Chlamydial pelvic inflammatory disease

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Pelvic inflammatory disease (PID) is the most important complication present in the female lower genital tract, causing major medical, social and economic problems. Although PID can be caused by multiple microorganisms, it results most frequently from the ascent of sexually transmitted Chlamydia trachomatis or Neisseria gonorrhoeae infections from the cervix to the upper genital tract. The importance of cervical chlamydial infection in the pathogenesis of PID is well recognized. Recent data from many developed countries have shown a striking decrease in the incidence of gonococcal infections, while the rates of chlamydial infections remain high in most countries. Complications of PID are common and usually irreversible. Emerging evidence suggests that universal or selected screening of defined populations for cervical chlamydial infection leads to a dramatic reduction in the incidence of PID. Recent technological advances should further enhance efforts to prevent chlamydial infection and PID. Gene amplification-based diagnostic tests, screening by testing first-void urine, and single dose antimicrobial therapy greatly facilitate chlamydia control programmes. Thus, screening for chlamydia is the key approach in the secondary prevention of PID. The obvious challenge is to make screening for chlamydia the standard for health care for young, sexually active individuals. Since PID is the most important consequence of sexually transmitted bacterial infections, it is also imperative to develop better treatments to prevent the long-term sequelae of this disease. The development and implementation of new and effective intervention programmes for prevention and control of PID is one of the major challenges for the year 2000 and beyond.

Key words: C.trachomatis/Neisseria gonorrhoeae/pelvic inflammatory disease

Introduction

Pelvic inflammatory disease (PID) causes major medical, social and economic problems. Worldwide, the magnitude of PID-related morbidity is enormous. For instance, in the USA at least 5.5 billion dollars are spent on PID annually. Expensive medical high-technology, including in-vitro fertilization (IVF) and gynaecological keyhole surgery, has emerged largely because of the reproductive tract damage caused by PID. This is paradoxical since most PID and its consequences is preventable.

Aetiology of PID

Chlamydia trachomatis is the major cause of cervicitis (Brunham et al., 1984) and PID (Mårdh et al., 1977; Paavonen, 1980). According to the World Health Organization (WHO), 50–70 million genital C.trachomatis infections are detected worldwide annually (Piot and Islam, 1994). The proportion of PID associated with C.trachomatis infection varies depending on the study population (Table I). Overall, more than half of PID cases seem to be caused by C.trachomatis, Neisseria gonorrhoeae, or both. PID develops in between 10 and 40% of women with inadequately treated chlamydial or gonococcal cervicitis (Stamm et al., 1984). Recent data from many European countries, Canada and elsewhere have shown a striking decrease in the incidence of...
gonococcal infections (Kohl, 1994), but in European countries the numbers of genital chlamydial infections are still on the rise, with few exceptions (Ripa and Bauman, 1995). The role of bacterial vaginosis (BV) in the aetiology of PID is under great scrutiny at the present time, since most non-chlamydial, non-gonococcal micro-organisms detected in the upper genital tract of women with proven PID are also known to be associated with BV (Eschenbach et al., 1988; Soper et al., 1994; Korn et al., 1995).

Clinical manifestations of PID

PID is an ascending infection in which pathogenic micro-organisms spread from the lower genital tract to the upper genital tract (McCormack, 1994; Figure 1). The clinical spectrum of PID ranges from subclinical endometritis to frank salpingitis, pelvic peritonitis, periappendicitis and perihepatitis (Berger and Weström, 1992; McCormack, 1994). Most studies of chlamydial PID have focused on inpatients with acute symptoms and severe disease. However, such cases may represent only the tip of the iceberg of all upper genital tract infections. When the relative role of C. trachomatis in the aetiology of PID has increased, the clinical spectrum of the manifestations of PID has also changed. More cases are atypical or silent, and the ‘textbook’ PID has become a rare disease, at least in many developed countries (Berger and Weström, 1992). Therefore, fewer PID patients need to be hospitalized. The change in the clinical manifestations makes it even more problematic to study time trends in the incidence of PID. Demonstration of plasma cell endometritis by endometrial biopsy in women with cervicitis but no signs or symptoms of PID has focused attention on subclinical or silent PID (Paavonen et al., 1985c; Table II). Sero-epidemiological studies also support the concept of silent chlamydial PID by demonstrating a strong link between serum antibodies to C. trachomatis and tubal factor infertility or ectopic pregnancy in patients both with and without a history of PID (Cates and Wasserheit, 1991).

Table I. Prevalence of C. trachomatis* in patients with proven pelvic inflammatory disease: selected studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>% (no./total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mördh et al. (1977)</td>
<td>Gyn inpatients</td>
<td>36 (19/53)</td>
</tr>
<tr>
<td>Paavonen (1980)</td>
<td>Gyn inpatients</td>
<td>30 (69/228)</td>
</tr>
<tr>
<td>Ripa et al. (1980)</td>
<td>Gyn inpatients</td>
<td>33 (52/156)</td>
</tr>
<tr>
<td>Kinghorn et al. (1986)</td>
<td>STD clinic</td>
<td>40 (17/43)</td>
</tr>
<tr>
<td>Wasserheit et al. (1986)</td>
<td>Emergency room</td>
<td>61 (14/23)</td>
</tr>
<tr>
<td>Kiviat et al. (1986)</td>
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<td>38 (21/55)</td>
</tr>
<tr>
<td>Paavonen et al. (1987)</td>
<td>Gyn inpatients</td>
<td>52 (16/35)</td>
</tr>
<tr>
<td>Brunham et al. (1988)</td>
<td>Gyn outpatients</td>
<td>16 (8/50)</td>
</tr>
<tr>
<td>Wolner-Hanssen et al. (1988a)</td>
<td>Gyn outpatients</td>
<td>65 (15/23)</td>
</tr>
<tr>
<td>Heinonen et al. (1989)</td>
<td>Gyn inpatients</td>
<td>42 (15/36)</td>
</tr>
<tr>
<td>Sellors et al. (1991)</td>
<td>Primary care</td>
<td>25 (11/44)</td>
</tr>
<tr>
<td>Livengood et al. (1992)</td>
<td>Emergency room</td>
<td>30 (7/23)</td>
</tr>
<tr>
<td>Cacciapuoti et al. (1992)</td>
<td>Gyn outpatients</td>
<td>14 (7/51)</td>
</tr>
<tr>
<td>Dan et al. (1993)</td>
<td>Gyn inpatients</td>
<td>35 (14/40)</td>
</tr>
<tr>
<td>Soper et al. (1994)</td>
<td>Gyn inpatients</td>
<td>77 (65/84)</td>
</tr>
<tr>
<td>Bevan et al. (1995)</td>
<td>Severalb</td>
<td>38 (40/104)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>37 (390/1048)</td>
</tr>
</tbody>
</table>

STD = sexually transmitted disease; Gyn = gynaecological.
*a C. trachomatis detected in the cervix, endometrium or Fallopian tubes.
*b Emergency room, STD clinic, family planning clinic, general practitioners.
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Figure 2. Life cycle of Chlamydia trachomatis.

Table II. Plasma cell endometritis (determined by endometrial biopsy) in women with mucopurulent cervicitis (Paavonen et al., 1985c)

<table>
<thead>
<tr>
<th></th>
<th>No./total (%)</th>
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<tr>
<td>Chlamydial cervicitis</td>
<td>14/22 (64)</td>
</tr>
<tr>
<td>Non-chlamydial cervicitis</td>
<td>2/13 (15)</td>
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</tbody>
</table>

Pathogenesis and host response to C. trachomatis in PID

Chlamydiae are small intracellular bacteria with a complex life cycle (Figure 2). Eighteen distinct serotypes of C. trachomatis have been identified. Although serotypes E, F and D account for 60–70% of urogenital C. trachomatis infections, there is no convincing evidence in women that specific genital syndromes or clinical manifestations, such as PID, are serotype-specific (Persson and Osser, 1993; Workowski et al., 1994; van de Laar et al., 1996).

Progress in understanding the pathogenesis of PID has come with better understanding of the immunopathogenesis of C. trachomatis infection (Morrison et al., 1989). C. trachomatis is a strong immunogen which stimulates both humoral and cell-mediated arms of the immune system. Chlamydia can induce immune system perturbations that may assist its own survival in the infected host (Morrison et al., 1989; Paavonen and Lehtinen, 1994). The ability of chlamydia to convert from resting (elementary body) to replicating forms (reticulate body) within host cells creates increasing difficulties in eliminating this microbe.

Understanding the dynamic nature of the endometrium in the upper genital tract infection is one of the keys to the understanding of the host response. Normal endometrium is an immunologically active tissue with lymphoid aggregates and scattered interstitial lymphocytes (Morrison et al., 1985; Marshall and Jones, 1988) regulated by sex-steroid hormones (McDermott et al., 1980). The oestrous cycle is associated with the inhibition of CD8-positive suppressor T cell activity (Paavonen et al., 1981), and concomitant physiological (Wira and Sandoe, 1977) or pathological (Punnonen et al., 1989) plasma cell infiltration. Following local antigen stimulation by C. trachomatis, mucosal CD4-positive T cells provide their helper function for the maturation of the plasma cells and antibody response (Zeitz et al., 1988, 1990). Heavy plasma cell and T cell infiltration accompanied by lymphoid follicle formation is pathognomonic for chlamydial endometritis (Paavonen et al., 1985a; Lehtinen et al., 1986; Kiviat et al., 1990b) (Figure 3). However, little is known about the interactions of specific chlamydial antigens and T cell subsets in the endometrium during different phases of the reproductive cycle, or during an ascending infection. The role of CD8-positive cytotoxic T cells in C. trachomatis infections is not well known either (Pavia and Schachter, 1983; Qvigstad and Hirschberg, 1984).

The relative role of the two subclasses of T helper cells, Th1 cells and Th2 cells, in the immunopathogenesis of chlamydial infections and infections caused by other intracellular micro-organisms (e.g. mycobacteria or Schistosoma mansoni) is under keen investigation (Uyemura et al., 1992; Paavonen and Lehtinen, 1994). Th1 response, primarily mediated by cytokines IL2 and interferon-γ, is responsible for delayed type hypersensitivity. Th1 response is beneficial in mycobacterial infections, but seems to lead to fibrosis and scarring in repeated or persistent chlamydial infections (Patton et al., 1987, 1994; Patton and Kuo, 1989). Th2 response, primarily mediated by cytokines IL4, IL6 and IL10, is responsible for the production of immunoglobulin (Ig)A and IgE antibodies in chlamydial infections. C. trachomatis elementary bodies are mitogenic (Räsänen et al., 1986), but most likely take part in the polyclonal B cell proliferation, and cause immune perturbations characteristic of some forms of chlamydial infections. Future studies on the induction of the two types of T helper cell responses are critical for understanding the immunopathogenesis of chlamydial PID.

The role of the antigen-presenting cell (APC) in the induction of the immune response is important. After recognition of the antigen, professional APC (e.g. Langerhans cells) present the antigen together with MHC class II molecules and the accessory molecules (e.g. B7) to the T helper cells. If unprofessional antigen-presenting cells (e.g. epithelial cells) express MHC II antigens, they also become able to present antigenic peptides to the T helper cells without activation. Whether or not there exists hierarchy or predominance in the interactions between
different antigens, APC populations and Th1 and Th2 cells should be studied further. For instance, if autoantibody-producing B cells became loaded with antigenic peptides stemming from repeated exposure to chlamydial heat-shock proteins (hsp), this could serve as a strong continuous stimulus to Th1-dependent reactivity. Most of the available data suggest that microbial counterparts of human hsp60 and hsp70 are involved in the immunopathogenic reactions. A number of studies have already looked at the antibody responses to hsp induced by *C. trachomatis*, and generally they have found a good correlation between serum antibodies to hsp60 and PID, tubal factor infertility or ectopic pregnancy (for review, see Paavonen and Lehtinen, 1994; Dieterle and Wollenhaupt, 1996). In women with chlamydial PID, prior history of PID, cervicitis, or chlamydial infection, laparoscopically observed tubal obstruction, laparoscopically observed degree of tubal inflammation and the presence of moderate to severe adhesions were all associated with hsp60 antibodies (Stamm et al., 1994). The association between the presence of serum antibodies to chlamydial hsp60 and tubal occlusion underlines the significance of chlamydial hsp60 in the pathogenesis of tubal infertility (Dieterle and Wollenhaupt, 1996). Chlamydial genes coding for the 60- and 75-kDa hsp have been sequenced, and the B cell epitopes of the hsp60 have been studied in detail (Yi et al., 1993; Paavonen et al., 1994).

Compared to the humoral immune response, much less is known of the cell-mediated immune response to hsp. A positive lymphocyte proliferation response of peripheral blood mononuclear cells to recombinant hsp60 was more common in women with PID than in women without PID or in controls (Witkin et al., 1993, 1994). Most of those with positive response had a history of PID or ectopic pregnancy, suggesting that duration of exposure plays an important role in the chlamydia-specific T cell response. It is a major task of chlamydia immunology to define the human T helper cell epitopes of chlamydial hsp60 and chlamydial hsp70. Epitopes recognized by γδ T cells are also of interest, since these cells seem to be present in tissues with increased expression of human hsp60. However, although autoimmune reactions may play some role in chronic sequelae of chlamydial infections, delayed type hypersensitivity response clearly plays a more important role. Modulation of the immune response, for instance with cytokines or their antagonists, is not possible without thorough knowledge of the immunopathogenesis of chronic chlamydial infections, where delayed type hypersensitivity to the chlamydial hsp60 plays a central role (Patton et al., 1994).

### Table III. Minimum criteria for the syndromic diagnosis of pelvic inflammatory disease (Rolls, 1991)

| Lower abdominal tenderness |
| Bilateral adnexal tenderness |
| Cervical motion tenderness |
| No evidence of competing diagnosis (positive pregnancy test, acute appendicitis, etc.) |
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Table IV. Center for Disease Control and Prevention and World Health Organization guidelines for the treatment of pelvic inflammatory disease

**CENTER FOR DISEASE CONTROL AND PREVENTION**

**Inpatient treatment**

Regimen A: Cefoxitin, 2 g i.v. every 6 h or cefotetan, 2 g i.v. every 12 h, plus doxycycline, 100 mg i.v. or orally every 12 h

Regimen B: Clindamycin, 900 mg i.v. every 8 h, plus gentamicin loading dose i.v. or i.m. (2 mg/kg of body weight) followed by a maintenance dose (1.5 mg/kg) every 8 h.

**Outpatient treatment**

Regimen A: Cefoxitin, 2 g i.m., plus probenecid, 1 g orally, in a single dose, or ceftriaxone, 250 mg i.m., or other parenteral third-generation cephalosporin (e.g. ceftriaxone ime or cefotaxime), plus doxycycline, orally two times a day for 14 days

Regimen B: Ofloxacin, 400 mg orally two times a daytimes for 14 days, plus either clindamycin, 450 mg orally 4 times a day, or metronidazole, 500 mg orally two times a day for 14 days

**WORLD HEALTH ORGANIZATION**

**Inpatient therapy**: recommended regimens

1. Ceftriaxone, 250 mg i.m. twice daily, plus doxycycline, 100 mg orally or i.v twice daily, or tetracycline, 500 mg orally four times daily, plus metronidazole, 400–500 mg orally or i.v. twice daily

2. Clindamycin, 900 mg i.v. every 8 h, plus gentamicin, 1.5 mg/kg i.v. every 8 h

3. Ciprofloxacin, 500 mg orally twice daily or spectinomycin, 1 g i.m. four times daily, plus doxycycline, 100 mg orally or i.v. twice daily, or tetracycline 500 mg four times daily, plus metronidazole, 400–500 mg orally or i.v. twice daily

**Ambulatory therapy**: recommended regimen

Single dose therapy for uncomplicated gonorrhoea, plus doxycycline, 100 mg orally twice daily, or tetracycline 500 mg orally four times daily for 10 days, plus metronidazole, 400–500 mg orally twice daily for 10 days

*Duration of therapy should be least 4 days or 48 h after the patient has improved and this treatment should then be followed by either doxycycline, 100 mg orally twice daily, or tetracycline, 500 mg orally four times daily, for 10–14 days.

**Diagnosis of PID**

The traditional clinical and laboratory criteria for the diagnosis of PID are insensitive and non-specific (Jacobson and Weström, 1969; Jacobson, 1980; Sellors et al., 1991). Therefore, laparoscopy, endometrial biopsy, transvaginal ultrasonography (TVS) and magnetic resonance imaging (MRI) have been introduced in order to increase the accuracy of the clinical diagnosis of PID. Laparoscopy has been universally recommended as the gold standard for the diagnosis of PID (Jacobson and Weström, 1969). However, even laparoscopy has not been properly validated (Kahn et al., 1991). One recent study among primary care patients with low abdominal pain showed surprisingly low accuracy for laparoscopy in the diagnosis of PID when the gold standard was the histopathological diagnosis of salpingitis (Sellors et al., 1991). Special techniques can be used during laparoscopy to obtain upper genital tract specimens for C.trachomatis, including fimbrial minibiopsies, endotubal swabs, or endometrial aspirations (Kiviat et al., 1986; Sellors et al., 1991; Vallee et al., 1994). Endometrial biopsy using either a Vabra aspirator or Pipelle aspiration catheter (Eddowes et al., 1990; Stovall et al., 1991) is a novel procedure for the diagnosis of PID among outpatients (Paavonen et al., 1985c; Cacciatore et al., 1992). Endometrial aspirate is suitable both for histopathological and microbiological studies. The presence of plasma cell endometritis can be used as a presumptive diagnosis of PID (Paavonen et al., 1985a,b, 1987; Kiviat et al., 1990a). TVS and MRI are non-invasive imaging techniques currently being evaluated in the diagnosis of PID (Putten et al., 1990; Cacciatore et al., 1992; Tukeva et al., 1996) (Figure 4).

Figure 4. Magnetic resonance image of severe pelvic inflammatory disease. An oblique axial T2-weighted image showing (arrow) a tubo-ovarian abscess (histologically proven).
Concern about the problem of unrecognized PID has led to a most fundamental change in the recommendations for PID diagnosis (Rolfs, 1991). A set of simple, easily ascertained minimum clinical criteria (Table III) should trigger antibiotic treatment for probable PID unless a competing diagnosis is certain. This means moving away from laboratory-based and laparoscopy-based diagnosis towards syndromic diagnosis. Use of risk assessment and syndromic diagnosis should further increase sensitivity. Although the more sensitive approach will in some cases result in unnecessary antibiotic treatments, it will also lead to earlier therapy for PID. In addition to undiagnosed PID, delay of care is also an important cause of impaired fertility, particularly in chlamydia PID (Hillis et al., 1993).

Management of PID

The polymicrobial origin of PID makes broad-spectrum antibiotic coverage essential. However, although recommended antibiotic therapies are effective in achieving clinical cure, their success in preventing complications is less certain. Treatment appears to prevent tubal infertility and ectopic pregnancy if initiated within 2 days of the onset of abdominal pain (Hillis et al., 1993). However, most women with PID delay seeking care. Women with chlamydial infection are the most likely to delay, because their symptoms are usually minimal or absent. Furthermore, among minimally symptomatic women who do seek care, the rate of non-compliance with antibiotic regimens may be surprisingly high (Katz et al., 1992).

Because a wide variety of micro-organisms can be involved in PID and a specific microbial diagnosis cannot be made before the initiation of antimicrobial therapy, treatment must be directed at all potential pathogens (McCormack, 1994; Table IV). However, the current guidelines recommended by WHO and Centers for Disease Control and Prevention (USA) have not been critically evaluated in randomized controlled trials. In many instances, anecdotal evidence suggests that longer courses of antimicrobial drugs are both necessary and beneficial to eliminate chlamydial infection from the upper genital tract. Treatment with single agents such as penicillins or tetracycline does not provide adequate coverage and has been associated with unacceptable failure rates. Monotherapy with cephalosporins has been associated with a clinical response, but a failure to eliminate C. trachomatis (Sweet et al., 1983). Thus, multiple drugs that have activity against C. trachomatis, N. gonorrhoeae, facultative gram-negative rods and anaerobes are included in the practice guidelines. Although the recommended regimens have been shown to eliminate gonococci and chlamydiae and to be associated with a clinical response in most treated patients (Wasserheit et al., 1986; Wølner-Hanssen et al., 1988a,b; Landers et al., 1991), their efficacy in the prevention of long-term sequelae such as infertility is unproven (see also Table I). It should be determined whether more aggressive treatment aimed at anaerobic bacteria and other micro-organisms not susceptible in vitro to currently recommended antimicrobial agents (Hasselequist and Hillier, 1991) improve the long-term outcome. Similarly, the role of adjunctive medications, such as corticosteroids and non-steroidal anti-inflammatory agents, in reducing long-term complications requires further study (McCormack, 1994).

Close follow-up of patients, especially those treated as outpatients, is an integral part of management. Patients should be reassessed 24–48 h after treatment is begun. Clinical improvement should be apparent. The absence of an improvement in, or the worsening of, a patient’s clinical condition means that the diagnosis of PID should be reassessed. Laparoscopy, TVS or MRI should be considered, as should the hospitalization of patients being treated as outpatients. Medical management is usually sufficient. Surgical intervention to drain pelvic abscesses or to resect chronically infected pelvic organs is rarely required. Intrauterine devices should be removed once antimicrobial treatment has begun, and contraceptive counselling provided.

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence (%)³</th>
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<tr>
<td>1990</td>
<td>8.3</td>
</tr>
<tr>
<td>1991</td>
<td>6.7</td>
</tr>
<tr>
<td>1992</td>
<td>7.0</td>
</tr>
<tr>
<td>1993</td>
<td>5.6</td>
</tr>
<tr>
<td>1994</td>
<td>4.5</td>
</tr>
</tbody>
</table>

³Screening activity remained stable, i.e. there was no significant change in the total number of specimens obtained annually.

Most women with PID are currently treated as outpatients. Although one might predict that hospitalization would be more beneficial than outpatient management with oral antibiotics, there have been few studies comparing inpatient and outpatient management. According to guidelines prepared by the Centers for Disease Control and Prevention, hospitalization is recommended when the diagnosis is uncertain, the possibility of surgical emergencies cannot be excluded, a pelvic abscess is suspected, the patient is pregnant, the patient is an adolescent, severe illness precludes outpatient management, the patient is unable to follow or tolerate an outpatient regimen, the patient has not responded to outpatient therapy, or clinical follow-up can-
not be arranged within 72 h of the initiation of antibiotic treatment (McCormack, 1994). The Centers for Disease Control and Prevention recommends hospitalization and i.v. antibiotic treatment for women with PID known to be infected with human immunovirus (HIV).

Evaluation of the male sexual partners of patients with PID is an integral part of management, since chlamydial and gonococcal infection are often asymptomatic in men (McCormack et al., 1977; Karam et al., 1986), and the men should also be examined for other sexually transmitted infections.

**Morbidity following PID**

The sharp worldwide increase in the incidence of PID during the past decades has now led to the secondary epidemics of infertility and ectopic pregnancy (Mäkinen, 1988; Cates and Wasserheit, 1991). Chlamydial PID is the most important preventable cause of infertility and adverse pregnancy outcome. The proportion of infertility due to tubal factor ranges from 37% in developed countries to 85% in developing countries (WHO, 1987). Each repeat episode of PID doubles the risk of tubal damage and increases the risk of infertility and ectopic pregnancy (Weström et al., 1992; Hillis et al., 1994; Weström, 1994). Most women who have tubal factor infertility have never been diagnosed as having chlamydial infection or PID. Prospective studies (Weström, 1980) have also highlighted other adverse outcomes, such as chronic pelvic pain caused by extraluminal scarring (Hillis and Wasserheit, 1996).

There is some evidence that *C.trachomatis* may also contribute to other pregnancy complications, including premature rupture of membranes, preterm birth, low birth weight and stillbirth (McGregor and French, 1991). Early pregnancy loss may be induced by asymptomatic *C.trachomatis* infection through the operation of immune mechanisms (Witkin, 1995). Worldwide, huge amounts of money are spent on PID sequelae. For instance, the cost of a successful delivery following IVF (most often performed for post-PID infertility) is extremely high, ranging from US $67 000 for the first cycle to US $114 000 by the sixth cycle (Neumann et al., 1994).

Second-look laparoscopy is the fastest and easiest technique to evaluate the effect of treatment of PID on the anatomy and function of the Fallopian tubes (Wølner-Hanssen and Weström, 1983; Teisala et al., 1987; Brihmer et al., 1989). However, thorough epidemiological studies of overall outcomes following PID are extremely difficult. First, there are problems with accurate identification of cases, since symptoms and signs are non-specific, and visualization of the Fallopian tubes may be the only reliable method of diagnosis. Secondly, consequences of infection may only become apparent many years after the index episode. The usual difficulties of follow-up are compounded by non-compliance among the women most at risk of complications. Therefore, it is not surprising that outcome studies are rare. Linked medical records provide one way of studying remote morbidity or mortality in women following an episode of PID. However, it is only possible to study hospitalized disease, and the specific criteria used for making the PID diagnosis will not be known. Such a longitudinal approach does, however, provide a relatively inexpensive and easy means of comparing the subsequent hospitalizations of women discharged with a diagnosis of PID with those of women discharged with non-gynaecological diagnoses. In one study, women with a diagnosis of PID were 10 times more likely to be admitted for abdominal pain, four times more likely to be admitted for gynaecological pain, and six times more likely to be admitted for ectopic pregnancy (Buchan et al., 1993). A substantially higher risk of hysterectomy after PID was also found. Hysterectomy rates were approximately eight times higher in cases of PID than in the controls. Women with a history of hospitalization for PID had greatly increased rates of subsequent hospital admission for a variety of other conditions, suggesting that these women suffer substantial long-term gynaecological morbidity.

Tubal factor infertility remains the most common indication for IVF. Although some studies suggest that the presence of tubal factor infertility and hydrosalpinx is associated with decreased implantation rate, decreased pregnancy rate and increased early pregnancy loss (Andersen et al., 1994; Kassabji et al., 1994; Strandell et al., 1994; Vandromme et al., 1995), one recent study among 123 patients with or without hydrosalpinx did not confirm this negative effect on IVF outcome when antibiotic treatment (doxycycline, 100 mg twice daily for 10 days) was given prior to the first IVF cycle (Sharara et al., 1996).

**Table VI.** Randomized intervention trial: selective screening for *C.trachomatis* reduces the incidence of pelvic inflammatory disease (PID) in patients (*n* = 380 000) at the Group Health Cooperative of Puget Sound (Scholes et al., 1996). Both the intervention group and the control group were followed for 12 months.

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence and rate of PID</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate</td>
</tr>
<tr>
<td>Intervention group</td>
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<td>8</td>
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<tr>
<td>Control group</td>
<td>33</td>
<td>18</td>
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</table>

*a*Rate per 10 000 women-months.

*b*Comprised 2607 (13%) of 20 836 eligible women.
Table VII. Selected pelvic inflammatory disease (PID) research issues.

<table>
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<tr>
<th>Basic research issues</th>
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<td>Host or pathogen characteristics associated with high risk of ascending infection/sequelae</td>
</tr>
<tr>
<td>Genetic determinants of PID sequelae pathogenesis</td>
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<tr>
<td>Better definition of mucosal immune responses to infection; effects of sex steroid hormones</td>
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<tr>
<td>Is the hsp theory of chlamydial PID immunopathogenesis valid?</td>
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<td>Better animal models</td>
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hsp = heat-shock protein; FVU = first-void urine; STD = sexually transmitted disease; IVF = in-vitro fertilization.

**Prevention of PID**

PID is the most important preventable cause of infertility and adverse pregnancy outcome. PID and its complications are an important public health problem. However, linking the cost of complications to primary and secondary prevention of PID has not been easy. Since *C. trachomatis* is the most common sexually transmitted pathogen and a major cause of PID, it is logical to focus prevention efforts on chlamydia. The asymptomatic nature of cervicitis makes screening for chlamydial infection the mainstay for prevention of PID. Disease prevention can be primary, secondary or tertiary. Tertiary prevention of acute and chronic chlamydial infections of the upper genital tract has largely failed because substantial tubal damage has already occurred by the time symptoms develop, or the patient presents with infertility or ectopic pregnancy. Primary prevention involves preventing both exposure to and acquisition of chlamydial infection through lifestyle counselling and health education. Clinicians play an important role in the primary prevention by asking questions about high-risk sexual behaviour, by encouraging screening tests for those at risk, by ensuring that male sex partners are evaluated and treated, and by counselling about safer sex practices. Although primary prevention by health education has not proved to be very effective so far, studies of the efficacy of primary prevention are slow and extremely complicated to conduct.

Clearly, more emphasis should be directed to primary prevention by implementing health education programmes among adolescents.

Secondary prevention by universal screening is likely to play a critical role in the prevention of PID and long-term sequelae, although this still needs to be proven in randomized controlled intervention trials. Secondary prevention means early detection of subclinical disease by screening in order to prevent (acute) lower genital tract infection from becoming (chronic) upper genital tract infection. Health care and provider behaviours play important roles in secondary prevention. Chlamydial infection fills the general prerequisites for disease prevention by screening, since chlamydial infections are highly prevalent, are associated with significant morbidity, can be diagnosed, and can be treated.

Emerging evidence suggests that systematic screening of asymptomatic populations decreases the incidence of *C. trachomatis* infections. This has been documented both in nationwide screening programmes (Ripa and Bauman, 1995; Figure 5) and in screening programmes performed in other defined populations with stable screening activity (Table V). Furthermore, a recent randomized controlled trial has provided strong evidence that intervention with selective screening for chlamydial infections effectively reduces the incidence of PID (Scholes et al., 1996; Table VI). Recent technological advances should further enhance
efforts to prevent chlamydial infection. These include single-dose therapy using azithromycin (Martin et al., 1992), DNA amplification tests (Lee et al., 1995; Quinn et al., 1996) and the use of first-void urine specimens for the diagnosis (Paukku et al., 1996; Quinn et al., 1996). However, it still remains to be seen whether such intervention will also have a significant effect on the incidence of long-term sequelae. Thus, the socio-economic benefits of prevention largely depend on secondary prevention of short-term and long-term complications of PID. Preliminary cost–benefit analyses demonstrate that the benefits of screening clearly exceed the costs, not only in high prevalence populations (Genc and Mårdh, 1996) but also in low prevalence populations (J.Paavonen et al., unpublished data). Key basic science, clinical science, epidemiological science and behavioural sciences are the areas outlined for future research by the Expert Committee on Pelvic Inflammatory Disease (1991; Table VII).

References


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