Pelvic Inflammatory Disease: a serious public health issue

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Introduction

Women present to various doctors, including general practitioners, family planning doctors and hospital specialists, with symptoms that may be due to pelvic inflammatory disease (PID). PID is predominantly a sexually transmitted infection (STI), and the public health implications must be addressed as well as the clinical issues. As in other STIs, at least two people are involved and require investigation and treatment.

Notification and treatment of partners (contact tracing) is the most challenging aspect of good management but is frequently ignored or forgotten. Male partners of women with PID may carry asymptomatically Chlamydia trachomatis and other bacteria which ultimately may cause complications such as orchitis, epididymitis, urethritis and reactive arthritis.

The definition of PID used by the US Centers for Disease Control (CDC) is “a clinical syndrome resulting from the ascending spread of micro-organisms from the vagina and endocervix to the endometrium, fallopian tubes and/or contiguous structures” (1). This definition is useful in recording acute clinically apparent illness, but it does not include subclinical disease (“silent” PID). Undetected infection such as Chlamydia trachomatis ascends from the cervix to the endometrium and/or fallopian tubes, resulting in inflammation and damage to tubal structures, yet produces either no symptoms or only minor, non-specific symptoms which are ignored by women or doctors. An alternative definition which recognises the impact of subclinical disease is offered by Berger et al: “An infection which ascends from the lower female genital tract (vagina and cervix) to the level of the fallopian tubes and sometimes their contiguous structures as well (2). With increasing recognition of the importance of silent PID, it is better to use this wider definition.

Epidemiology

Acute PID is a serious and common illness, often requiring hospitalization and sometimes surgery. In the long term, both acute and subclinical PID carry a risk of preventable infertility, ectopic pregnancy and chronic pelvic pains (3-5). A large follow up study in Sweden demonstrated rates of tubal infertility following single episodes of salpingitis to be 2.6% in mild disease, 13% in moderate disease and 28.6% in severe disease (6). Rates of tubal infertility and ectopic pregnancy increase 2-fold with each new episode of PID (7).

Documenting the epidemiology of PID is problematic. PID is a clinical diagnosis but is notoriously difficult to differentiate from other causes of lower abdominal pain. The clinical criteria for diagnosis have proved hard to validate and are inconsistently applied; the microbial causes vary over time and between populations; women present in a variety of clinical settings with a range of symptoms; and the importance of silent PID as a major public health hazard is becoming increasingly apparent.

In the UK in 1992, 21,168 cases were diagnosed in hospital inpatients (8), and 5735 in Genitourinary medicine clinics (9). Surveillance data from a small but representative sample of general practice for the same year recorded a prevalence of 1.7% in women 16-44 years (10). Calculated over the whole population, this suggests that 165,000 cases of PID would have occurred in women of reproductive age in 1992. Over the last 30 years, there has been an upward trend, as in other developed countries, however unlike some European countries and the USA which have initiated policies to reverse this trend with some success, UK rates continue to increase.

STIs in the armed forces

A retrospective peacetime survey of the British military suggested that the incidence of STIs differed little from that in the civilian population. However, this evidence from 1970-1983 is now outdated (11) and relates only to forces based at home. A study of British forces stationed in the tropics showed a 25-fold increased risk of STI compared with controls in the UK, and recorded 39% of cases as resulting from commercial sex; 70% of those questioned did not normally use a condom (12). Data from US military forces also demonstrate high levels of risky sexual behaviour during postings (13).

Although these data relate to men, their high levels of STI are clearly relevant to the
female population with whom these men also have sex. In a prospective American study, 30.3% of military dependent sexually active adolescent females attending for gynaecological examination had an STI (14).

This evidence raises concerns about the acquisition of other STIs and suggests that PID is likely to be a significant health problem in the military, as in other populations. Bacterial STIs are a proven risk factor for HIV transmission (15) and the question of past or ongoing risk of HIV infection should always be considered. In New York, women hospitalized for PID and a seroprevalence for HIV 6.5 times higher than those giving birth in the same hospital (16). In the USA, HIV seroprevalence in women with acute PID ranges from 2.7% to 22% (17).

A review of STI control measures in the US military concludes that screening programmes and collaboration with other government agencies have proved effective, whereas punishment and stigmatization are unhelpful (18). The latter have therefore been abandoned. It is sometimes not fully appreciated that PID is, at least in the majority of cases, a sexually transmitted infection. The same principles must therefore be applied to its management as to other STIs.

**Aetiology and pathology.**

Berger's definition of PID, cited above, reflects general acceptance that the ascent of bacterial pathogens from the cervix causes most PID. The two major pathogens implicated are *C. trachomatis* and *Neisseria gonorrhoeae*. In the UK, chlamydial infection is more common, with a median prevalence of 4.5% among women of reproductive age attending general practice in the UK (19). In women with acute PID at laparoscopy, 38% had chlamydial infection, 14.4% gonococcal, with dual infection on 7.7% (10). In a recent study (20), 38% and *C. trachomatis* is an obligate intracellular organism which causes disease by infecting genital mucosal cells. Ciliated cells die, or lose their cilia becoming “clubbed” (21). A process of chronic inflammation ensues, during which *Chlamydiae* may often still be found (22). There is evidence that delayed hypersensitivity occurs, leading to increasingly severe damage with subsequent infections.

PID due to *N. gonorrhoeae* typically results in more severe systemic illness, with the result that women are likely to present earlier with symptoms (23). There is again mucosal damage to the fallopian tubes, but gonococcal infection may also result in septicemia, septic arthritis and even endocarditis.

In hospitalized cases of PID, at least one STI organism is isolated in 65% of cases (24). However, in 25-50% of proven PID cases, neither chlamydial or gonococcal infection can be detected (25). Anaerobic or facultative bacteria are found and may have a pathogenic role, although whether as primary or secondary pathogens remains unresolved. *Mycoplasma hominis* has been implicated in the aetiology of PID. *Mycoplasma genitalium* and *Ureaplasma urealyticum* have also been suspected of having a role, but substantive evidence does not exist.

As inflammation continues, microscopic deciliation of the mucosa is compounded by fibrosis and adhesions which distort the anatomy of the upper reproductive tract. The consequent tubal damage results in infertility and ectopic pregnancy; intraovarian pressure may also increase and chronic pelvic pain is a common sequela.

**Risk factors and risk variables**

Only 10-17% of women infected with *C. trachomatis* or *N. gonorrhoeae* will go on to develop overt PID (26). However *C. trachomatis* has been identified in the upper genital tract of women with no symptoms of abdominal pain who have cervical infection. The causal factors which directly increase risk of developing PID in the presence of an STI are only partially understood. A meta-analysis by Washington et al (27) describes risk variables: these reflect numerical risk but it is not clear whether they are true causal factors or confounders.

There is evidence that the following risk variables are associated with PID: young age, single marital status, low socioeconomic status, insertion of an IUCD or other instrumentation in the past 40 days (e.g suction termination of pregnancy, dilatation & currettage), delay in seeking health care, compliance with therapy, smoking, menstruation at the onset of symptoms and douching. A new sex partner in the last month or multiple sexual partners are also associated with increased risk of PID (28). Partner notification and referral should decrease the risk of recurrent PID from reinfection (29). Use of the contraceptive pill is associated with lower risk of symptomatic PID, even though it predisposes the acquisition of *Chlamydia trachomatis*. It is uncertain whether it reduces or increases the risk of silent PID. Medroxyprogesterone acetate (the “Depot” injection) reduces the risk (30).

Increased risk associated with IUCD insertion has now been shown to be low in women at low risk of STIs and to revert to baseline after 40 days (31,32). Moreover, levonorgestrel-medicated IUCDs are associated with a lower risk than copper devices (33). However, instrumentation during termination of pregnancy is dangerous: the median prevalence of
chlamydial infection in women seeking termination of pregnancy in the UK is 8% but under 20's have much higher prevalence (19,34). The incidence of post-abortal PID is 12% (35). Screening for STIs prior to termination of pregnancy has been shown to reduce infection rates and to have cost benefits (36,37).

**Diagnosis and differential diagnosis**

The clinical diagnosis of PID is unreliable - and the fact that subclinical disease is an important cause of sequelae complicates the picture still further. Even laparoscopy, the “gold standard” since the 1960s has been questioned. In reviewing the current state of diagnosis (38), Kahn et al look forward to a diagnostic gold standard which “closely correlates with acute and long term clinical outcomes, assessed with prospective studies”.

The clinical picture of PID varies between settings: accident and emergency departments and gynaecologists are likely to see the more systemically ill cases. General practitioners will see women with various presentations but because of insidious disease may fail to consider the diagnosis of PID in women with “non specific” lower abdominal pain.

Symptoms may include abdominal pain (usually bilateral and often for >4 days), intermenstrual bleeding, menorrhagia, preceding vaginal discharge and fever. There may also be urinary tract symptoms, nausea and vomiting.

Classically, the clinical signs of PID are adnexal tenderness and cervical motion tenderness on bimanual pelvic examination. Up to 80% of patients have abnormal vaginal discharge on examination, often purulent, and only 50% have fever.

Laboratory tests, including a raised erythrocyte sedimentation rate, or an increase in C reactive protein, or antichymotrypsin, are significant diagnostic indicators. Similarly, identification of *N.gonorrhoeae* or *C.trachomatis* increases the likelihood of the diagnosis.

None of these symptoms, signs or laboratory tests predict PID well. Researchers have sought to find combinations which give higher sensitivity and specificity. A combination of pelvic pain, adnexal tenderness, temperature >38°C, erythrocyte sedimentation rate >15mm/hr and a palpable mass has a 99% specificity for PID — unfortunately only one sixth of women with PID have all these features (39).

In Scandinavia, diagnostic laparoscopy is undertaken routinely, and this approach has its advocates in the UK. However, even this so-called “gold standard”, has limitations. Compared to histological diagnosis on specimens of fimbrial microbiopsy, the sensitivity of laparoscopy is only 50% and its specificity 80% (40).

The significance of these findings is disputed, but better alternatives have not been established.

No validated, generally accepted algorithm for diagnosis of PID exists as yet. It is therefore important to follow up patients receiving empirical treatment for presumed PID in a few days, to assess the response and reconsider the diagnosis.

The differential diagnosis depends upon the age and sexual history of the patient. The most dangerous missed diagnosis is ectopic pregnancy. A menstrual and sexual history is essential in any woman with abdominal pain. The pregnancy test may be negative in early ectopic pregnancy.

Appendicitis, rupture or torsion of an ovarian cyst, endometriosis, urinary tract infection, irritable bowel syndrome and diverticulitis must also be considered. Actinomycosis occasionally gives a picture similar to PID, and the possibility of pelvic tuberculosis should not be forgotten.

Clinical PID is only the tip of the iceberg (41). Silent PID and its consequences can only be addressed at the present time by population measures designed to reduce the incidence and duration of causative STIs. The Centre of Disease Control in USA have recommended screening for *C.trachomatis* in target populations in the wake of evidence that screening can reduce the incidence of overt PID (42,43). Similar recommendations have been made in the UK (19,44).

**Management**

Delay in seeking medical help increases the probability of complications in PID (45) and a delay of 10 days in therapy increases the risk of subsequent infertility threefold, to 17.8% (46). Delay in offering treatment in a woman who may have PID thus puts her fertility at risk. It is therefore important to start treatment quickly, whether or not laparoscopy is undertaken. A diagnosis of PID should be considered in young sexually active women with abdominal pain, and a low threshold for treatment is essential. Prompt treatment with correct antibiotics protects tubal function.

The objectives of treatment are to resolve inflammation, eradicate infection, preserve fertility, and prevent the complications of ectopic pregnancy and chronic pelvic pain. Initial therapy must cover *N.gonorrhoeae, C.trachomatis* and anaerobic bacteria.

Few randomised controlled trials of antibiotic therapy have been undertaken, and those that exist suffer from problems with entry criteria and comparability of populations. A meta-analysis of antimicrobial regimen efficacy has been published (47). The CDC in the USA...
advise regimens for inpatient and outpatient treatment as follows (full details are in the reference and on the CDC website) (43).

**Intravenous regimen A:**
- Cefotetan 2g IV 12 hourly or Cefoxitin 2g IV 6 hourly
- Gentamicin loading dose IV or IM (2mg/kg body weight) followed by a maintenance dose (1.5mg/kg) every 8 hours. Daily dosing may be substituted.
Parenteral therapy may be changed to oral 24 hours after clinical improvement and oral doxycycline or clindamycin should be continued to a total of 14 days.

**Oral regimen A:**
- Ofoxacin 400mg orally, twice daily for 14 days
- Metronidazole 500mg orally twice daily for 14 days

**Intravenous regimen B:**
- Clindamycin 900mg IV every 8 hours
- Parenteral therapy may be changed to oral 24 hours after clinical improvement and oral doxycycline or clindamycin should be continued to a total of 14 days.

**Oral regimen B:**
- Ceftriaxone 250mg IM once
- Cefoxitin 2g IM plus Probenecid 1g orally in a single dose concurrently once
- Other parenteral third-generation cephalosporin (e.g cefotaxime or ceftriaxone)
- Doxycycline 100mg IV or orally every 12 hours.

These regimes can be expected to be effective in a wide range of settings with differing prevalences of antimicrobial resistance.

Hospital admission for gynaecological assessment should be arranged if a woman has severe symptoms, the diagnosis is in doubt, there is a pelvic mass, or the woman is pregnant. As well as intravenous antibiotic therapy and laparoscopy, laparotomy may be needed for ruptured tubo-ovarian abscess. Other interventions in severe disease include colpotomy, adnexectomy, hysterectomy with salpingo-oophorectomy. Perihepatitis (Fitz-Hugh-Curtis syndrome) should be considered.

If the illness is mild, treatment can be undertaken at home. Basic investigations, including endocervical samples for gonococcal culture and chlamydial antigen detection are nevertheless essential in any woman who may have PID or another sexually transmitted infection. These are usually best undertaken in a genitourinary clinic, where immediate microscopy can be done, but therapy should not be delayed. Sex should be avoided until results of tests are available and adequate therapy has been given to both partners.

If the woman has an IUCD, if there is clinical improvement at 5 days this may be left in place. If it is removed, alternative contraception, and possibly emergency contraception, will need to be discussed.

The patient needs to be reassessed at 5-7 days to ensure that there has been clinical improvement. As well as clinical assessment, her compliance with therapy, partner notification, and information needs should be checked. In published partner studies for PID, the majority of men have non-specific urethritis, C.trachomatis or N.gonorrhoeae but are asymptomatic (48,51). It is essential that she understands the importance of partner referral and the need to avoid sexual intercourse until both partners have completed treatment. This should reduce rates of re-infection.

**Conclusions**

PID is a common sexually transmitted infection which requires early, active treatment to reduce the probability of complications. Partner notification is an essential part of management and can be facilitated by genitourinary clinics, even when treatment is undertaken in primary care. Patients are often unwilling to offer full sexual histories to their primary care doctors, who may in any case not be in a position to offer treatment to all partners. Genitourinary clinics are familiar with these problems and well placed to deal with them.

Standards for partner notification in genital chlamydial infection have recently been published (44), which delineate the essentials of any protocol for ensuring partner notification and treatment compliances. Where treatment is provided outside the genitourinary clinic, adherence to these guidelines will maximise the chances of a good long term clinical outcome.

PID is difficult to diagnose, and often insidious in its presentation: doctors in primary care need to have a high level of suspicion. The financial burden to healthcare providers and personal costs to affected individuals are substantial (52). In Scandinavia, a programme of screening for STIs, together with an education campaign aimed at public and professionals, has been followed by a decrease in PID and ectopic pregnancy rates. Prevention is better than cure: screening for STIs is likely to be effective in military populations.

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