Sexual Health Strategy, while monitoring and setting components for addressing teenage pregnancy and STI and HIV. These are within the wider public health agenda of the New Labour Government. In the future of whatever form the Strategy, the integration of sexual health services is highlighted as one priority for development. This poses a considerable challenge to those responsible for service provision since sexual health encompasses a diverse range of services.

Briefing 3

March 2000

Data sources (Table 1)

<table>
<thead>
<tr>
<th>Sexual behaviour</th>
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<td>Monitoring sexual behaviour should play a fundamental role in sexual health service planning. The National Survey of Sexual Attitudes and Lifestyles (N.S.A.L.) was the first national survey of sexual behaviour in the UK. It is a well-conducted, comprehensive survey of 18,500 men and women aged 16–59 that is representative of the UK population. The study is being repeated with improvements made to the questionnaires and panel. For further information about the release of results and forthcoming government policy see NPSA briefing 2. The New NHS: Implications for HIV and Sexual Health Promotion March 2000: Information and sexual health are the subject of a future briefing paper that the Health Development Agency (HDA) plans to publish 2000.</td>
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</table>
Sexual Health in England

Contraception use is monitored in two CNS surveys - the National Family Health Survey and the Omnibus Survey. The National Family Health Survey is a random sample of UK households selected to represent the country, whereas the Omnibus Survey is a multiple survey carried out on behalf of government departments, public bodies, charities and academics. Its results are based on a random sample of 2000 people aged 16 and over each month, and achieves a response rate of around 70%. Questions on sexual behaviour are included for men and women aged 16 months each year, and the survey carried out in June 1999 contains data on social exclusion. NASHA (see Sexual Behavior also includes denominator data on contraceptive use and fertility).

Conceptions, births and terminations of pregnancy (abortion)

The Government's national goal for contraception failure is a 90% probability of not becoming pregnant over 18 menstrual cycles in England in 2010. In March 2000, all health authorities will have submitted a profile of teenage pregnancy to the Department of Health's (DH) Pregnancy Unit (TPU). By September 2000, local benchmarks for measuring progress of programmes will have been agreed with the TPU. Data on conceptions, births and terminations of pregnancy cover non-marital abortions at national, health authority and service level for producing by ONS.

Conception data consists of all pregnancies in women leading to either live births, still births or TOP by abortion. Births are derived from registrations, whereas TOP data come from notifications under the terms of the 1967 Abortion Act. Data are generally published within twelve months from the end of the year. The method of presentation used by ONS changed in 1999; publications now use four data categories, but discuss collection methods and interpret data in more detail. Detailed data on local or national data may be accessed either through the ONS website or directly from CNS. Conceptions, live births and TOP data are also published and displayed in the publications from NASHA.

High TOP rates may reflect good provision of abortion services or as may be very high levels of researchers who are combining with their services. Conceptions to contraception and willingness to accept services also affect TOP rates, as does provision and demand background. However, women choosing to access services outside of these areas may skew local rates. The type of contraception should also be considered, as this is associated with duration of pregnancy and access to services. Consequently, it is important to interpret TOP data within the context of other sexual health and social data, and knowledge of local demography and culture.

Sexually transmitted infections (STI)

Information is currently derived from two data sources: data from CNS (mainly from the OMNIA and, from the 1970s onwards, from the Confidential Enquiry into Maternal and Child Health (CEMACH)), and data from the Communicable Disease Surveillance Centre (CDSC).

The CDSC surveillance data are an authoritative source to report to
Sexual Health in England

CD4 cell count for the benefit of the DHF. Data collected on form K1040 refer to disease episodes and in their CD4 cell count, condition, sex, number of male cases homosexual/orientated sexual behaivity conditions only, and age group restricted conditions only.

Cites complete sections to standard guidelines and emerging approach 300 per cent. Data are processed and interpreted in an annual report. Unfortunately, in common with almost all sexual health datasets available for English demographic data, the example ethnic groups, socioeconomic and sexual behaviour datasets are not collected as part of the K1040 dataset. Gathering these data would greatly improve both understanding of STI epidemiology and health care provision needs. However, data have to be collected in demographic form data collected on individual encounters, which would require changing from the present method of aggregate data collection data collated into totals at closing.

Microbiological Laboratories are asked to report cases of central Chlamydia trachomatis infection, genital Hepatitis B virus, and Neisseria gonorrhoeae on CD4. Data on screening laboratories are age, gender, gender, identified, ethnic method and minipub manuscript to process only. No national collection and processed in the CHP Weekly.

Output similar to all STI and other reports, periodic report, periodic report in London where K1040 reports indicate that STI levels are highest. Another reason in the labour data is that it currently does not capture data relating to the clinical setting where the infection was diagnosed. Consequently, it is not possible to distinguish between cases originating from GUM clinics and those diagnosed in general practice; when a large burden of infection in teenagers occurs. Data presentations may also be used to compare broader patterns, i.e. people in one district that receive care in another.

HIV and AIDS

The CHP has a role in Child Health, London, conduct surveillance on HIV and AIDS. The patterns represent the most detailed and comprehensive sexual health data available. The main data sources include reporting of AIDS cases and deaths by diagnosis, laboratory reports of HIV infections or of CD4, from treatment centres, and since January 2000, HIV diagnoses made by clinicians. As further HIV infections and AIDS are notified, CDC relies on voluntary voluntary voluntary reporting of these cases. Nevertheless, it has been estimated that AIDS cases, HIV infection and prevalent diagnoses according to the source. Data on HIV infections and AIDS are notified. Data on HIV infections and AIDS are notified.

Cervical cytology and sexually related cancer

Information from the population-based comprehensive surveillance system for Cervical Cancers will be collected for the UK's "Cervical Cancers" and compiled for the (CSP) colleagues. Cervical cytology and sexually related cancer are also available for individual general practices from health authorities.

Cancer registration data, including cervical, ovarian and testicular cancer, are published by the ONS, and recent information on patients with first registration is received within 12-15 months from diagnosis. Data are presented in age, gender, socioeconomic, and geographical region and are the disease. The data are collected and considered to have good completeness. The current methodology is consistent with the information that is used to monitor the prevalence, severity, and representativeness. Cancer mortality data are presented in the Health and five-year summaries from the cancer registries. Information on these conditions is collected and presented in detail.

General data sources

For "Cervical and associated Population Panther" gather data on age groups, country of birth, and other demographic data on specific groups. However, the dataset is limited in that it only undertakes since every two years and is not sensitive to recent changes, for example any increase in international or external migration.
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<td>Data not collected for older groups or hard-to-reach groups, although future plans to improve.</td>
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<tr>
<td>National</td>
<td>Annual</td>
<td>NHP</td>
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<td>Data not collected for older groups or hard-to-reach groups, although future plans to improve.</td>
</tr>
</tbody>
</table>

**Note:**
- Data are collected through surveys, but not all data may be available for key groups.
- Data may not be fully comparable across different surveys.
- Some data may be estimated or provisional.
- Some data may be available for specific populations, such as older groups, injecting drug users, etc.
A number of diseases are collected from clinical settings, which includes data that could be used for sexual health planning.

The Public Health Command Data Set uses census data but also presents the most up-to-date national data concerning a variety of communicable and non-communicable disease and causes of death, for example HIV and AIDS, configurations data, cancer data and trends in obesity. Data is presented down to both health authority level and includes geography and maps. Most of the presentations relate to current DH targets and disease health care issues, some of which relate to sexual health.

Hospital Episode Statistics (HES) are published after 12 months of the end of each financial year. They contain data on inpatient episodes by age, sex, region and local diagnosis. Data on HIV, infections, cancer, pregnancy and infectious diseases are available. A detailed electronic record of patient data including patient information, but direct access is limited for reasons of confidentiality. Analyses can be accessed from the HES branch of the DH. The coverage of HES aims to be 98% per cent of all patient episodes. Currently, it does not include outpatient visits.

The Morbidity Statistics from General Practice (MSGP) is a survey carried out by CNS since every ten years in all general practices, and is a comprehensive source of primary care data. The population included is considered to be representative of the general population with respect to age, sex, marital status, socio-economic status, smoking behaviour and disease burden. The MSGP does not focus on sexual health, but it also includes data on conditions such as osteoporosis, PPD and erotic and female infertility. Final diagnosis, specific, clinical background, socio-economic status, marital and celibate status are collected for each patient. The dataset contains a denominator. CNS have produced a publication that summarises and discusses the main trends and the data are also available electronically.

The General Practice Research Database (GPRD) and the MedicAlert's UK Primary Care Database are based on general practice attendees. The GPRD is widely used and contains records for 2.5 million patients (6% of the UK population). The data covers morbidity, treatment and patterns of prescriptions. The sample is broadly comparable to the 1991 CENS Census in terms of age and sex. The dataset is also validated and validated. MedicAlert has collected descriptive clinical and prescribing data from approximately 1.5 million patients exceeding 100,000 general practices since 1991. It is consistent to be representative of the general population in terms of age and sex. The data is also incomplete in general practice.

Local use of data

While sexual health is important to virtually everyone, some sections of society are in higher risk of sexual ill health than others. The needs of particular groups vary from one and health qualifications and quantitative data should be used to identify and estimate emerging need and provide culturally sensitive interventions. Key groups are difficult to define or identify within a local population, are spread unevenly across the country and may be marginalised in society. Gay and bisexual men, refugees, people in prison, homeless people, commercial sex workers, injecting drug users (IDU) and some ethnic minority groups are all likely to have important sexual health needs. Planning services, specific activities and service provision audits by any group requires knowledge of their numbers and distribution in the community. For some groups, for instance sex workers, this is relatively easy— their numbers can be ascertained from training services, including cocaine, the local authorities and schools. Local sexual ill health data may be available from GPs, clinics, family planning clinics and health authorities. Many, of course, the new Income, Population and Community Survey will be a further source for this information.

For other important groups, once where sexual ill health data does exist to be available, it may simply reflect existing assumptions or service provision and access to care.

A number of health authorities are developing sexual health strategies. Optimally these are based on a national database comparing local health authorities and sexual health services, including information on the local authorities and schools. Local sexual ill health data may be available from GPs, clinics, family planning clinics and health authorities. Many, of course, the new Income, Population and Community Survey will be a further source for this information.

A range of local use are available which may be used to make comparisons between national and local data. Table 2 gives an example of the information that has been compiled by the East Sussex, Bournemouth and South West for their sexual health strategy to give a broad view of sexual health within the district. The measures are concerned with fertility, STIs, HIV and AIDS. Many include demographic data produced by CNS and compare local rates against national rates. Letchworth, Southwark and Lewisham Health Authority (LSA) has looked at trends as birth rates amongst young men comparing those whose data is being used in a comparable way. A number of data-sharing initiatives are at various stages and their impact on these initiatives is currently unclear.
Table 2. The local picture: key statistics

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Measure</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Fertility rate in females (000/1000 women aged 15-44)</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
<tr>
<td>Live births per 1000 women</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
<tr>
<td>Registration area of those having children in Great Britain</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
<tr>
<td>UK-wide</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
<tr>
<td>Mortality and survival</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
<tr>
<td>Registration area of those having children in Great Britain</td>
<td>Office of National Statistics</td>
<td></td>
</tr>
</tbody>
</table>

Local contacts for developing sexual health strategies:
- Sexual Health centres or clinics
- Hospitals/Trusts
- CHW
- Primary Care Groups
- Regional epidemiologists
- Consultant Gynaeologists and Endocrinologists
- Genetic Counseling
- Health Protection
- Local Health Authority
- School Nurses
- Voluntary Groups
- Professional Bodies

Figure 1. Age-specific birth rates in 0-19 year-olds, Lambeth, Southwark and Lewisham Health Authority and England and Wales, 1993-1997

Sexual Health in England

Challenges and opportunities

Sexual health is an evolving field. The integration of sexual health services and emergency and public health services will present new challenges for delivering and commissioning sexual health services. As the balance of service delivery changes towards a primary-care model, more data will be required and these data should be easily accessible and provide information on the management of conditions such as sexual transmitted infections.

The Sexual Health strategy seeks to address new targets and guidelines for health authorities. The NHP public health role involves in planning and implementing sexual health interventions. It also provides a clearer route to improve the national and local coordination of data between disciplines and settings.

However, at the same time, there is scope for better collection, interpretation and use of data at the local level, for example:

- Clinical settings could adopt data monitoring procedures that address the lack of standardized and capturing data. More can be made of data collected from other settings, for example Accident and Emergency departments, walk-in centres, NHS Direct and the commercial sector (for example sexual health services).
- Prescriber data could be used to better effect, in particular to assess the impact of new interventions, for example campaigns to reduce numbers of emergency contraception.
- Professionals could learn from the new Learning Programme.
- Commissioners to establish the most useful way to collect and feedback data to help low numbers and outcomes whose priorities is a particular outcome.
- Primary care settings could achieve greater consistency in their audit that data is collected.
- Professionals could take advantage of the opportunities offered by electronic sharing of data to move from reporting to feedback to better access to data.
- Data should be communicated to all parts of the data.

Further reading


Acknowledgements

We would like to thank Drs. Fiona Hopenaul, Dr. Alyson Helfron, Dr. Anjale Akram, Pam Allen, Dr. Caroline Mamer, Ros Kers, Karen Wellings, Dr. Gordon Reid, Professor Anne Johnson, Neil Macfarlane, lee Cohn, Lisa Ellis and Christine Berends for their invaluable contribution to this briefing.

The views expressed in this briefing are those of the authors and do not necessarily reflect those of the Health Education Authority.

NHPIS is a free specialist information service on HIV health promotion for professionals in England. It is funded by the Department of Health and based at the Health Education Authority, 10 Great Peter Street, London SW1F 9ET (020 7413 3929).
Appendix 2  Questionnaire (chapter 4)

Audit of Pelvic Inflammatory Disease (PID) in General Practice

**Part A  ABOUT YOUR PRACTICE**

1. Number of persons on the age/sex register: please estimate to the nearest 100. MALE ______ FEMALE ______

2. Which of the following best describes the community served by the clinic?
   - UNSTATED
   - RURAL
   - URBAN

3. How many practitioners are in the practice?
   - MALE ______ FEMALE ______

4. Do you have a computer in your practice that is used for clinical purposes?
   - YES ______ NO ______

5. What target level do you usually achieve for cervical cytology and immunisation? (please give percentage) Cytology ______ Immunisation ______

**Part B  HOW ARE PID CASES DIAGNOSED AND TREATED IN YOUR PRACTICE?**

6. In your view, what symptoms would suggest a diagnosis of PID?

7. On examination, which signs would suggest a diagnosis of PID?

8. Do you undertake microbiological investigation on suspected PID cases?
   - USUALLY ______ NOT OFTEN ______
   - HIGHLY TYPICAL ______ MARGINAL ______ UNLIKELY ______ INDECISION ______

9. What organisms are most commonly isolated from investigations taken in your practice?

10. Do you give antibiotics whilst waiting for the results of microbiological investigation?
    - YES ______ NO ______
    - IF YES, which do you give?

11. Are partners of PID cases treated?
    - USUALLY ______ SOMETIME ______ NOT OFTEN ______ NEVER ______

12. Which specialties are PID cases referred to?
    - GYNAECOLOGY ______ GASTRO  ______ FAMILY PLANNING ______ OTHER ______

**Part C  ABOUT THE LAST CASE OF PID YOU SAW**

(please consult the appropriate clinical records before responding)

13. Which signs and symptoms did the case present with?

14. Was a microbiological investigation undertaken?
    - YES ______ NO ______
    - IF YES, was it for: CHLAMYDIA ______

15. What drug therapy was used?

16. Was drug therapy instituted before the results of the microbiological investigation were known?
    - YES ______ NO ______

17. Was the patient referred?
    - YES ______ NO ______ NOT KNOWN ______

18. Was the partner of the case treated?

THANK YOU FOR COMPLETING THE QUESTIONNAIRE.
PLEASE RETURN IT TO CSIC USING THE PREPAID ENVELOPE PROVIDED.
Appendix 3 Case-control study: questionnaires

Patient questionnaire used in obstetrics & gynaecology, and genitourinary medicine clinics

EVALUATION OF RISK FACTORS FOR PELVIC INFLAMMATORY DISEASE (PID)
Confidential patient questionnaire

Please give your hospital number: ____________________________

How old are you? ____________________________ years

What is your current or past occupation? 

To which of the following groups do you consider you belong? tick one box

- BLACK CARIB
- BLACK AFRICAN
- BLACK AFRICA, RED
- RED
- PAKISTAN
- BANGLADESH
- CHINESE
- OTHER

If other, please specify: ....................................................................

Have you or have you been a regular smoker? YES, NO

How old were you when you first had sexual intercourse? 

What is your current marital status? 

- SINGLE
- MARRIED
- SEPARATE
- DIVORCED
- OTHER

Are you or have you been a regular smoker? YES, NO

Have you or have you been a regular smoker? YES, NO

Are you or have you been a regular smoker? YES, NO

Are you or have you been a regular smoker? YES, NO

Have you ever had:

- A TUBAL LIGATION? YES, NO
- A MISCARRIAGE? YES, NO
- A BIRTH? YES, NO
- AN ECTOPIC PREGNANCY? YES, NO

Thank you for completing the questionnaire

Clinical questionnaire used in obstetrics & gynaecology, and genitourinary medicine clinics: cases

EVALUATION OF RISK FACTORS FOR PELVIC INFLAMMATORY DISEASE (PID)
Confidential patient questionnaire

Please return to: Ian Simms, PHLS AIDS and STD Centre, PHLS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
Clinical questionnaire used in obstetrics & gynaecology: tubal ligation controls

<table>
<thead>
<tr>
<th>General Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of attendance</td>
</tr>
<tr>
<td>Hospital number</td>
</tr>
<tr>
<td>Name of patient's general practitioner/practice name</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Date of birth</td>
</tr>
<tr>
<td>First three digits of post code</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous history of PID?</td>
</tr>
<tr>
<td>Previous history of ectopic pregnancy?</td>
</tr>
<tr>
<td>Previous history of infertility?</td>
</tr>
<tr>
<td>Has the patient undergone any procedure that has involved instrumentation through the cervix, e.g. ERPC, coil insertion?</td>
</tr>
<tr>
<td>If yes, please specify:</td>
</tr>
<tr>
<td>Was antibiotic treatment given as part of this episode?</td>
</tr>
</tbody>
</table>

Thank you for completing the questionnaire

Please return to: Ian Sturms, PHS AIDS and STD Centre, PHS Communicable Disease Surveillance Centre, 61 Colindale Avenue, London NW9 5EQ
Appendix 4  Case-control study: standard operating procedures

Pelvic Inflammatory Disease Study

Standard Operating Procedures

for

Obstetrics & Gynaecology

&

Genitourinary Medicine
Background

Pelvic inflammatory disease (PID) is a leading cause of reproductive ill health in women. PID can cause ectopic (tubal) pregnancy, infertility and chronic abdominal pain. It has also been associated with ovarian cancer. In England and Wales, the majority of cases are caused by Chlamydia trachomatis, a bacterial infection which is the commonest, curable sexually transmitted infection (STI) in England.

Why is this study required?

A substantial burden of PID exists in reproductive age women, with a prevalence of 1.7% in women attending general practice. This means that between 1 in 50 and 1 in 100 reproductive age women have PID at any one time. However, very little is known of the risk factors for PID in England.

Study aims

- To determine the demographic and behavioural factors, serological parameters and causative agents associated with PID
- To estimate the proportion of PID cases attributable to past/present chlamydial infection and the number that could be prevented by chlamydial screening

Method

The study will use a case-control methodology, that is a population of women with PID (cases) will be contrasted with two groups of women who do not have PID (controls). The case group and one of the control groups will be derived from Depts of Obstetrics & Gynaecology. The second control group will be derived from General Practice.

Data to be collected

Data will be collected using self-administered questionnaires. Blood samples and swabs will be used to assess immunological and microbiological parameters.

Procedure

Cases

The procedure for the selection of cases is summarised in figure 1. Patients invited to take part in the study have to be woman aged 16 to 46 with a diagnosis of PID (table and figure 3). They should not have taken part in the study before.

Eligible patients will be told about the study and given the information sheet to read. If they are willing to take part, the patient will be asked to sign the consent form (supplied by CDSC, attached) and complete the patient questionnaire (supplied by CDSC attached). It should be stressed to the patient that neither the hospital nor their General Practitioner will have access to any of the data on the patient questionnaire. The clinician should also sign the consent form and give a copy to the patient. The consent form should be held in the Dept of Obstetrics & Gynaecology. After the questionnaire has been completed, the patient should place it in the envelope provided. The patient should then seal the envelope and write an 'X' across the seal. The physician should then write the patient hospital number on the label on the outside of the envelope. No patient name will be recorded on either the patient questionnaire or the envelope. The sealed envelope should be sent to CDSC using the prepaid envelopes provided. The physician should complete the clinical questionnaire.

Three swabs will be taken by the physician, one high vaginal swab and two endocervical swabs (one each for C. trachomatis and N. gonorrhoeae). A study label will be attached to each sample, the samples will be handled in the usual way (hospital number will be used as the personal identifier). The phlebotomist will take the blood sample. In the case of the serological samples, if there is insufficient antibody, the patient will be recalled six weeks later to have a further blood test. Liverpool PHL will return the test results to the Dept of Obstetrics & Gynaecology. The patient will be advised of the test result either by letter if the result is negative, or 'phone if positive. Appropriate counselling, treatment and partner notification will be given where necessary. The physician will complete the clinical questionnaire after the diagnosis has been made.
(after the laparoscopic investigation if required), and will send it to CDSC in the prepaid envelopes provided.

The test result and questionnaire will be linked at CDSC using the patient’s hospital number. All data held on the CDSC password protected database will be anonymous.

### Table  Clinical criteria for the diagnosis of salpingitis (PID), after Hager

<table>
<thead>
<tr>
<th>All 3 of the following:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Abdominal direct tenderness, with or without rebound tenderness</td>
<td></td>
</tr>
<tr>
<td>Tenderness with motion of cervix &amp; uterus</td>
<td></td>
</tr>
<tr>
<td>Adnexal tenderness</td>
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<tr>
<td>plus 1 or more of the following:</td>
<td></td>
</tr>
<tr>
<td>Gram stain endocervix - positive for gram-negative, intracellular diplococci</td>
<td></td>
</tr>
<tr>
<td>Temperature &gt;38°C</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis &gt;10 000</td>
<td></td>
</tr>
<tr>
<td>Purulent material (white blood cell count present) from peritoneal cavity by culdocentesis or laparoscopy</td>
<td></td>
</tr>
<tr>
<td>Pelvic abscess or inflammatory complex on bi-manual examination or sonography</td>
<td></td>
</tr>
</tbody>
</table>

**Controls**

The procedure for the selection of controls (laparoscopic sterilisation) is summarised in figure 2. Patients will attend for pre-operative assessment between 3 months and 1 day before their operation and, during the consultation, the patient will be invited to take part in the study. This will give the patient 24 hours to consider whether they would like to take part in the study. The patients should be aged 16 to 46 years old, have no history of PID, tubal damage or chronic lower abdominal pain and should not have taken part in the study before. A record stating that the patient has agreed to take part in the study should be made in their notes so they can be identified easily when they re-attend for laparoscopic sterilisation.

Eligible patients will be given the information sheet to read and, if they are willing to take part, will be asked to sign the consent form and complete the patient questionnaire. It should be stressed to the patient that neither the hospital nor their General Practitioner will have access to any of the information written on the patient questionnaire. The clinician should also sign the consent form and give a copy to the patient. The consent form should be held in the Dept. of Obstetrics & Gynaecology. After the patient has completed the questionnaire, the patient should place it in the envelop provided, seal the envelope and write an ‘X’ across the seal. The patient’s hospital number should then be written on the label on the outside of the envelope. No patient name is to be recorded on either the questionnaire or the envelope. The sealed envelope together with the clinical questionnaire should be sent to CDSC using the prepaid envelopes provided.

The blood sample will be taken by the phlebotomist and sent to Dr Harry Mallinson, Liverpool PHL for testing. Laparoscopic sterilisation will then be carried out. If there is evidence of PID on laparoscopy, do not proceed with the study. If there is no evidence of PID, take swabs as for cases above. The laboratories will send the test results to the Dept. of Obstetrics & Gynaecology. The patient will be advised of laboratory test results by letter if negative, or ‘phone if positive. If necessary, appropriate counselling, treatment and partner notification will be provided. The physician will complete the clinical questionnaire after the sterilisation has been carried out (example attached), the questionnaire should be returned to CDSC in the prepaid envelope provided. The test result and questionnaire will be linked at CDSC using the patient’s hospital number. All data held on the CDSC password protected database will be anonymous.
Overall study plan

Step 1a A pilot study of 30 cases and 60 controls (30 laparoscopic sterilisation: 30 from general practice) will be undertaken initially. This will be used to test the methodology and evaluate the sample size calculations. The data will be analysed at the end of the pilot phase and the methodology, including the sample size calculations will be re-evaluated. In particular, the control group strategy will be re-assessed to determine whether the GP control group is necessary for the main study.

Step 1b Production of brief report on the pilot study to be circulated to the Department of Health and local collaborators. The study budget will also be reassessed.

Step 2a The main study will then be undertaken and include a further 170 cases and 340 controls (170 laparoscopic sterilisation: 170 from general practice).

Step 2b Production of the final report to the Department of Health.

Materials provided to each clinic Copies of patient and clinical questionnaires, envelopes for the patient questionnaire and prepaid envelopes for the return of the questionnaires to CDSC will be supplied. Further supplies can be ordered from Ian Simms at the address below. Swabs will be provided by Liverpool PHL, Liverpool PHL will also co-ordinate blood sample collection.

Interpretation of results Laboratory testing will be undertaken by Dr Harry Mallinson (Liverpool PHL) who will send clinics individual test results.

Ethical approval The project has been approved by the PHLS, Wirral Health Authority and Liverpool Health Authority research ethics committees.

Funding Department of Health.

Contacts

General enquiries
Ian Simms, Communicable Disease Surveillance Centre, 61 Colindale Ave, London NW9 5EQ
Tel: 0181 200 6868 ext 4571
FAX: 0181 200 7868
email: isimms@phls.nhs.uk

Questions within Obstetrics & Gynaecology
Liverpool Women’s Hospital: Dr Kevin Thomas/Dr Vicky Cording
Arrowe Park Hospital: Dr Courtney Watson

Transportation of specimens, laboratory testing & results
Harry Mallinson, Liverpool PHL, Fazakerley Hospital, Lower Lane Liverpool L9 7AL
Tel: 0151 529 4932
FAX: 0151 529 4918
email: hmallinson@nw.phls.nhs.uk
References


Figure 1  Summary of procedure - Cases of PID: Obstetrics & Gynaecology and Genitourinary Medicine

**PID Case**

Confirmed PID diagnosis using Hager definition No competing diagnosis

Patient fulfils inclusion criteria is given information sheet & invited to take part in study

Patient agrees to take part in the study

No

Yes

Patient & clinician sign consent form & patient completes patient questionnaire

Receptionist sends patient questionnaire to CDSC

1st blood sample taken

Endocervical & high vaginal swabs taken

Samples sent to laboratory for testing

Clinical questionnaire completed by physician & sent to CDSC

Laboratory test results sent to CDSC

Patient advised of results of laboratory tests, with appropriate counselling, treatment and partner notification

Test results & questionnaires linked on patient clinic number at CDSC

2nd blood sample taken 6 weeks later and tested at laboratory
Figure 2  Summary of procedure – Controls: women requesting bilateral tubal ligation

Control Group 1
Women requesting laparoscopic sterilisation

No history of PID, tubal damage or chronic lower abdominal pain

Patient fulfils inclusion criteria, is given information sheet at pre-operative assessment & is invited to take part in study

Patient & clinician sign consent form & patient completes patient questionnaire

Receptionist sends patient questionnaire to CDSC
Laparoscopic sterilisation carried out
Blood sample taken

Evidence of PID

Yes
Don't proceed with study

No

Endocervical & high vaginal swabs taken

Control clinical questionnaire completed by physician & sent to CDSC

Laboratory test results sent to CDSC

Test results & questionnaires linked on patient hospital number at CDSC

Laboratory test results sent to O&G

Patient advised of results of laboratory tests, with appropriate counselling, treatment and partner notification
Figure 3  Summary of PID diagnosis in obstetrics & gynaecology and genitourinary medicine

Clinical history taken

All competing diagnoses excluded

A: Meets PID clinical criteria
   - Treated with antibiotics
     - Sent home

B: Clinical presentation meets Hager definition
   - More ill than A
     - Admitted
       - Sent home

C: PID suspected but may be pregnant
   - Pregnant
     - Yes
       - Given laparoscopy to resolve diagnosis
         - Sent home
     - No

D: PID suspected but missing some elements of Hager definition
   - Likely to have laparoscopy to resolve diagnosis
     - Sent home
THANK YOU FOR HELPING US WITH OUR RESEARCH

You are being invited to take part in a research study. Please read the following information carefully, discuss it with your physician. Ask if there is anything that is not clear. If you would like more information your physician will be able to advise you. Take time to decide whether or not you wish to take part.

What is Pelvic Inflammatory Disease?

Pelvic Inflammatory Disease (PID) is only found in women. A variety of germs cause PID but the majority of PID cases are thought to be caused by the bacterium Chlamydia trachomatis. Chlamydia can be passed from men to women or women to men during sex but can easily be treated by a short course of antibiotics. Because many women with PID have few symptoms, PID cases can go unrecognised. If left untreated PID can cause infertility, ectopic pregnancy (pregnancy in the tubes which cannot be carried to term) and recurrent abdominal pain.

Why have I been asked to take part in this study?

Our study aims to improve the diagnosis of PID. To do this we need to find out what factors are associated with PID and investigate whether blood tests can be used to improve diagnosis. Over the 9 months of the study, we will be asking 200 women with suspected PID and 400 who do not have PID to take part in this study. You have been asked to take part in the study because you have a suspected diagnosis of PID.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet and asked to sign a consent form. You will also be given a copy of the consent form to keep. If you decide to take part, you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive.
If I take part, what do I need to do?

You will be asked to complete a questionnaire. Some questions are intimate in nature. Your GP will never see this information. Parts of the blood and swab samples taken as part of your routine clinical management will also be used in the study.

Why have I been asked to give blood and swab samples?

Your blood sample will be tested to see whether you have ever had chlamydia. The swab samples will also be used to detect chlamydial infection and other possible infections. The blood test looks for chlamydial antibody, if present, the antibody could be from either a current or a previous infection. The test result will be available within 2 weeks. If your result is negative we will write to you. If the result is positive we will telephone you and arrange for you to receive treatment if necessary. A positive result may mean that you may have a partner who shares the infection and who should also be examined and treated.

Confidentiality: who will see the results?

All information collected about you during the course of the research will be kept strictly confidential. Your questionnaire will only be seen by the researcher at the Public Health Laboratory Service (PHLS) and not by anyone else. Your name will not be given to the PHLS. Your GP will only be informed of your participation in the study if you give us permission to contact them.

Availability of study results

A report on the study findings will be given to the Department of Health and the results published in the medical literature.

If you have any further questions about the study or about your own results please do not hesitate to contact:

Dr P Hay, The Courtyard Clinic  
St George’s Hospital  
Blackshaw Road, LONDON SW17 0QT  

Tel: 0208 725 3353 (Monday to Thursday 9am – 5.30pm & Friday 9.30 to 11.30am, & 2 to 4pm)

Other information

Consumers for Ethics in Research (CERES) publish a leaflet entitled ‘Medical Research and You’. It gives more information about medical research and looks at questions you may want to ask. A copy may be obtained from: CERES, PO Box 1365, London N16 0BW

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Why have I been asked to take part in this study?

Our study aims to improve the diagnosis of PID. To do this we need to find out what factors are associated with PID and investigate whether blood tests can be used to improve diagnosis. Over the 9 months of the study, we will be asking 200 women with suspected PID and 400 who do not have PID to take part in this study. You have been asked to take part in the study because you do not have a suspected diagnosis of PID.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet and asked to sign a consent form. You will also be given a copy of the consent form to keep. If you decide to take part, you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive.
**If I take part, what do I need to do?**

You will be asked to complete a questionnaire. Some questions are intimate in nature. Your GP will never see this information. You will be asked to give a blood sample. Swab samples will also be taken during your operation.

**Why have I been asked to give blood and swab samples?**

Your blood sample will be tested to see whether you have ever had chlamydia. The swab samples will also be used to detect chlamydial infection and other possible infections. The blood test looks for chlamydial antibody, if present, the antibody could be from either a current or a previous infection. The test result will be available within 2 weeks. If your result is negative we will write to you. If the result is positive we will telephone you and arrange for you to receive treatment if necessary. A positive result may mean that you may have a partner who shares the infection and who should also be examined and treated.

**Confidentiality: who will see the results?**

All information collected about you during the course of the research will be kept strictly confidential. Your questionnaire will only be seen by the researcher at the Public Health Laboratory Service (PHLS) and not by anyone else. Your name will not be given to the PHLS. Your GP will be informed of your participation in the study if you give us permission to contact them.

**Availability of study results**

A report on the study findings will be given to the Department of Health and the results published in the medical literature.

**If you have any further questions about the study or about your own results please do not hesitate to contact:**

Dr P Hay, The Courtyard Clinic  
St George's Hospital  
Blackshaw Road, LONDON SW17 0QT

Tel: 0208 725 3353 (Monday to Thursday 9am – 5.30pm & Friday 9.30 to 11.30am, & 2 to 4pm)

**Other information**

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. It gives more information about medical research and looks at questions you may want to ask. A copy may be obtained from: CERES, PO Box 1365, London N16 0BW
Pelvic Inflammatory Disease study

Patient Consent Form

Suspected PID cases (GUM)

The patient should complete the whole of this sheet him/herself and be given a copy to keep

Please delete as necessary

Have you read and understood the Patient Information Sheet? YES/NO

Have you had an opportunity to ask questions and discuss this study? YES/NO

Have you received satisfactory answers to all your questions? YES/NO

Have you received enough information about the Study? YES/NO

Who have you spoken to? Dr/Mr/Mrs .........................

Do you understand that you are free to withdraw from the Study:
   at any time
   without having to give a reason for withdrawing
   and without affecting you future medical care? YES/NO

PLEASE NOTE

If you decide not to take part in the study or you withdraw from the study at any time this will in no way interfere with your normal medical care.

Your GP will only be informed of your participation in the study if you give us permission to contact them.

I ................................. agree to take part in the study

Signed .................................(patient) Date ............... 
(NAME IN BLOCK LETTERS) ........................................

Signed .................................(investigator) Date ............... 
(NAME IN BLOCK LETTERS) ........................................
Pelvic Inflammatory Disease study

Patient Consent Form - control group
(O&G)

The patient should complete the whole of this sheet him/herself and be given a copy to keep

Please delete as necessary

Have you read and understood the Patient Information Sheet? YES/NO

Have you had an opportunity to ask questions and discuss this study? YES/NO

Have you received satisfactory answers to all your questions? YES/NO

Have you received enough information about the Study? YES/NO

Who have you spoken to? Dr/Mr/Mrs .........................

Do you wish to be informed of the test results? YES/NO

Do you understand that you are free to withdraw from the Study:
  at any time
  without having to give a reason for withdrawing
  and without affecting you future medical care? YES/NO

PLEASE NOTE

If you decide not to take part in the study or you withdraw from the study at any time this will in no way interfere with your normal medical care.

Your GP will only be informed of your participation in the study if you give us permission to contact them.

I ....................................................... agree to take part in the study

Signed .............................................. (patient) Date ....................

(NAME IN BLOCK LETTERS) ..................................................

Signed .............................................. (investigator) Date ....................

(NAME IN BLOCK LETTERS) ..................................................
Pelvic Inflammatory Disease Study

Standard Operating Procedures

for

General Practice
Background

Pelvic inflammatory disease (PID) is a leading cause of reproductive ill health in women. PID can cause ectopic (tubal) pregnancy, infertility and chronic abdominal pain. It has also been associated with ovarian cancer. In England and Wales, the majority of cases are caused by Chlamydia trachomatis, a bacterial infection which is the commonest, curable sexually transmitted infection (STI) in England.

Why is this study required?

A substantial burden of PID exists in reproductive age women, with a prevalence of 1.7% in women attending general practice. This means that between 1 in 50 and 1 in 100 reproductive age women have PID at any one time. However, very little is known of the risk factors for PID in England.

Study aims

- To determine the demographic and behavioural factors, serological parameters and causative agents associated with PID
- To estimate the proportion of PID cases attributable to past/present chlamydial infection and the number that could be prevented by chlamydial screening

Method

The study will use a case-control methodology i.e. a population of women with PID (cases) will be contrasted with two groups of women who do not have PID (controls). Most of the cases and controls will be derived from Departments of Obstetrics & Gynaecology.

Why do general practices need to be involved?

Although the project is focused on Departments of Obstetrics & Gynaecology, attendees at this clinical setting to be included in the control group may not be representative of the general population. Consequently a general practice control group is needed which consists of women who do not have PID.

Data to be collected

Data will be collected using self-administered questionnaires. Blood samples will be used to assess immunological and microbiological parameters. Patients included in the case-control study will also be included in the pilot genital chlamydial screening programme. Results of the antigen tests undertaken as part of the pilot screening programme will be used in the PID case-control study.

Procedure

The procedure to be used for data collection in the general practice control group is summarised in figure 1. Patients invited to take part have to be women aged 16 to 46 with no history of PID, tubal damage or chronic lower abdominal pain and who are going to have a blood sample taken as part of routine management and have not already taken part in the study. During the consultation, eligible patients will be given the information sheet (supplied by CDSC, attached) to read and keep. If they are willing to take part, will be asked to sign the consent form (supplied by CDSC, attached) and complete the patient questionnaire (attached). It should be stressed to the patient that the general practitioner will not have access to any of the data on the patient questionnaire. After the patient questionnaire has been completed, the patient should place it in the envelope provided. The patient should seal the envelope and write an 'X' across the seal. The general practitioner should then write the patients ID number on the label on the outside of the envelope. No patient names should be recorded on either the questionnaire or the envelope. The sealed envelope containing the patient questionnaire should be placed inside the large white prepaid envelopes provided and sent to CDSC. All data held on the CDSC password protected database will be anonymous.

The blood sample will be taken by the practice nurse/plebotomist. Part of the sample (approximately 5ml) will be sent to Dr Mallinson using one of the study labels provided. The patient's NHS number will be used as the personal identifier. Dr Mallinson will return the test results to the general practice. The patient will
be advised of laboratory test results either by letter if the result is negative or 'phone if positive, with appropriate counselling, treatment and partner notification. The test result and questionnaire will be linked at CDSC using the patient ID number.

Overall study plan

Step 1a A pilot study of 30 cases and 60 controls (30 laparoscopic sterilisation: 30 from general practice) will be undertaken initially. This will be used to test the methodology and evaluate the sample size calculations. The data will be analysed at the end of the pilot phase and the methodology, including the sample size calculations will be re-evaluated. In particular, the control group strategy will be reassessed to determine whether the GP control group is necessary for the main study.

Step 1b Production of brief report on the pilot study to be circulated to the Department of Health and local collaborators. The study budget will also be reassessed.

Step 2a The main study will then be undertaken and include a further 170 cases and 340 controls (170 laparoscopic sterilisation: 170 from general practice).

Step 2b Production of the final report to the Department of Health.

Materials provided to each clinic Copies of patient and clinical questionnaires, envelopes for the patient questionnaire and prepaid envelopes for the return of the questionnaires to CDSC will be supplied. Further supplies can be ordered from Ian Simms at the address below. Liverpool PHL will co-ordinate blood sample collection.

Interpretation of results Laboratory testing will be undertaken by Dr Harry Mallinson (Liverpool PHL) who will advise general practitioners of individual test results.

Ethical approval The project has been approved by the Public Health Laboratory Service, Wirral Health Authority and Liverpool Health Authority ethics committees.

Funding The study is being funded by the Department of Health

Contacts

General enquiries
Ian Simms, Communicable Disease Surveillance Centre, 61 Colindale Ave, London NW9 5EQ
Tel: 0181 200 6868 ext 4571
FAX: 0181 200 7868
e-mail: isimms@phls.nhs.uk

Transportation of specimens, laboratory testing & results
Harry Mallinson, Liverpool PHL, Fazakerley Hospital, Lower Lane Liverpool L9 7AL
Tel: 0151 529 4932
FAX: 0151 529 4918
e-mail: hmallinson@nw.phls.nhs.uk
References


Figure 1  Summary of procedure, controls: general practice

Patient fulfils all three inclusion criteria:

- Woman aged 16 to 46 with no history of PID, tubal damage or chronic lower abdominal pain
- Blood sample to be taken as part of routine management
- Not previously included in the study

Patient fulfils inclusion criteria, is given information sheet and invited to take part in study by the GP

Patient agrees to take part in the study

Yes

Patient given consent form & questionnaire

Patient and clinician sign consent form & patient completes patient questionnaire

Blood sample taken by phlebotomist.
Patient gives urine samples

Samples sent to Liverpool PHL for testing

Laboratory test results returned to GP from Liverpool PHL

Patient advised of laboratory test results, with appropriate counselling, treatment and partner notification

No

Patient and clinical questionnaires sent to CDSC by GP receptionist

Laboratory test results sent to CDSC by Liverpool PHL

Test results and questionnaire linked on patient NHS number at CDSC
Pelvic Inflammatory disease study

Patient Consent Form - GP

Funded by the Department of Health and Public Health Laboratory Service

Approved by the Research Ethics Committee

1. I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care or legal rights being affected.

3. I understand that sections of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give my permission for these individuals to have access to my records.

4. I agree to take part in the above study

PLEASE NOTE
If you decide not to take part in the study or you withdraw from the study at any time this will in no way interfere with your normal medical care.

...............................................  ...../..../.....  ........................................
Name of patient  Date  Signature

...............................................  ...../..../.....  ........................................
Name of person taking consent  Date  Signature
(if different from researcher)

...............................................  ...../..../.....  ........................................
Researcher  Date  Signature
THANK YOU FOR HELPING US WITH OUR RESEARCH

You are being invited to take part in a research study. Please read the following information carefully, discuss it with your physician. Ask if there is anything that is not clear. If you would like more information your physician will be able to advise you. Take time to decide whether or not you wish to take part.

What is Pelvic Inflammatory Disease?

Pelvic Inflammatory Disease (PID) is only found in women. A variety of germs cause PID but the majority of PID cases are thought to be caused by the bacterium Chlamydia trachomatis. Chlamydia can be passed from men to women or women to men during sex but can easily be treated by a short course of antibiotics. Because many women with PID have few symptoms, PID cases can go unrecognised. If left untreated PID can cause infertility, ectopic pregnancy (pregnancy in the tubes which cannot be carried to term) and recurrent abdominal pain.

Why have I been asked to take part in this study?

Our study aims to improve the diagnosis of PID. To do this we need to find out what factors are associated with PID and investigate whether blood tests can be used to improve diagnosis. Over the 9 months of the study, we will be asking 200 women with suspected PID and 400 who do not have PID to take part in this study. You have been asked to take part in the study because you do not have a diagnosis of PID.

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part, you will be given this information sheet and asked to sign a consent form. You will also be given a copy of the consent form to keep. If you decide to take part, you are still free to withdraw at any time without giving a reason. This will not affect the standard of care you receive.

Please turn over
**If I take part, what do I need to do?**

You will be asked to complete a questionnaire. **Some questions are intimate in nature. Your GP will never see this information.** Part of the blood sample taken as part of your routine clinical management will also be used in the study.

**What do I need to do?**

All you will be asked to do is to complete a questionnaire and give a blood sample. **Some questions are intimate in nature. Your GP will never see this information.**

**Why have I been asked to give a blood sample?**

Your blood sample will be tested to see whether you have ever had chlamydia. The blood test looks for chlamydia antibody, if present, the antibody could be from either a current or a previous infection. The test result will be available within 2 weeks. If your result is negative we will write to you. If the result is positive we will telephone you and arrange for you to receive treatment if necessary. A positive result may mean that you may have a partner who shares the infection and who should also be examined and treated.

**Confidentiality: who will see the results?**

All information collected about you during the course of the research will be kept strictly confidential. Your questionnaire will only be seen by the researcher at the Public Health Laboratory Service (PHLS) and not by anyone else. Your name will not be given to the PHLS. Your GP will be informed of your participation in the study.

**Availability of study results**

A report on the study findings will be given to the Department of Health and the results published in the medical literature.

**Who will see the results?**

Your questionnaire will only be seen by the researcher at the Public Health Laboratory Service (PHLS) and not by anyone else. Your name will not be given to the PHLS.

**If you have any further questions about the study or about your own results please do not hesitate to contact your General Practitioner.**

**Other information**

Consumers for Ethics in Research (CERES) publish a leaflet entitled 'Medical Research and You'. It gives more information about medical research and looks at questions you may want to ask. A copy may be obtained from: CERES, PO Box 1365, London N16 0BW
Appendix 5  Published papers


The rate of diagnosis and demography of pelvic inflammatory disease in general practice: England and Wales

I Simms¹, P Rogers¹ and A Charlett²
¹HIV & STD, Communicable Disease Surveillance Centre and ²PHLS Statistics Unit, UK

Summary: Knowledge of pelvic inflammatory disease (PID) epidemiology is essential to the understanding of reproductive morbidity in women. This paper estimates the rate of PID diagnosis in general practice (GP) and the level of association between PID diagnosis and demographic factors. Diagnoses of PID were made at 1.7% of attendances amongst women aged 16 to 46. Increased risk of PID was associated with smoking (P < 0.0001), younger age groups (P < 0.0001) and lower socioeconomic groups (P < 0.0001). Compared to patients who were married, increased risk was also associated with those patients who were widowed, separated or divorced and not cohabiting (adjusted rate ratio (RR) = 1.62; confidence limits (CI) 1.35 to 1.97), and with those who were unmarried but cohabiting (adjusted RR = 1.32, 95% CI 1.11 to 1.56).

General practice is an important focus for the diagnosis and treatment of PID. If intervention and surveillance are to be undertaken effectively, more needs to be known about the epidemiology of this important public health problem.

Keywords: Pelvic inflammatory disease, epidemiology, rate of diagnosis

BACKGROUND
Pelvic inflammatory disease, the clinical syndrome associated with upper genital tract infection, is a major health burden in women of reproductive age. It can cause ectopic pregnancy, tubal factor infertility and chronic abdominal pain, which is associated with an increased risk of hysterectomy. The dominant cause of PID is genital Chlamydia trachomatis which is the most common curable sexually transmitted infection (STI) in England and Wales. The recent report by the Chief Medical Officers' Expert Advisory Group on C. trachomatis highlighted the urgent need for information concerning the epidemiology of PID for health planning purposes, in particular the assessment of STI intervention programmes. The burden of disease and factors associated with PID are unknown in England and Wales, although the stable, high level of ectopic pregnancy suggests there is a substantial reservoir. This study estimated the number of PID diagnoses and their association with demographic and socioeconomic factors using data from the Mortality Statistics from General Practice Fourth National Survey: 1991-1992 (MSGP4).

METHODS
The MSGP4 data set was derived from attendances over a one-year period 1991/92 at 60 GP clinics in England and Wales which represent a 1% sample of the population. Although not a random sample, it is considered to be representative of the general population with respect to age, sex, marital status, socioeconomic status, smoking behaviour and disease burden. Diagnoses made by the general practitioner (ICD9 codes), age, ethnic background, socioeconomic status, current smoking habit, the length of time the person was registered at the practice during the year and marital status (a combination variable including marital and cohabitation status) were collected for each patient. One record per person was included in the analysis, records were only included where complete data were recorded. Technically the data are derived from consultations rather than the total age/sex register. However, since 78% of those on the age/sex register consulted their general practitioner at least once during 1991/92 this is a close estimate of the burden of disease in the general population, referred to here as the diagnostic rate (number of PID diagnoses/person-years at risk). The classification of ethnic group was simplified to: white, black (black Caribbean, black African, black other) and Asian (Indian, Pakistani, Bangladeshi). The analysis included 73,810 women aged 16 to 46.
The time patients were registered with their general practitioner varied from a day to a year. The denominator was thus calculated as person-years at risk by dividing the number of days each person was included in the survey by 366 (1992 was a leap year) giving a total of 70,791 person-years at risk. Single and multivariable analyses were undertaken using a Poisson regression model (STATA 5.0). The outcome variable was a diagnosis of PID made during the study period (ICD9 code 614). No distinction was made between whether these were new diagnoses or were a consultation for an episode first diagnosed outside the study period. The analysis thus gives a prevalence estimate. Interactions were investigated and a main effects model was used to describe the data. Unadjusted and adjusted rate ratios (RRs) were calculated.

**RESULTS**

The rate of PID diagnoses in women aged 16 to 46 attending GP was 167 per 10,000 person-years at risk (1189/70,791), or 1.7%. The number of diagnoses and the rate per 10,000 person-years at risk and RRs adjusted for other variables in the regression analysis together with 95% CI are shown in Table 1. The data were re-coded to avoid problems with sparse data in some categories. All 2 way interactions were investigated but none were found to be significant at the 5% level. There was a significant difference between age groups, with women aged 35 to 39 at half the risk of having a diagnosis of PID (P<0.0001, adjusted RR=0.34, 95% CI 0.40 to 0.72) and those aged 40 to 46 were at a quarter the risk (adjusted RR=0.25, 95% CI 0.19 to 0.36) compared to the 16 to 19-year age group. Smokers were at higher risk of PID than non-smokers (P<0.0001, adjusted RR=1.13, 95% CI 1.05 to 1.21). Patients in socioeconomic groups III to V were all at higher risk of PID than those in socioeconomic group I/II (P<0.0001). Compared to patients who were married, increased risk of PID was also associated with those patients who were widowed, separated or divorced and not cohabiting (adjusted RR=1.62, 95% CI 1.35 to 1.97), and with those who were unmarried but cohabiting (adjusted RR=1.96, 95% CI 1.11 to 1.56). The difference in the risk of PID between ethnic groups was not statistically significant (P=0.994), but there was evidence of increased risk in both black (adjusted RR=1.65, 95% CI 0.97 to 2.79) and Asian patients (adjusted RR=1.53, 95% CI 0.84 to 2.78) compared to Caucasians.

**DISCUSSION**

The epidemiology of PID is notoriously difficult to study and, to our knowledge, this is the first investigation to be undertaken in England and
Wales. This is, in part, due to the heterogeneity in the pattern of disease, the low specificity of clinical diagnosis, and the fact that women with PID present to a variety of different clinical specialties. In addition, it is becoming increasingly clear that many cases of PID go unrecognized because they are atypical or asymptomatic. The epidemiology of PID is also thought to vary with microbial aetiology which changes over time. There are thus a number of difficulties in both interpreting the surveillance data presented here and in comparing the results with other studies. However, the lack of published PID surveillance data for England and Wales indicates that this was a valid investigation to undertake and can be used as the basis for future validation studies.

The 1.7% rate of PID diagnosis suggests that 165,000 cases of PID would have been diagnosed in 1992. This contrasts with only 21,168 and 57,535 cases seen as hospital inpatients and attenders at genitourinary medicine clinics respectively in the same year. Although the case definition of PID is likely to have varied between settings, these data suggest that a substantial reservoir of PID is seen in general practice. This clinical setting should thus be an important focus for the diagnosis and treatment of PID.

Our study supports previous observations that women who smoke are at significantly higher risk of PID. Although hospital inpatient data indicate that women aged 20 to 24 years are at highest risk of PID, this multivariable analysis indicates that women between 16 and 34 years are at equal risk. This shows that, although highest rates of genital chlamydial infection peaks in teenage women, the morbidity associated with chlamydial infection affects the reproductive health of women over a substantial age range.

Recent studies have speculated whether black ethnic groups have a high burden of reproductive morbidity. Black and Asian ethnic groups are under represented in this analysis, accounting for only 1.6% of the study population, compared to 5.0% reported in the 1991 census. After adjusting for socioeconomic status, these groups were not found to be at higher risk of PID than whites. However, the higher RR and confidence intervals only just encompassing one indicate that risk of PID was approaching significance for blacks and, to a lesser extent, Asians. Clearly the burden of PID in different ethnic groups needs to be explored using larger studies.

Data on sexual behaviour are central to the study of a predominantly sexually transmitted disease such as PID. A relationship between risk of PID and divorced marital status has also been reported in studies in England and Wales. This association and that between PID and socioeconomic group are probably surrogate markers of sexual behaviour. For example, age at sexual debut and number of lifetime sexual partners are known to vary with marital status, cohabiting and socio-economic group. Unfortunately sexual behaviour data were not included in the MSCP data set; further studies using measures of sexual behaviour are required to validate these findings.

Knowledge of the epidemiology of PID is central to the reproductive health of women. We have shown that PID affects women over a broad age range, particularly those who smoke, are in lower socioeconomic groups, or are divorced or separated. There is also some evidence of increased risk in blacks and Asians. However, a number of problems have to be resolved if an accurate view of the epidemiology of PID is to be made. A standard case definition should be developed for future research, the diagnostic rate given here should be validated and the factors associated with PID need to be investigated. These are difficult problems to resolve, but it is only by doing this that epidemiological knowledge of this important public health problem will be improved.

Acknowledgements: We would like to thank Dr C Bevan (Consultant, Weston-Super-Mare General Hospital), Dr A Swan and Mr A Grant (PHLS Statistics Unit) for statistical advice and technical assistance.

References


(Accepted 18 February 1999)
Pelvic inflammatory disease epidemiology: what do we know and what do we need to know?

I Simms, J M Stephenson

"Pelvic inflammatory disease is a sexually transmitted disease with potentially serious sequelae usually managed badly by doctors with little interest in the condition."

Introduction

It is a decade since this bleak view of pelvic inflammatory disease (PID) management in the United Kingdom appeared in the BMJ. Since then a theme to emerge in sexually transmitted disease (STD) research has been increased awareness of genital chlamydial infection, which causes a substantial proportion of PID cases. In the United Kingdom, this culminated in the Chief Medical Officer’s expert advisory group on genital chlamydial infection which recognised PID as an important source of preventable reproductive morbidity in women. However, little is known of PID epidemiology in England and Wales. The burden of disease and risk factors associated with PID are poorly understood but need to be investigated to inform public health action and clinical practice. This paper aims to critically review current knowledge of PID epidemiology, with special reference to the United Kingdom and explore the epidemiological research needed to provide an evidence base for PID public health intervention.

Methods

A literature search was carried out on Medline using the key words "pelvic inflammatory disease" and was repeated using authors known to have published studies concerned with PID and Chlamydia trachomatis. The literature was also trawled for data presentations.

Aetiology of PID

PID is the clinical syndrome associated with upper genital tract inflammation caused by the spread of micro-organisms from the lower to the upper genital tract. PID can be caused by genital mycoplasmas, endogenous vaginal flora (anaerobic and aerobic bacteria), acrob streptococci, Mycobacterium tuberculosis, and sexually transmitted infections (STI) such as C. trachomatis or Neisseria gonorrhoeae. An association between PID and bacterial vaginosis has also been demonstrated in the absence of C. trachomatis and N. gonorrhoeae. A number of aetiological studies have been undertaken over the past 20 years in various clinical settings (table 1). In these studies, C. trachomatis was detected in 14%–65% of PID cases but, since these are small scale studies, this does not reflect substantial aetiological variation over time and between countries. Some studies report a higher prevalence of N. gonorrhoeae than C. trachomatis, but again it should be remembered that the studies are based on small sample sizes. Nevertheless, the studies do indicate that a substantial proportion of PID cases are caused by C. trachomatis. The largest UK study, based on only 147 women at one location, indicated that 39% (95% CI, 29% to 49%) of PID cases were caused by C. trachomatis and 14% were caused by N. gonorrhoeae. The proportion of PID cases caused by C. trachomatis is a vital consideration in any Chlamydia intervention programme as the number of PID cases that could be prevented should be estimated before and during intervention. PID aetiology should thus be assessed at the beginning and during any Chlamydia intervention programme.

Table 1

<table>
<thead>
<tr>
<th>Population</th>
<th>Country</th>
<th>Prevalence (%)</th>
<th>Sample size</th>
<th>Not of organism collected</th>
<th>Author (year of reference)</th>
</tr>
</thead>
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<tr>
<td>UK</td>
<td>59 (20–94)</td>
<td>40,104</td>
<td>Lower genital tract and upper genital tract</td>
<td>Beson (1994)</td>
<td></td>
</tr>
<tr>
<td>UK</td>
<td>10 (25–66)</td>
<td>10,250</td>
<td>Lower genital tract and upper genital tract</td>
<td>Nish (1994)</td>
<td></td>
</tr>
<tr>
<td>Finland</td>
<td>50 (28–53)</td>
<td>97,276</td>
<td>Lower genital tract</td>
<td>Parmen (1996)</td>
<td></td>
</tr>
<tr>
<td>Sweden</td>
<td>12 (7–17)</td>
<td>23,696</td>
<td>Upper genital tract</td>
<td>Balmer (1992)</td>
<td></td>
</tr>
<tr>
<td>USA</td>
<td>15 (9–52)</td>
<td>13,946</td>
<td>Upper genital tract</td>
<td>Soner (1996)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>14 (7–29)</td>
<td>8,766</td>
<td>Lower genital tract and upper genital tract</td>
<td>Broad (1998)</td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>17 (7–6)</td>
<td>7,61</td>
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<td>Gonsalvez (1992)</td>
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<tr>
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<td>USA</td>
<td>61 (50–90)</td>
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<td>Upper genital tract</td>
<td>Wasserman (1996)</td>
</tr>
<tr>
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<td>USA</td>
<td>25 (25–52)</td>
<td>21,35</td>
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<td>Koster (1996)</td>
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<td>USA</td>
<td>30 (15–55)</td>
<td>7,25</td>
<td>Lower genital tract and upper genital tract</td>
<td>Livengood (1992)</td>
</tr>
<tr>
<td>Primary care</td>
<td>USA</td>
<td>25 (10–40)</td>
<td>11,146</td>
<td>Lower genital tract and upper genital tract</td>
<td>Selko (1991)</td>
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</tbody>
</table>
The current understanding of the immunopathological pathways from infection to PID and tubal scarring is incomplete. Chronic sequelae of genital chlamydial infection such as ectopic pregnancy and tubal infertility are thought to be caused by a delayed hypersensitivity reaction to chlamydial 60 kDa chlamydial heat shock protein (HSP-60). \(^6\) The clinical presentation and course of PID in women with symptomatic HIV disease and/or severe immune suppression may be more aggressive than in HIV-negative women.

Between 10% and 40% of U. trachomatis cases develop PID. \(^7\) The risk of developing sequelae is dependent on the number of PID episodes; the risk of ectopic pregnancy and infertility increases after one PID episode (odds ratio 6) and again after two episodes (OR 17). Animal models indicate that PID can develop within 5 days of C. trachomatis infection. \(^8\) Failure to seek treatment within 1 day of onset of lower abdominal pain can result in a threefold increase in the risk of PID and infertility. \(^9\) Early diagnosis is thus essential.

Few studies have investigated the incidence of PID sequelae in women with a history of PID as large patient groups are difficult to follow up over long periods of time. In particular, the prevalence of infertility is difficult to estimate as it is only reported by those who wish to conceive. The definitive study of morbidity associated with PID included 2501 women in Lund (Sweden) between 1960 and 1984. \(^1^0\) Data from this study indicate that those women who had a history of PID were six times more likely to have an ectopic pregnancy and 14 times more likely to have tubal factor infertility than women who had no evidence of history of PID. In the United Kingdom, an 11 year record linkage cohort study showed that women with a history of PID were 6, 8, 10, and 10 times more likely to have diagnoses of endometriosis, hysterectomy, abdominal pain, and ectopic pregnancy, respectively, than controls. \(^1^1\)

Problems associated with PID surveillance

The problems associated with PID surveillance stem from the fact that a cheap, simple, and accurate diagnostic test does not exist. No single infection causes PID and no signs and symptoms are pathognomonic of the disease. These problems of case definition and diagnostic accuracy are compounded by the inaccessibility of the female upper genital tract to routine, large scale diagnostic methods. Consequently it is difficult to formulate a diagnostic "gold standard." PID surveillance data are also influenced by variations in case definitions (particularly between clinical settings), changes in disease chronicity associated with clinically mild chlamydial infection, variations in health seeking behaviour, and the increased management of PID in outpatient settings. \(^1^2\) Variations in the use of intrauterine devices (IUD) may also influence PID prevalence. Swedish data indicate that PID hospital admissions varied by less than 16% from year to year in the early 1970s and 1980s, but increased by 75% in the mid-1970s, fluctuations that reflected variations in IUD use. \(^1^3\)

Trends in PID cannot be inferred from genital chlamydial infections as the surveillance data are heavily influenced by case ascertainment bias and are thus unrepresentative of the true reservoir of genital chlamydial infection in the general population, a problem seen in the US surveillance data. \(^1^4\) The prevalence of C. trachomatis cannot be inferred from that of gonorrhoea as these infections have distinctly different epidemiologies. Gonorrhoea prevalence has declined in several European countries over the past 15 years \(^1^5\) whereas a decline in chlamydial prevalence has only been demonstrated in Sweden.

The biases inherent in the surveillance of PID related infections and sequelae make it difficult to assess trends in PID prevalence with certainty. Comparisons between countries are difficult, if not impossible, to make.

Incidence, prevalence, and recent trends in industrialised countries

Since a substantial proportion of PID cases are caused by STIs, epidemics of N. gonorrhoeae and C. trachomatis are followed by a secondary PID epidemic and tertiary epidemics of ectopic pregnancy and tubal infertility. An example of these relations is seen in Swedish surveillance data. The epidemic of N. gonorrhoeae experienced by industrialised countries in the 1960s peaked in Sweden in 1970, and then decreased. \(^1^6\) An associated PID epidemic peaked at 11.1000 women aged 15-39 between 1970 and 1974 and then declined as a tertiary ectopic pregnancy epidemic emerged. \(^1^7\) The decline in both STIs and first and repeat episodes of PID, together with a change in sexual behaviour brought about by intervention, suggest that the observed decrease in PID prevalence was real. In 1970, 15% of reproductive age women in Lund reported ever having been treated for PID, similar to the 10% reported in the United States. \(^1^8\) The incidence of 14.1000 women aged 14-34 seen in the United States in the same period was also similar to that seen in Sweden. \(^1^9\) Since 1970, the burden of STDS has varied considerably between countries in response to different STI transmission patterns and variations in intervention strategies.
Although a substantial burden of PID is thought to exist in many countries, surveillance data are only available for a few European countries, most in Scandinavia. In England and Wales, variations in gonorrhoea cases seen in STD clinics and hospital inpatient attendances for PID and ectopic pregnancy have followed a pattern similar to that seen in Sweden over the past five decades.\cite{1} Interpretation is, however, difficult. There are a number of gaps in reporting caused by either changes in collection methods or absence of data. However, the main concern is that the steep increase in gonorrhoea seen after the second world war is not reflected in a rise in attendances for PID as would be expected. This questions the representativeness and accuracy of attendance data for PID and ectopic pregnancy during the 1950s. Age-specific data from 1950 onwards indicates that highest PID prevalence and highest rates of increase are consistently seen in the 16-24 year age group, which reflect the substantial number of bacterial STIs seen in the 16-19 year age group (fig 1).

Hospital inpatient data consist of acute cases, women experiencing recurrent chronic pain, and long term reproductive health problems associated with PID.\cite{2} Consequently, these data will not be representative of the true reservoir of PID in the general population.\cite{3} Evidence to support this view comes from reports of ectopic pregnancy and the surveillance of PID in general practice. The incidence of ectopic pregnancy does not reflect the number of PID cases seen in the hospital inpatient admissions data. The stable ectopic pregnancy incidence of 1,100 conceptions (approximately 8,000 cases per annum) seen in England is similar to that reported in other European countries. To sustain this incidence, it would be expected that at least 72,000 PID cases would occur annually, assuming 9% of women with a history of PID develop ectopic pregnancy. Of course, this underestimates PID prevalence substantially as not all women with a history of PID become pregnant. In fact general practice data suggest that 165,000 cases occur every year in reproductive age women, a prevalence of 1.7%.\cite{4} Although the PID case definition is likely to have varied between clinical settings, these observations suggest the presence of a substantial reservoir of undiagnosed PID in primary care. The 41% increase in PID diagnoses seen in attendances in general practice between 1982 and 1992 suggests that PID may be increasingly managed in this setting, although this rise may also reflect increased case ascertainment.\cite{5} Primary care thus provides an important focus for the diagnosis and treatment of PID. Information derived from this setting provides a more complete view of PID epidemiology than hospital inpatient admissions, but diagnosis in primary care is likely to be less specific than in hospital.

Factors associated with PID
Risk factor studies can identify population subgroups at increased risk of PID, can be used to imitate timely, effective, intervention, and help formulate health education strategies. Risk factors for PID development are closely associated with those of STI acquisition.\cite{6} Aspects of sexual behaviour, such as age at first sexual intercourse, number of lifetime sexual partners, frequency of partner change, and unsafe sex are key determinants of STI transmission. Age at first sexual intercourse and the number of lifetime sexual partners are known to vary with marital status, cohabitation, and socioeconomic group.\cite{7} The relation between PID and socioeconomic status is likely to be a surrogate marker of sexual behaviour. Young people are Behaviourally vulnerable to STI acquisition as they generally have higher numbers of sexual partners and a higher frequency of partner change than older age groups.\cite{8} In addition, high PID rates in women aged 16-24 years could reflect longer duration of chlamydial infection or reduced clearance of chlamydial infection in younger women. This could be due to increased host susceptibility, such as a lower concentration of protective chlamydial antibodies, larger cervical ectopy, and greater permeability of cervical mucus than in older age groups.\cite{9}

A number of factors have been associated with PID: IUD insertion and termination of pregnancy have been associated with iatrogenic...
PID, which occurs when instrumentation facilitates the introduction of vaginal and cervical micro-organisms into the endometrial cavity. Cigarette smoking has been associated with increased risk of PID. Smoking is thought to either compromise the immune response to infection or the activity of oestrogen. It is also likely that smoking reflects poor health seeking behaviour in lower socioeconomic groups. The association between PID and oral contraceptives (OC) use is also complex and incompletely understood. Although OC use has been associated with a 50% decrease in PID in reported studies, it is unclear whether OC use prevents ascending infection or protects against symptomatic infection. Alternatively, both cigarette smoking and OC use may simply be confounding factors that reflect higher sexual risk. Douching has been associated with PID as it is thought to alter the microbiological environment of the vagina and flush bacteria into the uterus. However, although douching is common among women in the United States, less than 0.25% of UK women report this behaviour and thus it is unlikely that douching is an important factor associated with PID in the United Kingdom.

It would be unwise to extrapolate the findings of risk factor studies from other countries to England and Wales as sexual health behaviour and contraceptive practice vary between countries and over time. In England and Wales, higher risk of PID has been associated with age 15–34, marital status, lower socioeconomic group, and a history of smoking. These observations were, however, based on a prevalence study which did not use a consistent case definition, did not take sexual behaviour into account and did not evaluate disease aetiology. Consequently, although the study represents a starting point for epidemiological investigations, it should be treated with caution and cannot be used as the basis for planning and intervention strategies. Factors associated with PID in England and Wales are thus unknown and properly conducted studies are needed urgently.

**Disease burden (industrialised countries)**

PID accounts for 94% of morbidity in women associated with STI (including HIV) in established market economies (EMEs). The burden of PID among women, measured in terms of disability adjusted life years, was also higher than the burden of disease associated with HIV among men. This may appear strange as HIV infection causes a substantial burden of mortality and morbidity among homosexual and bisexual men in EMEs. However, although PID is not associated with high mortality it is associated with high morbidity. The absence of validation studies and an explanation of how these data were derived makes interpretation difficult. Nevertheless, the data indicate that PID is responsible for a considerable disease burden and represents an important healthcare issue in industrialised countries.

**Costs associated with PID**

In terms of economic cost, both PID and its sequelae are expensive to individuals, healthcare systems, and economies. These costs have increased substantially since the development of assisted reproduction techniques such as in vitro fertilisation. In 1992, the cost of a fertility service in one health district in England and Wales with a population of 46,000 women aged 20–44 years was estimated to be £0.88 million, a national total of £7.5 million. Ten percent (£7.5 million) of this cost was likely to be associated with genital chlamydial infection and thus could have been prevented (fig 1). The economic impact of PID has yet to be evaluated in the United Kingdom. In the United States, direct and indirect costs associated with PID and its sequelae were estimated at over $4.2 billion in 1990 and projected to exceed $10 billion by the year 2000, assuming a constant incidence. However, the economic burden associated with PID may have been underestimated as the true incidence of PID is unknown.

**Potential for health gain**

The high burden of PID in industrialised countries together with the associated high healthcare costs indicate that there are substantial health gains to be made from the prevention of PID and its sequelae. There are three approaches to effective disease control: education and behavioural change, screening for asymptomatic disease, and diagnosis and treatment of symptomatic disease. Since a substantial proportion of PID cases are chlamydial in origin, a large proportion of cases are potentially preventable through chlamydial intervention. The high level of asymptomatic genital chlamydial infection emphasises the role of screening for this infection.

Primary prevention, based on education and behavioural change, is fundamental to disease control. Behavioural change such as the increased use of barrier contraception and delayed sexual debut in response to HIV and STI health campaigns has been documented in European countries and some have been associated with reduced incidence of symptomatic PID. However, in the United Kingdom there is a low awareness of PID among healthcare professionals and the public which represents an obstacle to primary prevention. Secondary prevention, or the diagnosis and treatment of asymptomatic genital chlamydial infection, has been successful in reducing both the prevalence of genital chlamydial infection and associated PID. The only randomised controlled trial that has looked at the effectiveness of chlamydial screening indicated that decreases in the prevalence of genital chlamydial infection brought about reductions in PID prevalence. In the United States, intervention based on screening for genital chlamydial infection has also reduced the incidence of PID and ectopic pregnancy by more than 50% and 20% respectively. Swedish data also indicate that screening for genital chlamydial infection rapidly reduces the incidence of ectopic...
pregnancy among 20-24 year olds. No study has demonstrated that genital chlamydial screening can reduce the prevalence of tubal factor infertility.

The prevention of the substantial costs associated with PID and related sequelae is one of the key benefits to be gained from screening for genital chlamydial infection. A number of theoretical studies have attempted to quantify the cost effectiveness of such a screening programme. Based on various assumptions, the threshold prevalence of genital chlamydial infection at which chlamydial screening becomes cost effective has been estimated to be between 3.9% and 6% (using DNA amplification tests and antibiotics treatment). Threshold prevalences as high as 14% have also been suggested. One reason for this wide variation is that many studies only take the burden of symptomatic PID into account. Sensitivity analysis indicates that a key determinant in the assessment of chlamydial screening cost effectiveness is the prevalence of PID. If studies are extended to include subclinical or undiagnosed PID, the threshold prevalence at which screening is cost effective may be as low as 3.9%. This emphasises the importance of accurately estimating PID prevalence and incidence. Tertiary prevention, the prompt recognition and treatment of symptomatic PID, is also required to prevent repeat episodes and further sequelae. Although antibiotic prophylaxis before either IUD insertion or termination of pregnancy is considered to both reduce the risk of salpingitis and to be cost effective, this evidence is not based on double blinded, randomised controlled trials.

Broad spectrum antibiotic treatment will only treat symptomatic PID effectively and prevent sequelae if PID is recognised early. "Silent" or unrecognized PID, a term given to cases of tubal factor infertility with no history of PID, is thought to be characteristic of chlamydial PID and adds to the problems of effective diagnosis. However, it has also been suggested that unrecognized PID is a result of low diagnostic sensitivity. Prevention of re-exposure to infection through partner notification is another integral part of PID management. However, although this is routinely undertaken in genitourinary medicine clinics, less than a quarter of general practitioners undertake partner notification in suspected PID cases.

Healthcare professionals need to recognise disease symptoms, promote timely self referral to treatment centres, and encourage therapy compliance among both women and their partners. In the United Kingdom, PID management guidelines have been published by a variety of professional bodies but their impact is difficult to assess. Primary care must play a key part in the control and prevention of this important source of reproductive ill health.

Pelvic inflammatory disease—key epidemiological research priorities

- Develop case definition for use in epidemiological research
- Estimate the proportion of cases that present without a history of PID
- Improve surveillance in a range of primary care settings
- Establish diagnostic and management guidelines for use in patient management systems
- Implement validated, representative, active sentinel surveillance

Future research priorities

Epidemiological and surveillance data are crucial to effective disease control as they provide an evidence base for public health action: to define those at risk, to set priorities, plan interventions, and allocate resources. However, available data for England and Wales are clearly limited. Threshold prevalences as high as 14% have been suggested. One reason for this wide variation is that many studies only take the burden of symptomatic PID into account. Sensitivity analysis indicates that a key determinant in the assessment of chlamydial screening cost effectiveness is the prevalence of PID. If studies are extended to include subclinical or undiagnosed PID, the threshold prevalence at which screening is cost effective may be as low as 3.9%. This emphasises the importance of accurately estimating PID prevalence and incidence. Tertiary prevention, the prompt recognition and treatment of symptomatic PID, is also required to prevent repeat episodes and further sequelae. Although antibiotic prophylaxis before either IUD insertion or termination of pregnancy is considered to both reduce the risk of salpingitis and to be cost effective, this evidence is not based on double blinded, randomised controlled trials.

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Professional and public education is required to improve knowledge, attitudes, and skills to ensure effective case management.

New methods of monitoring PID are urgently required (see box), but a number of methodological issues have to be addressed before epidemiological studies can be undertaken. These problems are not new; many, such as the lack of a simple, specific diagnostic method, variations in reporting practice, and reliance on small scale studies, were described by Westrom in 1980. The fundamental prob-
The evaluation of risk factors associated with PID presents particular problems. Many studies have been based on small sample sizes and undertaken over several years. This makes results hard to interpret as the validity varies over time and associated risk factors vary with the patient. Ideally, risk factor studies should be representative, be undertaken over a short time, and should evaluate sexual behavior. A case-control study is the most efficient and cost-effective method of undertaking such studies. This is particularly relevant in view of the time constraints and high costs associated with large scale microbiological and immunological testing. However, there are a number of problems specifically associated with a case-control study investigating risk factors for PID, and the selection of both cases and controls is difficult. Again, use of a laparoscopic gold standard diagnosis for cases presents a problem. Few women with a clinical diagnosis of PID undergo a laparoscopy, and it is considered unethical to undertake laparoscopy if a competing diagnosis is not suspected and/or there is no need to alleviate symptoms. The dilemma researchers are then faced with is should a syndromic diagnosis be used or should a more biased group of laparoscoped cases be used. Control group selection is also difficult. Ideally, the control group should be taken from a randomly selected group of women of child-bearing age representative of the population from which cases were derived. In addition, to ensure there were no cases of PID among the controls, all controls would need to undergo laparoscopy. Women requesting laparoscopic sterilization would fit these criteria but are likely to be a biased control group. Parity is likely to be a factor associated with PID but those attending for laparoscopic sterilization are likely to have higher parity, on average, than the general population. This would lead to a biased view of the odds ratios associated with various factors such as the number of pregnancies, contraceptive use, and sexual behavior. While there is no perfect solution to these problems but risk factor data are needed and consequently compromises in study design would be necessary.

Conclusions

PID is a key issue facing women's reproductive health in England and Wales and many other countries. It is clear that the available data do not provide an accurate view of PID epidemiology and assumptions cannot be made based on these data. This review has evaluated the priority areas for epidemiological research which will create an evidence base for intervention and control. Such research is urgently required as PID remains the most important, preventable STD in industrialised countries; its impact is only just being recognised and control remains elusive.

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Contributors: JS designed the project and wrote the first draft; JS made a substantial contribution to the structure and content of the review.


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National assessment of PID diagnosis, treatment and management in general practice: England and Wales

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Summary: A questionnaire based audit was used to evaluate the diagnosis and management of suspected pelvic inflammatory disease (PID) cases by general practitioners (GPs) in England and Wales. Responses were compared against a clinical management 'gold standard' devised by an independent group of GPs and specialists. Two hundred and ninety-seven (38%) of the 781 questionnaires were returned. Only 21 (7.9%) had all 'gold standard' sections correct. Diagnostic equality was significantly higher when the clinician was female compared with male (odds ratio 2.34; 95% confidence limits (1.19-4.63) and diagnostic equality increased with increasing socioeconomic deprivation. This is the first evaluation of the diagnosis and management of PID by GPs in England and Wales. The unusually poor response rate to a Medical Research Council General Practice Research Framework study may reflect low disease awareness and sub-optimal management. This represents a fundamental obstacle to effective intervention and surveillance. Effective intervention will only be possible if diagnostic practice and management are improved substantially.

Keywords: Pelvic inflammatory disease, diagnosis, treatment, management

INTRODUCTION

With a prevalence of 1.7% in general practice, PID is a leading cause of reproductive morbidity in England and Wales. It can cause ectopic pregnancy, tubal factor infertility, and chronic abdominal pain, which is associated with increased risk of hysterectomy. Pelvic inflammatory disease is notoriously difficult to diagnose as no signs or symptoms are pathognomonic of PID. Risk of PID sequence increases with the number of PID episodes and, since the interval between PID and tubal damage can be as little as a week, it is important to diagnose and treat the first episode quickly. High diagnostic accuracy is essential to effective management and the accuracy of surveillance and other epidemiological studies. Unfortunately no simple diagnostic test is available. Laparoscopy is considered the definitive diagnostic tool. This is an invasive, expensive and potentially harmful procedure which is used in a minority of suspected cases and cannot be used in primary care where the majority of cases are diagnosed. Regional studies have attempted to document the management of PID in general practice but little is known of the way in which cases are diagnosed. This study, the first national evaluation, seeks to assess current diagnosis and management of PID in general practice.

METHODS

All 781 practices in the MRC GPRF, a network of general practice that participate in research, were invited to take part in the study. The GPRF covers 11% of the population of England and Wales but is a non-random sample of general practices. It includes practices with a broad range of Carstairs indices. The Carstairs index is a measure of deprivation based on the UK 1991 Census, and is derived from the number of persons per household, rate of male unemployment, social class and number of overcrowded households.

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Practitioners were asked to complete a structured questionnaire that covered practice characteristics (part A) and diagnosis, treatment and referral policy for suspected PID cases (part B) (Figure 1). All practices that did not return the questionnaire within 3 weeks were sent an additional questionnaire; if this copy was not returned a reminder was made by telephone.

Practices that responded were compared with those that did not in terms of size and Carstairs index using the Wilcoxon rank sum (Mann-Whitney) test. Practices were also compared in terms of the sex of the physician responsible for questionnaire completion using the z test.

Responses were compared against a 'gold standard' derived from the literature and consultation with experts drawn from general practice, genitourinary medicine (GUM), obstetrics and gynaecology, and microbiology (Table 1 and acknowledgements). For each answer that reached the gold standard, a '1' was added to a total field. Practices with total scores above 2 were satisfactory (diagnostic and management quality code=1), those of 2 or less were coded as being unsatisfactory (diagnostic and management quality code=0).

Single and multivariable analyses were undertaken using logistic regression (STATA 5.0). The outcome measure was diagnostic quality. The explanatory variables included in the analyses were the sex of the practitioner responsible for completing the questionnaire, number of patients per practitioner, whether or not the practice was computerized, cervical cytology coverage, immunization coverage, practice location and Carstairs index.

### Audit of Pelvic Inflammatory Disease (PID) in General Practice

#### Part A ABOUT YOUR PRACTICE

1. Number of persons on the age/sex register (please estimate to the nearest 100): Male □ □ □ Female □ □ □

2. Which of the following best describes the community served by the clinic?
   - Male □ □ □ Female □ □ □

3. How many practitioners are in the practice?
   - Male □ □ □ Female □ □ □

4. Do you have a computer in your practice that is used for clinical purposes?
   - Yes □ No □

5. What is your current level of computer use for clinical purposes?
   - Cytology □ □ □ Immunization □ □ □

#### Part B HOW ARE PID CASES DIAGNOSED AND TREATED IN YOUR PRACTICE?

6. In your view, what symptoms would suggest a diagnosis of PID?

7. On examination, which signs would suggest a diagnosis of PID?

8. Do you undertake microbiological investigation on suspected PID cases?
   - Usually □ Not often □
   - If usually, which sites are sampled?
     - Vaginal □ Rectal □

9. What organisms are most commonly isolated from investigations taken at your practice?

10. Do you give antibiotics whilst waiting for the results of microbiological investigation?
    - Yes □ No □

11. Are partners of PID cases treated?
    - Usually □ Sometimes □ Never □

12. Which specialties are PID cases referred to?
    - Gynaecology □ Family Planning □ General Medical Services □

Figure 1: Questionnaire

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Table 1. Gold standard definition

<table>
<thead>
<tr>
<th>Question</th>
<th>Gold standard definition</th>
</tr>
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<tbody>
<tr>
<td>Which symptoms?</td>
<td>Low or more of the following:</td>
</tr>
<tr>
<td></td>
<td>Irregular menstrual bleeding, lower abdominal pain (particularly where related to dyspareunia), vaginal discharge, dysuria, deep dyspareunia</td>
</tr>
<tr>
<td>Which signs?</td>
<td>Low or more of the following:</td>
</tr>
<tr>
<td></td>
<td>Lower abdominal pain, cervical motion tenderness, cervical discharge, pressure &lt; 50%, tender adnexa, adnexal mass</td>
</tr>
<tr>
<td>Do you undertake microbiological investigation?</td>
<td>Usually</td>
</tr>
<tr>
<td>Antibiotics, therapy</td>
<td>One of the following treatment regimen:</td>
</tr>
<tr>
<td></td>
<td>(1) Tetracycline, doxycycline or erythromycin if doxycycline not tolerated &amp; metronidazole</td>
</tr>
<tr>
<td></td>
<td>(2) Ofloxacin &amp; metronidazole</td>
</tr>
<tr>
<td>Are partners of pelvic inflammatory disease cases treated?</td>
<td>Usually</td>
</tr>
</tbody>
</table>

RESULTS

Of the 281 questionnaires sent out, 297 (98%) were returned. There was no statistically significant difference between responders and non-responders in terms of practice size (P=0.47), Carstairs index (P=0.55) and the sex of the contact physician (P=0.33). Of the male physicians 40% (243/619) responded compared with 33% (51/154) of female physicians. The sex of 1% of the responding physicians was unknown.

Of those practices that did respond, 95% were computerized, 96% were based in urban/small towns, 13% in rural areas and 21% mixed urban/rural areas. An immunization coverage of 90% or more was achieved by 86% of the practices and a cervical cytology target of 80% was achieved by 87% of practices. Seventy-two per cent of practices said they would refer patients with PID to obstetrics and gynaecology, 68% said they would refer to GUM clinics.

Comparison of reported practice against the 'gold standard' indicated that 100 (34%) named at least the required 2 signs and 2 symptoms, 160 (54%) named the correct antibiotic therapy, 64 (22%) usually treated the partner, 252 (85%) usually undertook microbiological investigation (91% took an endocervical swab). Only 21 (7%) answered all sections of the 'gold standard' correctly.

Adjusting for other variables strengthened the effects seen in the single variable analysis (Table 2). Significantly lower diagnostic and management quality (P=0.01) were associated with practices without computerized records compared with those that were computerized (OR=0.07, 95% CI: 0.005-0.906). Diagnostic quality was significantly higher (P=0.05) when the clinician was female compared with male (OR=2.34, 95% CI: 1.19-4.63) and diagnostic quality increased by 12% (95% CI: 5%-21%) with each unit increase in the Carstairs index, that is quality increased with deprivation. There were no interactions between the variables.

DISCUSSION

This is the first evaluation of PID diagnosis in general practice and the first national study of PID management to be undertaken in England and Wales. Prompt diagnosis and treatment of PID are essential as the interval between disease and tubal damage can be as little as a week. The Royal College of Obstetricians and Gynaecologists (RCOG) recommend that women presenting with a clinical diagnosis of PID are tested for Chlamydia trachomatis and Neisseria gonorrhoeae, receive appropriate antibiotic treatment and partner notification 13. Diagnostic and management guidelines are used in GUM clinics and similar protocols have been formulated for Accident and Emergency Departments in a number of districts. However, this study suggests that diagnostic practice falls well below the expectation of 91% of GPs that they manage PID effectively. Pelvic inflammatory disease should be monitored as part of a chlamydial intervention programme and the Chief Medical Officer’s expert advisory group on chlamydial infection recently highlighted the urgent need for information concerning PID epidemiology 1134. The lack of diagnostic quality inherent in the diagnosis of PID suggests that available surveillance data may be neither accurate nor representative. Consequently, the true burden of disease may be significantly underestimated. An accurate view of the epidemiology of PID in England and Wales will only be achieved when these diagnostic problems are resolved.

In this study only 7% of practices reached the most effective level of case management. This is consistent with low disease awareness and sub-optimal management reported from settings outside GUM in the UK, USA and Scandinavia 1135,136. Low awareness may be related to the number of cases seen by individual GPs. Evidence to support this view is the association between diagnostic quality and increased social deprivation, which may reflect increased familiarity with PID in more deprived areas where prevalence is highest. Low diagnostic quality was also significantly related to the absence of a
Pelvic inflammatory disease is a neglected area of women's sexual health, reflected in the poor performance and disappointing response to a MRC CIGRE study, a response rate of over 80% would be expected. Early recognition is essential to reduce this source of reproductive morbidity and the main opportunity for PID control lies in general practice. The results of this study have been disseminated to the GPs who took part in the study. A further audit will be required to close the audit loop and assess whether practice has changed as a result of this study. The substantial opportunity for health gain through PID prevention has been recognized but low awareness represents an obstacle to effective healthcare delivery.

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of Chlamydia trachomatis infections in the Vancouver county during 1 year.

Methods: For the study, contact tracing was centralized to 2-4 persons in each municipality. Samples for diagnosis of genital C. trachomatis were obtained from patients visiting all check-providing samples to the county hospital laboratories in Kehlstedt. A 960 bp fragment from the ompA gene was amplified by polymerase chain reaction (PCR) and a 600 bp segment was sequenced. Result: In total, 725 cases (6%) were positive in routine PCR test. The number of traced partners per index case increased from 1.5 before the study period to 1.9 (P = 0.05). Sequence analysis was achieved in 95% of detected C. trachomatis cases in a large unselected population, thus the distribution of genotypes is therefore representative of the studied community. Sequence analysis revealed that the most prevalent genotypes were B (36%), followed by F (15%), C (12%), K (6%), D (5%), E (4%), H (1%), and A (1%). Of those strains of H and one strain of B, altogether 26 sequence variants were found. Genotypes B, K, and R showed no variation. The predominating genotype F was highly conserved and only 5% differed from the reference sequence. In our study genotypes B and G comprised only 5% of the samples but produced 15% of sequence variants and provided the highest possibility of strain discrimination.

Conclusions: (1) The efficiency of contact tracing increased, although not statistically significant. (2) Sequencing of the ompA gene provided descriptive information about the epidemiology of C. trachomatis infections in the community.

O12 Risk factors associated with pelvic inflammatory disease: a UK study

Surname, M; Millar, IV; Peeling, K; Thomas, R; Gaskin, PA Rogers, P; Hay, M; Stevenson, J; Hopewell, Communicable Disease Surveillance Centre, Liverpool PHE UK; National Centre for Sexually Transmitted Diseases, Wessex Centre for Genital Health; Scottish Episcopal Hospital; Fulham Park Hospital; PMS Statistics Unit; St George's Hospital; University College London; North Middlesex Community Trust UK Objectives: (1) To identify demographic and behavioral factors, immunological parameters and investigative agents associated with pelvic inflammatory disease (PID); (2) To estimate the number of PID cases attributable to Chlamydia trachomatis infection.

Methods: Case-control study. Cases were women diagnosed with PID; controls were women attending for nonsexual medical reasons. Results: Three hundred and eighty-seven women were included; cases were significantly associated with age in 24 years of age (1:2 comparison), group 2: P < 0.01), marital status (married: group 1: P < 0.01), history of infection in the last 5 years (1:2: P < 0.01), and having been exposed to C. trachomatis (1:2: P < 0.01). Chlamydia trachomatis infection was associated with increased risk of PID (group 1: P < 0.01). In this study, 21% of PID cases were found in 25% of cases, 5% of tubal inflammatory lesions, and 8% of general medical conditions.

Conclusions: (1) The first risk factor study of PID to be undertaken in Europe. The study has shown that PID has a complex epidemiology and suggests that a large proportion of cases are not associated with a sexually transmitted infection.

O13 Associations between Mycoplasma genitalium, Chlamydia trachomatis and pelvic inflammatory disease

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Objectives: To investigate the relationship between Mycoplasma genitalium, Chlamydia trachomatis and pelvic inflammatory disease (PID).
Associations between Mycoplasma genitalium, Chlamydia trachomatis, and pelvic inflammatory disease

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Objective: To evaluate the association between Mycoplasma genitalium, Chlamydia trachomatis, and pelvic inflammatory disease (PID)

Methods: A case-control methodology was used. Swab eluates were processed using the QIAamp DNA mini kit. Polymerase chain reaction (PCR) for M genitalium was carried out using a real time in-house 16S based assay. An endocervical swab was taken and tested for the presence of C trachomatis (ligase chain reaction, Abbott Laboratories), and a high vaginal swab was taken and tested for the presence of Neisseria gonorrhoeae and bacterial vaginosis.

Results: Of the PID cases 13% (6/45) had evidence of M genitalium infection compared to none of the controls (0/37); 27% (12/45) of the cases had C trachomatis infection compared to none of the controls; and 16% (7/45) of cases only had serological evidence of C trachomatis infection compared to 5% (2/37) of controls. Cases were more likely to present with M genitalium and/or C trachomatis than controls (p<0.001).

Conclusions: This study indicates that there may be an association between M genitalium and PID, and that this relation is largely independent of C trachomatis. Future studies need to investigate the pathophysiological basis of the relation between M genitalium and PID using samples from women with PID diagnosed using laparoscopy and endometrial biopsy. Little is known about the epidemiology of M genitalium: large scale epidemiological investigations are needed to determine the prevalence, incidence, and factors associated with this emerging infection.

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seconds at 55°C, and 15 seconds at 72°C (program type: melting curves). After each cycle a single fluorescence reading was taken. The results were acquired using a melt cycle at 0.2°C per second with continuous fluorescence readings. A positive curve was judged to have a Tm within plus or minus 1°C of the positive control. This was approximately 88.5°C. Positive results were confirmed using a hemi-nested block based PCR.

Statistical analysis was undertaken using the Fisher's exact test (exact 6). Cases and controls were compared in terms of age using the Mann-Whitney test.

RESULTS
A total of 82 women were included in the study: 45 with a clinical diagnosis of PID and 37 from patients undergoing tubal ligation. The median age of the cases was 25 (range 16–43), whereas that of the controls was 34 (range 21–45). Cases were significantly younger than the controls (p<0.001).

Evidence of M genitalium infection was found in 13% (6/45) of the cases compared to none of the controls. 27% (12/45) of the cases had C trachomatis infection (LCR with or without serology) compared to none of the controls, and 16% (7/45) of the cases had only serological evidence of C trachomatis infection compared to 5% (2/37) of controls (table 1). BV was not detected in any of the cases and controls. Two cases had co-infections: one with C trachomatis and M genitalium, the other between M genitalium and C trachomatis (this patient also had serological evidence of C trachomatis infection). The remaining five M genitalium infected patients had no serological evidence of C trachomatis infection. Of the patients with M genitalium infection, half were over 30 years old. Cases were more likely to have had M genitalium and/or C trachomatis than controls (p<0.001).

DISCUSSION
This is the first case-control study of PID to test for M genitalium. The results suggest that there is an association between M genitalium and PID, and that M genitalium is not merely a commensal organism detected at the site of an STI infection. These findings are similar to those from studies of M genitalium in men with non-gonococcal urethritis.

There is no standard methodology for sampling the female genital tract for M genitalium. Here, the endocervix was used because it was thought to be the site from which M genitalium migrates to the upper genital tract. The performance of the LightCycler PCR assay was similar to that of the block based assay using the same primers, but detected fivefold less DNA (equivalent to 10 genome copies) of M genitalium in a dilution series. In tests using 28 common micro-organisms, none produced a product with the Tm typical of that from M genitalium. However, the testing methodology may lack sensitivity because many of the specimens had previously been tested for C trachomatis using the LCR test which includes an incubation step at 95°C in a high magnesium buffer. Anecdotal evidence suggests that mycoplasma DNA may be susceptible to degradation, perhaps due to a relatively low guanine and cytosine content. The inclusion of a serological test would have provided evidence of previous exposure to M genitalium but was not carried out because these specialist techniques were not available at the laboratory.

The Wagner definition of PID lacks specificity and consequently some patients included in this study may not have had PID. This problem is inherent to all studies of PID. However, the most crucial element in the design of a case-control study is not to include cases in the control group. Here all controls were laparoscoped to ensure that none of the controls had PID.

The multifactorial aetiology of PID is well established but the public health control of PID has largely centred on the control of genital chlamydial infection. The National Strategy for Sexual Health and HIV recently published by the Department of Health (England) emphasised the need to screen young women for genital chlamydial infection. Although this is a welcome development, this study is a timely reminder that chlamydial intervention alone is unlikely to eradicate PID. The antibiotics used to treat genital chlamydial infection may be less effective in the treatment of M genitalium and, since infection has been shown to be largely independent of C trachomatis, it is likely that the epidemiology of these infections may be different.

Effective PID prevention and control rests on improved knowledge of the pathogenesis and epidemiology of the aetiological agents that cause this clinical syndrome. Further studies need to investigate the pathological basis of the relation between M genitalium and PID using samples from women with PID diagnosed using laparoscopy and endometrial biopsy. This study was based on an opportunistic cohort and it was not specifically designed to examine the relation between M genitalium and PID. A bias within the study was the significant difference in age between the case and control groups. However, since half the patients with M genitalium were over the age of 30 years, this source of bias is unlikely to have significantly influenced the study. Nevertheless, results reported here give an interesting insight into the sequelae associated with M genitalium and provide directions for future studies. Little is known about the epidemiology of M genitalium and specifically designed large scale epidemiological investigations are needed to determine the prevalence, incidence and factors associated with this emerging infection. However, before such studies can be undertaken clear guidelines are needed on the diagnosis of M genitalium and the sites that should be sampled.

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Conflict of interest: none declared.

CONTRIBUTORS
IS initiated and designed the project and undertook the analysis with PR. KE and AS developed the M genitalium PCR and did the testing. HM undertook the LCR and serological testing. KB, RA, and PR recruited cases and controls for the study.

Table 1 Evidence of M genitalium and C trachomatis in cases and controls

<table>
<thead>
<tr>
<th>PID C trachomatis</th>
<th>C trachomatis (serology only)</th>
<th>PID no M genitalium</th>
<th>PID M genitalium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>2</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Includes 1 coinfection with C. trachomatis.
*Includes 1 coinfection with N. gonorrhoeae.
*7 had serological evidence of C. trachomatis infection. 
*1 had N. gonorrhoeae.

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