**Chlamydia trachomatis: impact on human reproduction**

J.Paavonen\(^1,3\) and W.Eggert-Kruse\(^2\)

\(^1\)Department of Obstetrics and Gynecology, University of Helsinki, Finland and \(^2\)Department of Gynecologic Endocrinology and Reproductive Medicine, Women’s Hospital, University of Heidelberg, Germany

*Chlamydia trachomatis* infections are the most prevalent bacterial sexually transmitted infections (STI) recognized throughout the world. Worldwide, the magnitude of morbidity associated with sexually transmitted chlamydial infections is enormous. *C.trachomatis* is a common cause of urethritis and cervicitis, and sequelae include pelvic inflammatory disease (PID), ectopic pregnancy, tubal factor infertility, epididymitis, proctitis and reactive arthritis. The sharp worldwide increase in the incidence of PID during the past two decades has led to the secondary epidemics of tubal factor infertility and ectopic pregnancy. Chlamydial PID is the most important preventable cause of infertility and adverse pregnancy outcome. Chlamydial infections, like STI in general, are primarily a woman’s health care issue since the manifestations and consequences are more damaging to the reproductive health in women than in men. Based on the available evidence, approximately 20% of women with chlamydial lower genital tract infection will develop PID, approximately 4% develop chronic pelvic pain, 3% infertility, and 2% adverse pregnancy outcome. However, these estimates are based on relatively weak evidence. Research on the link between *C.trachomatis* and male aspects of infertility has been much more limited. Currently recommended treatment regimens include azithromycin in a single dose or doxycycline for 7 days. These therapies are highly efficacious. Timely management of sex partners is essential for decreasing the risk for re-infection. Immunopathogenesis of *C.trachomatis* infection is one of the main focal points of current research into *Chlamydia*. Chlamydial infection fills the general prerequisites for disease prevention by screening, i.e. chlamydial infections are highly prevalent, usually asymptomatic, are associated with significant morbidity, can be reliably diagnosed, and are treatable. Screening programmes for *C.trachomatis* will be of paramount importance in the prevention of long-term sequelae. The cost of screening is only a fraction of the health care costs incurred due to complications resulting from undiagnosed and untreated chlamydial infections. Current strategies to control *C.trachomatis* still largely depend on clinic-based screening of symptomatic patients, and have not been successful. The development of highly sensitive and specific nucleic acid amplification tests for the diagnosis of chlamydial infections has been an important advance in the ability to conduct population-based screening programmes to prevent complications. Thus, the case for screening is clearly made, but much detail remains to be worked out.

**Key words:** *Chlamydia trachomatis*/immunopathogenesis/infertility/prevention/screening/treatment

### TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction</td>
<td>433</td>
</tr>
<tr>
<td>Cell biology of <em>Chlamydia trachomatis</em></td>
<td>434</td>
</tr>
<tr>
<td>Diagnosis of <em>C.trachomatis</em> infections</td>
<td>435</td>
</tr>
<tr>
<td>Clinical manifestation of chlamydial infection in women</td>
<td>435</td>
</tr>
<tr>
<td>Impact on reproduction: female aspects</td>
<td>436</td>
</tr>
<tr>
<td>Impact on reproduction: male aspects</td>
<td>437</td>
</tr>
<tr>
<td>Immunopathogenesis of <em>C.trachomatis</em> infections</td>
<td>441</td>
</tr>
<tr>
<td>Treatment of <em>C.trachomatis</em> infections</td>
<td>442</td>
</tr>
<tr>
<td>Prevention of <em>C.trachomatis</em> infections</td>
<td>443</td>
</tr>
<tr>
<td>References</td>
<td>444</td>
</tr>
</tbody>
</table>

*To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, University of Helsinki, 00290 Helsinki, Finland. Tel: 358 9 47172807; Fax 358 9 47174902; E-mail jorma.paavonen@huch.fi*
health care issue since the manifestations and consequences are more damaging to the reproductive health of women than of men. Worldwide, the magnitude of morbidity associated with sexually transmitted chlamydial infections is enormous.

Cell biology of Chlamydia trachomatis

Chlamydia spp. are intracellular bacteria that need living cells to multiply. The chlamydial chromosome consists of approximately one million base pairs, and has a capacity to encode for up to 600 proteins. There are 18 distinct serotypes of C.trachomatis currently identified. Serotypes D to K cause sexually transmitted genital infections and neonatal infections (Table I). There is no strong evidence that specific genital syndromes or clinical manifestations, such as PID, are serotype-specific. The cell cycle of Chlamydia is distinct from that of all other bacteria. Endocytosis leads to the formation of membrane-bound intracellular inclusions (Figure 1). The ability of Chlamydia to convert from resting to replicating infectious forms within host cells creates increasing difficulties in eliminating this microbe. However, much is not yet understood about specific mechanisms in the membrane events, attachment and endocytosis, multiplication of the organism in the cell, transformation from metabolically inactive elementary body (EB) into metabolically active replicative reticulate body (RB), and expression of different chlamydial antigens during the cell cycle. However, the amount of new information on the cell biology of Chlamydia infection that has emerged recently has been enormous. Richard S.Stephens and his colleagues from Stanford have recently sequenced the first Chlamydia genome (Stephens et al., 1998) Analysis of the 1,042,519-base pair C.trachomatis genome has revealed unexpected features related to the complex biology of Chlamydia, and several potential virulence-associated proteins have been characterized. The phylogenetic mosaic of chlamydial genes implies a highly complex evolution for adaptation to obligate intracellular existence (Stephens et al., 1998). Since molecular mimicry between microbial proteins and endogenous molecules has been implicated in various autoimmune diseases, it is now possible to provide in more detail in-vivo and in-vitro evidence of a causal link between C.trachomatis infection and specific disease syndromes. This molecular information has already revolutionized approaches to study these unique obligate intracellular pathogens.
Chlamydial infection begins by contact of infectious EB with the apical epithelial surface of a target cell (Beatty et al., 1994). The specific interaction triggers a series of early events which helps programme the Chlamydia and prime the host cell for productive infection. Proposed mechanisms of Chlamydia uptake are parasite-specified phagocytosis, receptor-mediated endocytosis and pinocytosis. Chlamydia primes the host cell early for its obligate intracellular growth and inclusion development. Early intracellular fate and early chlamydial gene expression results in vacuole modification to ensure trafficking of EB to the exocytic pathway. Chlamydia goes through a development cycle involving transition of EB to RB, RB to RB via binary fission, maturation of RB to EB, and release of infectious EB. C. trachomatis develops a single inclusion in which glycogen is retained. Glycogen may provide an extra energy source within the C. trachomatis inclusion.

### Diagnosis of C. trachomatis infections

Nucleic acid amplification tests (NAAT) must be considered the tests of choice for diagnosing C. trachomatis infection (Black, 1997; Puolakkainen et al., 1998). The NAAT for the first time provide diagnostic tests for C. trachomatis that are more sensitive than culture or antigen tests. Polymerase chain reaction (PCR) and ligase chain reaction (LCR) each target nucleotide sequences in the chlamydial cryptic plasmid. The plasmid is present at approximately 7 to 10 copies per elementary body, thus giving a sensitivity advantage over a chromosomal DNA target. Comparative studies of the performance of PCR and LCR suggest that the two tests perform similarly for both urogenital specimens and urine, each providing sensitivities over 90% (Black, 1997; Puolakkainen et al., 1998; Ostergaard, 1999), and NAAT have very few false-positive result-specificities approaching 100%. In some studies, reproducibility has been a problem with Amplicor PCR (Peterson et al., 1997), suggesting that reproducibility should be carefully tested before amplification tests are routinely used in clinical laboratories.

The NAAT have another major advantage in that they can be used with first void urine (FVU) specimens, and even with self-obtained vaginal or vulvar swabs. If a woman is undergoing a pelvic examination, a specimen should be collected from the cervix. However, if a pelvic examination is not performed, a urine specimen may be tested with reasonable assurance of obtaining an accurate result.

Although the NAAT are more expensive than the antigen tests, they still should be considered the tests of choice because they will detect many more infected individuals. It is cost-effective to use the more expensive test because the management of complications of chlamydial infections is very expensive. Detecting and treating the maximal number of infections is the goal of Chlamydia screening programmes. The use of non-invasive specimen collection, with no requirement for a physical examination for specimen collection to diagnose chlamydial infection will have a major impact on Chlamydia control programmes in the near future. The bottom line is that the prevalence of C. trachomatis infection in young populations is more than enough to justify broad-based use of screening using NAAT (Stamm, 1998). There is reason to be optimistic that expanding such screening programmes will have a dramatic effect in reducing the incidence and complications of genital C. trachomatis infection. Since asymptomatic infection is common in both men and women, screening sexually active adolescents for chlamydial infections should be routine during annual health examinations, even if symptoms are not present. Screening women aged 20–24 years is also suggested, particularly for those who have new or multiple sex partners and who do not consistently use barrier contraceptives (Centers for Disease Control and Prevention, 1998). Repeat screening would further lower the baseline prevalence of C. trachomatis infection, thus, making universal screening less favourable. More targeted screening approaches would then be required to maintain an acceptable cost-benefit (Paavonen et al., 1998b).

### Clinical manifestation of chlamydial infection in women

C. trachomatis is the major cause of mucopurulent cervicitis (MPC) (Brunham et al., 1984) and PID in women (Márđth et al., 1977). Urethritis or acute urethral syndrome is often associated with chlamydial cervicitis (Stamm et al., 1980). Chlamydial MPC can lead to at least three types of complications: (i) ascending intraluminal spread of organisms from the cervix, producing PID (McCormack, 1994); (ii) ascending infection during pregnancy resulting in premature rupture of the membranes, chorioamnionitis, premature delivery, and puerperal and neonatal infections (Beem and Saxson, 1977; Martin et al., 1982; Gravett et al., 1986; Gencay et al., 1995); and (iii) the development of cervical neoplasia. Although oncogenic types of human papillomavirus clearly cause most, if not all,

### Table I. Spectrum of human diseases caused by Chlamydia trachomatis

<table>
<thead>
<tr>
<th>Species</th>
<th>Acute diseases</th>
<th>Sequelae/chronic diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. trachomatis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotypes A–C</td>
<td>Conjunctivitis</td>
<td>Trachoma</td>
</tr>
<tr>
<td>Serotypes D–K</td>
<td>Urethritis, cervicitis</td>
<td>Proctitis, epidemicitis, Reiter’s syndrome, pelvic inflammatory disease, ectopic pregnancy, tubal infertility</td>
</tr>
<tr>
<td>LGV serotypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>neonatorum</td>
<td>Lymphogranuloma</td>
<td>Neonatal pneumonia</td>
</tr>
<tr>
<td>venerum</td>
<td>Lymphogranuloma</td>
<td></td>
</tr>
</tbody>
</table>
cervical carcinomas. *C. trachomatis* seems to play an important cofactor role (Paavonen et al., 1998a).

Although simple objective criteria (endocervical mucopus, erythema, oedema, induced mucosal bleeding) have been developed for the presumptive diagnosis of MPC (Brunham et al., 1984), most cases of chlamydial cervicitis are asymptomatic or minimally symptomatic, and show no specific clinical signs. Approximately half of all women with chlamydial infection have the infection both in the cervix and the urethra, one-third in the cervix only, and approximately 15–25% in the urethra only. Specific colposcopic (immature metaplasia), cytological (endocervical cell atypia, metaplastic cell atypia) and histopathological manifestations of chlamydial cervicitis have been described (Kivistö et al., 1985, 1990; Paavonen et al., 1988). Histopathological findings associated with chlamydial cervicitis include plasma cell infiltrations of cervical stroma, intraepithelial and intraluminal inflammation, and well-formed lymphoid follicles comprising transformed lymphocytes. PID refers to infection of the uterus, Fallopian tubes and adjacent pelvic structures that is not associated with surgery or pregnancy (McCormack, 1994). *C. trachomatis* is the major cause of PID not associated with pregnancy or invasive surgical procedures. The clinical spectrum of chlamydial PID ranges from subclinical endometritis to frank salpingitis, tubo-ovarian abscess, pelvic peritonitis, periappendicitis and perihepatitis. Most studies of chlamydial PID have focused on in-patients with acute symptoms and severe disease. However, such cases may represent only the tip of the iceberg of all chlamydial infections of the upper genital tract. The relative role of *C. trachomatis* in PID has increased as the gonorrhoea rates have recently dramatically decreased in many developed countries (Hiltunen-Back et al., 1998; Kamwendo et al., 1998). An increasing proportion of cases with chlamydial PID are atypical or silent. Simultaneously, there has been a dramatic drop in the incidence of in-patient PID. Hospitalizations of women with PID have rapidly decreased, which is probably due to a change in the clinical manifestations of PID (Kamwendo et al., 1998). However, this does not necessarily mean that the overall incidence of PID has decreased. In fact, minimally symptomatic patients usually delay in seeking medical care, which may further increase the risk for tubal damage and long-term sequelae (Hillis et al., 1993). Demonstrations of plasma cell endometritis by endometrial biopsy in women with MPC in the absence of symptoms or signs of PID has also focused attention on silent chlamydial infection of the upper genital tract (Paavonen et al., 1985). Studies have shown that not just clinical PID but also silent PID is associated with permanent tubal damage (Patton et al., 1989).

### Impact on reproduction: female aspects

The sharp worldwide increase in the incidence of PID during the past two decades has led to the secondary epidemics of infertility and ectopic pregnancy. Chlamydial PID is the most important preventable cause of infertility and adverse pregnancy outcome. The proportion of tubal factor infertility among all infertility ranges from less than 40% in developed countries to up to 85% in developing countries (World Health Organization, 1987). After a single episode of PID, the relative risk for tubal factor infertility is approximately 10%. Each repeat episode of PID doubles the risk so that it is approximately 20% after two episodes, and almost 40% after three or more episodes (Weström, 1980, 1994).

Seroepidemiological studies suggest that chlamydial infection may account for a large proportion of cases of tubal factor infertility and ectopic pregnancy. These studies have demonstrated a strong link between serum antibodies (Ab) to *C. trachomatis* and tubal factor infertility or ectopic pregnancy, both in women with or without self-reported history of PID (Cates and Wasserheit, 1991). Most women who have tubal factor infertility have never been diagnosed as having chlamydial infection or PID. Persistent chlamydial infections have been established in cell culture systems. Undoubtedly, unrecognized infection can progress, ascending to the upper genital tract and resulting in PID. A large proportion of *C. trachomatis* infections of the Fallopian tubes are asymptomatic or subclinical. This suggests that silent infections in fact are the most common cause of tubal infertility, as only a small proportion of such women have a history of frank PID. Thus, symptomatic PID is not a prerequisite for eventual development of tubal damage. Results of both epidemiological studies and animal model studies are consistent with the hypothesis that both symptomatic and asymptomatic *C. trachomatis* infection of the female genital tract can induce reproductive tract damage.

The first study linking past chlamydial infection and tubal factor infertility was published in 1979 (Pumpeen et al., 1979). In that study, the mean antichlamydial Ab titre of patients with bilateral tubal obstruction was significantly higher than that of infertile patients with normal hysterosalpingogram (HSG). In a recent meta-analysis (23 studies, 2729 patients), the discriminative capacity of chlamydial Ab titres in the diagnosis of any tubal pathology was comparable with that of HSG in the diagnosis of tubal occlusion (Mol et al., 1997).

Interestingly, ciliary activity in distal Fallopian tube biopsies of patients with tubal infertility varies by chlamydial serotype pattern, suggesting serotype-specific differences in virulence (Leng et al., 1998). Antibody to chlamydial 60 kDa heat-shock protein (HSP60) is strongly associated with occluded Fallopian tubes, but not with acute *C. trachomatis* infection (Eckert et al., 1997), suggesting that chlamydial HSP60 plays an important role in the immunopathogenesis of chlamydial infection. Similarly, plasma cell salpingitis in patients with tubal pregnancy correlates with serum Ab to HSP60 epitopes (Sziller et al., 1998). Antibody to HSP60 may indicate long-standing infection with persistent chlamydial antigen. Tubal factor infertility remains the most common indication for in-vitro...
fertilization (IVF) (Templeton et al., 1996; Templeton and Morris, 1998). Worldwide, huge amounts of money are spent on PID sequelae. The cost of IVF, most often performed for post-PID tubal factor infertility, is extremely high (Neumann et al., 1994). Several studies have specifically addressed the issue of whether serological evidence of past chlamydial infection affects IVF outcome. Most studies have found no differences in pregnancy rates or outcomes between patients with or without serological evidence of previous C.trachomatis infection (Osser et al., 1990; Claman et al., 1996). Several studies have also examined the impact of hydrosalpinx formation on IVF outcome. Most, but not all (Sharara et al., 1996), studies have suggested that the presence of hydrosalpinx is associated with decreased implantation rate, decreased pregnancy rate and increased early pregnancy loss. However, prospective studies of the effects of treatment of hydrosalpinx by tubal ligation, salpingectomy or tubostomy are needed in order to answer more definitively the question of the effect of hydrosalpinx on IVF outcome.

Adverse pregnancy outcome is another major complication of chlamydial infection. Ectopic pregnancy is the main cause of maternal mortality in the first trimester of pregnancy in developing countries. In the United States, deaths resulting from ectopic pregnancy account for 9% of all pregnancy-related mortalities. Women with a history of PID have 7- to 10-fold increased risk of tubal pregnancy compared with women with no history of PID (Weström, 1980; Weström et al., 1981). The incidence of ectopic pregnancy has been increasing during the past two decades. Ectopic pregnancy is also a marker of subsequent repeat ectopic pregnancy and infertility, the recurrence rate of ectopic pregnancy being approximately 20%.

In addition to infertility and ectopic pregnancy, other morbidity is also associated with history of PID, such as chronic pelvic pain caused by extraluminal scarring. Chronic pelvic pain following PID occurs in between 24% and 75% of women. In one study, women with a history of PID were 10 times more likely to be admitted for abdominal pain, four times more likely to be admitted for gynaecological pain, six times more likely to be admitted for ectopic pregnancy, and hysterectomy rates were approximately eight times higher (Buchan et al., 1993) than in the controls. Thus, women with PID suffer substantial long-term gynaecological morbidity later in their lives.

There is some evidence that C.trachomatis may also contribute to pregnancy complications other than ectopic pregnancy (Martin et al., 1982; Gravett et al., 1986), including premature rupture of membranes, preterm birth, low birth weight and stillbirth. Early pregnancy loss or recurrent pregnancy loss may be induced by asymptomatic C.trachomatis infection through the operation of immune mechanisms (Witkin and Ledger, 1992; Witkin, 1995; Witkin et al., 1998) although not all studies have found such a link (Paukku et al., 1999).

Impact on reproduction: male aspects

Compared with the data available on C.trachomatis infection in women, our knowledge concerning the impact of chlamydial infection on male fertility is much more limited. The clinical significance of C.trachomatis for non-gonococcal urethritis (NGU) and accessory sexual gland infection in men has been established during the past two decades (Holmes et al., 1975; Berger et al., 1978; Terho, 1978; Bruce et al., 1981; Suominen et al., 1983; Grant et al., 1987; Pearson et al., 1988; Paavonen and Wolner-Hanssen, 1989; Weströ, 1990; Pearlman and McNeeley, 1992; Zelin et al., 1995). NGU is the most common clinical genital syndrome seen in the male, and C.trachomatis is the most important aetiological agent for NGU, which may be complicated by epididymitis. In young men, ‘idiopathic’ epididymitis is often caused by C.trachomatis. Chlamydial proctitis may occur in homosexual men. Most cases of ocular chlamydial infection have a genital source (Garland et al., 1995). Little attention has been paid to another extra-genital manifestation—chlamydia-induced arthritis (CIA)—although it has been shown that 21% of patients with unexplained arthritis had urogenital chlamydial infection (Wollenhaupt et al., 1995). To recognize CIA it is necessary to examine male patients for C.trachomatis, even if they are asymptomatic. Reiter’s syndrome, including urethritis, uveitis and arthritis, is more frequent in men than in women (Pearlman and McNeeley, 1992).

The prevalence of male chlamydial infection is highly dependent on age, number of sex partners and socioeconomic factors. Chlamydial infections of the male are asymptomatic, or offer only discrete signs of infection in the majority of patients. Asymptomatic infections are of particular concern because of the risk of transmission to female partners resulting in PID, ectopic pregnancy or infertility. Attachment of C.trachomatis to spermatozoa has been demonstrated in vitro (Wolner-Hansen and Märdh, 1984), and spermatozoa with attached Chlamydia have been observed in the cul-de-sac fluid of women with acute salpingitis (Friberg et al., 1987). Spermatozoa may serve as vectors for C.trachomatis. It has been hypothesized that as ‘bacterial hitchhikers’, these microorganisms might reach the female upper genital tract in a very short time after coitus.

Apart from sexual transmission, transmission of C.trachomatis by artificial insemination has been demonstrated (Nagel et al., 1986), and persistence after cryoconservation (Sherman and Jordan, 1985). This is particularly important in case of donor inseminations, and further underlines the necessity of careful and frequently repeated donor screening for this and other sexually transmitted diseases (STD) (Marks et al., 1990). Little is known about the potential transmission of C.trachomatis with other methods of assisted reproduction such as IVF or intracytoplasmic sperm injection (ICSI).
The role of *C. trachomatis* with regard to inducing male factor infertility is a matter of debate. Chlamydial infection could potentially exert a strong influence on male fertility, as it is the main cause of urethritis and accessory gland inflammation in men. Sequelae of ascending infections might be occlusions in the canalicular system of the genital tract, damage of the epithelial cells involved in spermatogenesis, and immunoreaction with the production of anti-sperm antibodies (ASA). *C. trachomatis* epididymitis and urethritis have been provoked experimentally in a male monkey model (Moller and Märdh, 1980), in mice (Kuzan *et al.*, 1989) and in rats (Jantos *et al.*, 1992). Many observations support that STD infections of the male may cause obliterations or occlusions in the genital tract. In the pre-antibiotic era, both gonococcal and ‘unspecific’ bilateral epididymitis caused infertility in a considerable proportion of cases (Berger, 1990). In acute epididymitis, damage to the tubular tracts and to the cells involved in spermatogenesis have been demonstrated (Nilsson *et al.*, 1968; Berger, 1990; Villegas *et al.*, 1991). Histopathological changes of *C. trachomatis* epididymitis differ considerably from bacterial infection of this organ (Hori and Tsutsumi, 1995). When epididymitis is accompanied by orchitis, this may cause testicular atrophy and decreasing sperm production (Berger, 1990). However, in unselected males of subfertile couples, azoospermia due to occlusions or complete testicular atrophy is a very rare phenomenon (<1% in our population).

The relationship of chlamydial infection with semen quality is controversial (Close *et al.*, 1987; Eggert-Kruse *et al.*, 1987, 1990; Custo *et al.*, 1989; Ruijs *et al.*, 1990; Wolff *et al.*, 1991, 1994; Bjercke and Purvis, 1992; Munoz and Witkin, 1995; Witkin *et al.*, 1995), One problem when analysing a potential association with reduced fertilizing capacity was the lack of adequate non-invasive screening methods for detection of asymptomatic chlamydial infection in the male genital tract. For use in semen samples, McCoy cell culture is an inappropriate procedure due to cytotoxic effects of seminal plasma on cell layers (Märdh *et al.*, 1980). Enzyme immunoassays (EIA) developed to detect chlamydial antigens are compounded by low sensitivity. Amplification techniques with a higher sensitivity have now been introduced and are replacing cell culture techniques (Jeremias and Witkin, 1996; Ridgway *et al.*, 1996). The potential to screen large groups of males for *C. trachomatis* is offered by urine-based strategies. Urine testing performs well when compared with urethral swabs (Chernesky *et al.*, 1994; van Doornum *et al.*, 1995). In asymptomatic patients, it has to be shown if the cost-effectiveness can be improved by pre-screening for leukocytes or other seminal markers (Shafer *et al.*, 1993). Amplification methods may also be used in semen (van den Brule *et al.*, 1993; Wolff *et al.*, 1994; Dieterle *et al.*, 1995), although inhibitors in ejaculates might interfere with this procedure.

The use of LCR/PCR to examine urine and genital secretion samples is a promising means to screen large populations, and this will offer more information about the impact of *C. trachomatis* on male fertility in the near future. Screening in unselected asymptomatic males of subfertile couples by urethral swabs, examined either with cell culture, EIA or amplification techniques, usually showed low prevalences of these microorganisms which did not allow sufficient statistical evaluation (Hellström *et al.*, 1987; Wolff *et al.*, 1994; Weidner *et al.*, 1996; Kjaergaard *et al.*, 1997). Therefore, our current knowledge is mainly based on serological studies for either anti-chlamydial antibodies (Chlam Ab) in serum or in local secretion (mostly in seminal plasma). Anti-chlamydial IgG Ab are used as markers for previous exposure to these microorganisms (Puolakkainen *et al.*, 1986).

In studies from different countries, no convincing evidence was found to demonstrate a significant relationship between previous exposure to *C. trachomatis* and semen quality (Close *et al.*, 1987; Eggert-Kruse *et al.*, 1987, 1990; Gregoriou *et al.*, 1989; Ruijs *et al.*, 1990; Bjørke and Purvis, 1992; Dieterle *et al.*, 1995; Weidner *et al.*, 1996). A weak relationship with semen abnormalities was shown by early reports in patients attending a genitourinary medicine clinic (Custo *et al.*, 1989), and in a small group of serologically positive males (Hodgson *et al.*, 1990), but this was not proven by other studies. However, a markedly higher incidence of Chlam Ab was noted in patients with obstructive azoospermia ( Gerrits *et al.*, 1985).

In unselected subfertile males, the lack of relationship of serum Chlam Ab with semen quality could be shown, for example with regard to sperm count, motility, ejaculate volume, total count, total motility, pH, viability, fructose concentration and morphological characteristics, determined according to WHO classification and the so-called ‘strict’ or ‘Norfolk’ morphological criteria (Ruijs *et al.*, 1990; Eggert-Kruse *et al.*, 1995a, 1997a; Weidner *et al.*, 1996). Serological results were not associated with the outcome of clinical andrological examination. Serum anti-chlamydial Ab were also not related to other tests evaluating sperm functional capacity. Sperm ‘intrinsic motility’ as an important indicator of sperm function may be examined with spermatozoa-cervical mucus (CM) penetration testing, which corresponds to sperm fertilizing capacity (Ulstein, 1972; Eggert-Kruse *et al.*, 1989a; Bostofte *et al.*, 1992). The use of fresh human CM, particularly when obtained from patients’ partners, provides an excellent multidetermined filtering system. When partners’ CM was used for the standardized in-vitro sperm penetration test (SCMPT), taking into account penetration distance, number of penetrated spermatozoa, motility grade and duration of motility in CM, the outcome was not impaired in Chlam Ab-positive males. This could also be demonstrated with CM of donors in the crossed penetrability test (Eggert-Kruse *et al.*, 1997a). No significant relationship was found between chlamydial IgG Ab in serum and results of the hamster oocyte test (sperm
penetration assay) (Close et al., 1987). Post-coital testing (PCT) is an integral part of basic infertility investigation (Hull et al., 1982; Eimers et al., 1994), but the outcome was not influenced by the presence of Chlam Ab in large groups of subfertile couples. This could be shown for PCT in spontaneous cycles, as well as under hormonally standardized conditions and after control for other influencing variables such as cervical index or pH (Eggert-Kruse et al., 1990, 1997b).

In asymptomatic patients, Chlam Ab in serum were not associated with subclinical male genital tract infection as indicated by elevated white blood cell (WBC) counts in semen or an increased leukocyte ratio of the seminal round cells (Close et al., 1987; Eggert-Kruse et al., 1992). In recent studies, there was also no relationship with other potential infection or inflammation markers such as the complement fraction C3, or some cytokines [e.g. interleukin (IL) 6, or IL-8] in same-day seminal plasma samples, or with IgA Ab to the human 60 kDa HSP (Eggert-Kruse et al., 1998a,b, 1999).

With regard to subsequent fertility in prospective studies, pregnancy rates, under in-vivo conditions of conception, in couples with a male partner showing elevated titres of Chlam IgG Ab in serum were significantly reduced. However, this was caused by tubal factor infertility, and not by poor semen quality (Eggert-Kruse et al., 1990). No difference between subfertile males and fertile controls (Auroux et al., 1987) and, in an IVF programme, no differences in the fertilization rate of semen of Chlam Ab-positive or -negative men was found (Torode et al., 1987). Infertility or subfertility is always a problem not only of individuals, but also of couples. The relationship of chlamydial serology with the male factor was further evaluated in a population of 1303 asymptomatic, involuntarily childless couples (median duration of infertility was 4 years). A comprehensive infertility investigation was performed. Simultaneous screening for Chlam Ab in the serum of both partners confirmed that elevated Chlam Ab levels were significantly more frequent in consorts of seropositive patients (in 52% of women with a Chlam Ab-positive partner, compared with 16% of the other women). After exclusion of couples with a tubal infertility factor, semen quality and fertilizing capacity as determined by pregnancy rates was not impaired in Chlam Ab-positive male patients. In this subgroup of more than 800 patients, pregnancy (in vivo) was achieved within 6 months in 20% of couples with elevated IgG titres of the male partner compared with 22% of the other couples (Eggert-Kruse et al., 1997a).

These studies suggest that chlamydial serology in asymptomatic men is not helpful in identifying risk groups for male factor infertility. On the other hand, Chlam Ab in serum as marker for previous exposure to this microorganism might not sufficiently reflect the situation in the male genital tract, because of the blood–testis barrier. IgA is a locally produced immunoglobulin, and assays to detect anti-chlamydial IgA in seminal plasma [mostly major outer membrane protein (MOMP) -directed immunoassays or recombinant chlamydial lipopolysaccharide (LPS) fragment-directed enzyme-linked immunosorbent assays (ELISA)] have been used by several groups to detect asymptomatic chlamydial infection. However, the problem with many commercial tests for routine use is that chlamydial infection can only be identified to the genus level (Moss et al., 1993).

Findings in different subfertile populations did not demonstrate a marked association of local Chlam IgA Ab in clinically asymptomatic patients with standard variables of semen quality such as sperm count, motility or morphology, ejaculate volume or pH (Bjercke and Purvis, 1992; Dieterle et al., 1995; Munoz and Witkin, 1995; Weidner et al., 1996). This was shown when using chlamydial MOMP- or LPS-directed assays. Furthermore, the presence of Chlam IgA antibody in semen samples did not influence the outcome of PCT, or sperm ability to penetrate cervical mucus in vitro when the standardized SCMPT was used to evaluate sperm function (Eggert-Kruse et al., 1996a,b).

Some correlation of local Chlam Ab with reduced volume and sperm motility, associated with an inflammatory response was found in an early study (Wolff et al., 1991). Later, a higher concentration of yud T cells in semen in a small group of patients was reported (Munoz and Witkin, 1995), while others (Bjercke and Purvis, 1992) found an increased seminal leukocyte count in samples with seminal plasma anti-chlamydial IgA; however, this was not related to semen quality in either study. No marked association of seminal Chlam IgA Ab with subclinical male genital tract infection could be demonstrated in other studies which used an immunocytological approach to detect seminal leukocytes in aliquots of the same ejaculates (Eggert-Kruse et al., 1996a). Leukocytes are considered as an established infection and inflammation marker, and a count of >1×10^6/ml WBC in semen has been recommended by WHO as a critical cut-off for leukocyto-spermia (Comhaire et al., 1980). However, the role of seminal leukocytes for male fertility has been the subject of considerable controversy (Eggert-Kruse et al., 1992; Tomlinson et al., 1993; Wolff, 1995; Yanushpolsky et al., 1995). More information might be obtained by further differentiation of the WBC to evaluate the impact of certain subpopulations and localization of genital tract inflammation (Baratt et al., 1990).

In patients with local Chlam IgA, increased levels of polymorphonuclear (PMN) elastase have been found in seminal plasma (Wolff et al., 1991). The PMN elastase is secreted by activated granulocytes and is considered a suitable inflammation marker (Wolff and Anderson, 1988). Concentrations of this enzyme in seminal plasma correlated significantly with the number of WBC in semen (Eggert-Kruse et al., 1996c). However, in unselected subfertile males this seminal marker was not related to local serological findings. Furthermore, albumin as a relatively stable constituent of seminal plasma indicating an impaired blood–testis barrier induced by inflammation did not correlate with the presence of anti-chlamydial IgA in semen. This could also be shown with
regard to other biochemical parameters used to detect subclinical male genital tract infection or inflammation, such as the C3 fraction of complement (Blenk and Hofstetter, 1991) or cytokines in seminal plasma, which may indicate a local inflammatory response. No association of IL-8 and IL-6 with anti-chlamydial IgA Ab in semen was found (Eggert-Kruse et al., 1998b).

The role of chlamydial HSP or human HSP-directed IgA Ab, potentially indicating an autoimmune response to *C. trachomatis* in males, must be substantiated in future studies. In an unselected group of asymptomatic patients, seminal plasma IgA Ab to the human 60 kDa HSP was associated significantly with seminal anti-chlamydial IgA (Eggert-Kruse et al., 1997c), confirming results of others who determined HSP60 in semen (Munoz et al., 1996). This might suggest that chronic subclinical infection of the male genital tract may result in induced expression of the cross-reactive human HSP60 in some men. However, the presence of HSP60 IgA Ab *per se* in the seminal plasma of subfertile males was not significantly related to semen quality, as determined with standard semen analysis, sperm functional capacity or fertilizing capacity (Eggert-Kruse et al., 1999).

The presence of seminal Chlam Ab is not associated with male fertility, but these local Ab are associated with a tubal infertility of female partners (Eggert-Kruse et al., 1996a). These results indicate that, in asymptomatic patients, the presence of Chlam IgA or IgG Ab in semen determined with the currently available assays does not indicate reduced sperm functional capacity or subclinical male genital tract infection in unselected low-risk populations.

In males without symptoms of genital tract infection, chlamydial serology was not associated with other aerobic or anaerobic bacteria detected by simultaneous semen cultures (Eggert-Kruse et al., 1995b, 1997a). Seroepidemiological findings also show a poor correlation between direct methods of detection of *C. trachomatis* in the male genital tract, and either EIA, culture or amplification methods (Wolff et al., 1994; Dieterle et al., 1995; Eggert-Kruse et al., 1996a, 1997; Weidner et al., 1996).

In patients with culture-positive urethral swabs, no relationship with semen quality was found. In a group of males, selected because of a positive or negative PCT, and including males with prostatovesciculitis, a relatively high prevalence of *Chlamydia* by urethral swabs was reported (Soffer et al., 1990). Half of these patients were also infected with mycoplasmas, but no differences were found in sperm count, motility and morphology compared with the other uninfected patients, and no impairment in hamster oocyte testing (Soffer et al., 1990). Positive urethral cultures associated with an impaired motility pattern in some men was reported by other authors (Diquelou et al., 1989). Among a group of five infected patients, detected by amplification methods of semen, a reduced sperm count was identified in two cases (Dieterle et al., 1995). Parallel screening of FVU and semen, and FVU and cervical swabs of their female partners in our unit (by means of the LCR) identified genital *C. trachomatis* in 2.2% (7/402) either in one or both partners of asymptomatic subfertile couples (0.8% of 402 women and 1.7% of 402 men). No evidence of markedly impaired semen quality and sperm function was noted in these *C. trachomatis*-positive patients. However, the number of *C. trachomatis*-infected patients was too small to draw meaningful conclusions (W.Eggert-Kruse, unpublished observations).

A frequently discussed mechanism regarding how *C. trachomatis* might influence male fertility is the induction of immune-phenomena resulting in the production of ASA (Soffer et al., 1990; Munoz and Witkin, 1995; Witkin et al., 1995). In general, infections of the male or female genital tracts might induce an immune response, leading to the production of ASA in serum or in genital secretions (Witkin and Toth, 1983; Ingerslev et al., 1986; Shamanesh et al., 1986). Cross-reactivity between certain epitopes on the bacterial surface and spermatozoa—particularly involving carbohydrate determinants—might be one potential triggering mechanism for the induction of ASA (Kurpisz and Alexander, 1995). Furthermore, epididymitis could result in unilateral epididymal obstruction, a condition supposed to be associated with the induction of sperm Ab (Hendry, 1989).

Sperm Ab can be detected in serum (circulating ASA) and/or in genital tract fluids, e.g. semen or CM (local ASA). These Ab show poor correlation between systemic and local findings. The clinical significance of circulating ASA is a matter of considerable debate (Bronson et al., 1984; Kremen and Jager, 1988; Schumacher, 1988; Hendry, 1989; Marshburn and Kutteh, 1994; Eggert-Kruse et al., 1995b, 1995c). Local ASA may be important regarding subsequent fertility. A higher frequency of ASA in a group of males infected either with *Chlamydia* or mycoplasmas, or both (but not in the *Chlamydia*-only group) has been reported (Soffer et al., 1990). An association has also been shown between serum Ab to *Chlamydia* and agglutinating serum sperm Ab, but not with other types of sperm ASA (Close et al., 1987). Other studies have not found any relationship between anti-chlamydial IgG Ab in serum and circulating anti-sperm Ab. This has been shown using several different assays for immunological screening, e.g. the tray-agglutination test (TAT) (Friberg, 1974), radio-immunoassays (RIA), and two different types of ELISA for the detection of circulating sperm Ab (Eggert-Kruse, 1989b, 1993a, 1995c; Dieterle et al., 1995).

Sperm Ab in semen—particularly of the IgA class—are more important as they may exert a strong influence on sperm functional quality, e.g. the ability to penetrate CM, and thus may considerably impair subsequent fertility (Kremen and Jager, 1988; Schumacher, 1988; Eggert-Kruse et al., 1991; Andreou et al., 1995). A *Chlamydia*-triggered immune response was suggested (Munoz and Witkin, 1995) which induced local ASA as an important pathogenic pathway in male fertility and, in a group of patients selected because of suspected immunological infertility, a significant association of genus-specific IgA was reported, with results of immunobead testing (IBT) to detect seminal ASA (Munoz and Witkin, 1995; Witkin et al., 1995).
However, in large groups of unselected asymptomatic males of subfertile partnerships, there was no association with Chlam Ab in seminal IgA Ab in semen when the direct mixed antiglobulin reaction (MAR) test was used for ASA screening (Eggert-Kruse et al., 1997, 1998a). The MAR test is a reliable method for detection of seminal ASA (Jager et al., 1978, 1980; Marshburn and Kutteh, 1994; Andreou et al., 1995). A relationship of serum Ab to Chlamydia in women with male partners with ASA in their semen (detected with IBT in selected couples), as suggested previously (Witkin et al., 1996) could not be proven in large groups of unselected subfertile couples when the more specific MAR test was used for IgG and lgA ASA detection in semen (Eggert-Kruse et al., 1995c, 1998a; Witkin et al., 1995). Population characteristics are important for the consideration of C. trachomatis infection, and might lead to conflicting results.

Findings in patients without signs or symptoms of genital tract infection do not exclude induction of ASA in the local compartment, in men with acute infection of the accessory sexual glands. Follow-up studies of Chlamydia-infected patients are needed to evaluate this further. However, when elevated leukocyte counts, increased concentrations of PMN elastase, or IL-6 and IL-8 were used as markers of subclinical infection in subfertile males, there was no relation to local ASA production. There was also no evidence for any correlation of lgA Ab directed to the human HSP60 with local ASA of the IgG or IgA class (Eggert-Kruse et al., 1999).

Future efforts are necessary to analyse the role of C. trachomatis in the pathogenesis of male infertility, and to evaluate the significance of an autoimmune response in males. One of the problems is that most studies have started only after infertility had already developed. Prospective follow-up studies of infected men using highly sensitive and specific methods are necessary to analyse further the impact of C. trachomatis on the male factor. Fertility is always a problem of couples, and therefore female infertility factors have also to be taken into account. In asymptomatic patients with a long history of infertility, screening for current C. trachomatis infection seems to be too late, as the sequelae are already apparent. Chlamydial serology suggests that a high percentage of asymptomatic subfertile males have been infected with these microorganisms. Screening for C. trachomatis in large groups of young men is necessary to avoid long-term consequences, particularly in women. Screening and identifications of infected males, followed by appropriate treatment, will reduce the burden of infertility.

**Immunopathogenesis of C. trachomatis infections**

C. trachomatis is a strong immunogen which stimulates both humoral and cell-mediated immune responses. In addition to the immunogenetic antigens, the outcome of C. trachomatis infection depends on interaction and balance of cytokines secreted by the activated lymphocytes. Interferon-γ (IFN-γ), a typical product of T helper (Th1) cells, has been described as a single most important factor in host defence against Chlamydia, while disease susceptibility has been linked with enhanced expression of IL-10, a marker of T helper 2 (Th2) cell activation (Beatty et al., 1993). Immune system perturbations induced by C. trachomatis may in fact assist its own survival in the infected host, and induce persistent infections. Several previous clinical or epidemiological observations suggest that there is an intimate relationship between Chlamydia and the host immune system (for a review, see Paavonen and Lehtinen, 1996). Such observations suggest that a single acute episode of chlamydial infection persists and cannot account for all the striking pathology associated with Chlamydia disease. Persistent inflammation after proper curative therapy for chlamydial infection has been a puzzling phenomenon in many clinical studies. For instance, persistent inflammation of the cervix that could not be explained by relapse or re-infection was still present three months after proper curative therapy in one-third of women treated for chlamydial PID (Paavonen et al., 1989). Similarly, not only adhesion formation and tubal occlusions but also persistent striking inflammation of the Fallopian tubes was frequently seen during second-look laparoscopy which was performed 4–6 months after the index episode of PID (Teisala et al., 1987). Experimental studies in the monkey ‘pocket’ model support the role of T-cell response to HSP60 in the pathogenesis of chlamydial salpingitis (Patton et al., 1994). Pig-tailed monkeys were sensitized by inoculation of live C. trachomatis organisms into subcutaneous pockets containing salpingeal autotransplants. When recombinant chlamydial HSP60 was injected into such pockets, either previously sensitized or not sensitized in the same monkey, a typical delayed hypersensitivity reaction was observed. However, much less is known of the cell-mediated immune response to HSP in humans (Beatty et al., 1994). Induction of Th1- or Th2-type T helper cell response may be an important determinant of chlamydial disease pathogenesis. Th1 response induces IFN-γ, which turns on the efferent arm of the cell-mediated immunity. High concentrations of IFN-γ have been detected in endocervical secretions of patients with chlamydial cervicitis, and in the sera of patients with chlamydial PID (for reviews, see Beatty et al., 1994; Paavonen and Lehtinen, 1996). Many in-vitro studies have shown that treatment of infected cells with IFN-γ limits the replication of Chlamydiae. Interestingly, IFN-γ mediates the development of atypical chlamydial forms in vitro (Beatty et al., 1994). These persistent organisms not only exhibit a highly unusual intracellular morphology but also display differential expression of key chlamydial antigens (Beatty et al., 1994). Such atypical forms display reduced levels of chlamydial MOMP and LPS antigens, but continued high production of chlamydial HSP60. In vivo, such persistently...
infected cells could serve as accumulations of HSP60 antigen capable of inducing chronic inflammation and scarring.

Heat shock proteins serve as important antigens of infectious agents, and are among the most conserved molecules in phylogeny. HSP are important in a variety of cellular functions and are highly conserved between mammalian and bacterial species. Among the most studied HSP is the HSP60 family which includes, for instance, HSP65 of mycobacteria, and mitochondrial P1, the mammalian cognate of bacterial HSP60. One current hypothesis is that chronic sequelae of chlamydial infection are caused by a delayed hypersensitivity reaction to chlamydial HSP, particularly the 57 kDa HSP which belongs to the HSP60 family (Morrison et al., 1989). The amino acid homology between microbial and human HSP60 counterparts is high (Paavonen and Lehtinen, 1994).

Many studies show a good correlation between serum antibodies to HSP60 and PID, tubal factor infertility or ectopic pregnancy. In women with a prior history of chlamydial PID, laparoscopically observed tubal obstruction, laparoscopically observed degree of tubal inflammation, and the presence of moderate to severe adhesions were all associated with serum antibodies to HSP60 (Eckert et al., 1997). Although the antigenic structure of HSP60 has been analysed in detail by monoclonal Ab and polyclonal antisera, data on specific B-cell epitopes or T-cell epitopes of chlamydial HSP60 recognized by human sera are still limited. However, antibody response to specific B-cell epitopes of C.trachomatis HSP60 have been described in infants with chlamydial infection (Paavonen et al., 1994) and in women with PID (Domeika et al., 1998).

The high molecular mimicry of human and chlamydial HSP may also induce an autoimmune response (Domeika et al., 1998). Chlamydial and human HSP60 are candidate targets for autoimmune T cells. However, little is known of possible cross-reactive T-cell epitopes. Local accumulation of chlamydial HSP and cross-reactive immune response can generate an autoimmune reaction that explains part of the inflammatory reaction and pathology seen after chlamydial infection. Although autoimmune reactions may play some role in the chronic sequelae of chlamydial infections, a delayed hypersensitivity response to chlamydial HSP60—associated with persistent or recurrent infections—probably plays a more important role. Nevertheless, this assumption is based on weak evidence.

Future studies should characterize the relevant T helper cell epitopes of C.trachomatis HSP60. The working hypothesis is that Th1 and Th2 type cells discriminate between specific peptides, that CD8+ cells suppress the Th1 type response, and that these findings show significant correlation with the histopathological severity of upper tract infection and immune perturbations, subsequently leading to long-term sequelae.

### Treatment of C.trachomatis infections

New guidelines for the treatment of patients with sexually transmitted chlamydial infection have been recently published (Centers for Disease Control and Prevention, 1998). Recommended regimens are azithromycin (Pfizer Co., USA) 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days. Alternative regimens include erythromycin 500 mg orally four times daily for 7 days, or ofloxacin 300 mg orally twice daily for 7 days. Azithromycin prescribed as a single oral 1-g dose is equivalent to the traditional 7-day regimen of doxycycline (100 mg twice daily) for treating uncomplicated genital chlamydial infections (Martin et al., 1992; Stamm et al., 1995). Compared with conventional therapy, azithromycin has excellent pharmacokinetic characteristics, such as bioavailability, lower incidence of gastrointestinal tract side effects, and increased concentration in mucus, macrophages and tissues, with a half-life of 5–7 days (Rakita, 1998). These characteristics allow for single dosing, which alleviates the problem of patient non-compliance or delayed care with multi-day regimens. At present, limited data are available on the use of single-dose therapy during pregnancy, and for syndromes such as PID. The existing data suggest that azithromycin is a valid treatment option for chlamydial infection during pregnancy (Bush and Rosa, 1994; Brocklehurst and Rooney, 1996) if erythromycin or amoxycillin are not tolerated. Although the higher cost of azithromycin may prohibit its use in resource-limited settings, selective use in persons at high risk or in those with a history of non-compliance may prove cost-effective. The cost of re-treatment as a result of non-compliance, and the additional cost of contact tracing, can make single-dose azithromycin more cost-effective than doxycycline.

### Table II. 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. (From Scholes et al., 1996)

<table>
<thead>
<tr>
<th>Group</th>
<th>Incidence of PID</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>Rate</td>
</tr>
<tr>
<td>Intervention group</td>
<td>9</td>
</tr>
<tr>
<td>Control group</td>
<td>33</td>
</tr>
</tbody>
</table>

---

**Annotations:**
- a: Both the intervention group and control group were followed for 12 months.
- b: Rate per 10 000 women-months.
- c: Relative risk (95% confidence interval).
- d: Comprised 2607 (13%) of 20 836 eligible women.
Patients should be instructed to abstain from sexual intercourse until they and their sex partners have completed treatment. Timely treatment of sex partners is essential for decreasing the risk of re-infecting the index patient. Patients do not need to be re-tested for *Chlamydia trachomatis* after completing treatment, unless symptoms persist or reinfection is suspected, because the recommended therapies are highly efficacious (Centers for Disease Control and Prevention, 1998).

Studies show that recurrent chlamydial infection increases the risk for ectopic pregnancy and PID (Hillis et al., 1997). Thus, the detection of any genital chlamydial infection presents a unique opportunity to implement interventions that will markedly reduce the risk of subsequent recurrence and, as a consequence, the risk of complications. Preventive measures include making chlamydia screening the standard of care for sexually active women, using single-dose therapy to avoid treatment failures in patients who may have difficulty with compliance, identifying and treating male sex partners, and providing personalized risk reduction counselling.

Studies are needed to determine if these antibiotic regimens achieve clinical and microbiological cure while preserving fertility and preventing further tissue damage to the upper genital tract. It has been suggested that early treatment of chlamydial infection is successful, whereas antibiotic therapy during the chronic phase generally might be less effective, although this is not proven. There are several reasons to suspect that persistent Chlamydiae may not respond to antibiotics as well as normally growing Chlamydiae. If the former are found to exhibit decreased susceptibility to antibiotics, and if persistence can be documented in actual cases of chlamydial disease, these findings could profoundly influence the clinical management of chlamydial infections in the future.

**Prevention of *C. trachomatis* infections**

The control of STD is a public-health priority and one that has become even higher priority with the HIV epidemic. Since STD and HIV share many behavioural risk factors, efforts to encourage individuals to modify sexual behaviours and adopt safer sexual practices will have a beneficial impact on both. Screening for *C. trachomatis* is of paramount importance in the prevention of long-term sequelae associated with PID. Chlamydia control programmes should include development of diagnostic services with proper quality control, guidelines for clinicians in the clinical diagnosis and management of cervicitis and PID, screening to identify asymptomatic carriers of *C. trachomatis*, establishment of surveillance systems, training of health care workers, and periodic monitoring and evaluation of control measures, routine evaluation of sex partners, and effective patient education in Behavioural aspects and contraception (Centers for Disease Control and Prevention, 1998).

Disease prevention can be primary, secondary or tertiary. Primary and secondary prevention programmes need to be strengthened and integrated into health care systems, and must be accessible to all. 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. 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 risk-taking sexual behaviour, by encouraging screening tests for those at risk, by ensuring that male sex partners are evaluated and treated, and by counselling about safe sex practices. Unfortunately, primary prevention by health education has not proven to be very effective so far. However, studies of the efficacy of primary prevention are slow and extremely complicated to conduct. Clearly, more emphasis should be directed toward primary prevention. Effective school-based health education programmes should be implemented among adolescents.

### Table III.
The health-related outcomes of *C. trachomatis*-infected patients predicted by the decision model. (From Paavonen et al., 1998)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No screening (%)</th>
<th>Screening (%)</th>
<th>Health benefits of screening (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cured</td>
<td>44.6</td>
<td>71.6</td>
<td>+62.3</td>
</tr>
<tr>
<td>Infertility</td>
<td>11.0&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>–50.9</td>
</tr>
<tr>
<td>Tubal pregnancy</td>
<td>13.8</td>
<td>7.0</td>
<td>–50.7</td>
</tr>
<tr>
<td>Pain</td>
<td>30.3</td>
<td>15.5</td>
<td>–51.2</td>
</tr>
<tr>
<td>Laparotomy</td>
<td>0.3</td>
<td>0.2</td>
<td>–66.7</td>
</tr>
</tbody>
</table>

<sup>a</sup>Percentages have been calculated from the original numbers.

<sup>b</sup>8.3% will need ≥1 IVF (96 IVF attempts per 10 000 individuals).

<sup>c</sup>4.2% will have ≥1 IVF (49 IVF attempts per 10 000 individuals).
Secondary prevention by universal screening is likely to play a critical role in the prevention of PID and long-term sequelae. Chlamydial infections fill the general prerequisites for disease prevention by screening, since they are highly prevalent, are associated with significant morbidity, can be diagnosed, and are treatable. Secondary prevention means early detection of asymptomatic disease by screening in order to prevent lower genital tract infection from becoming upper genital tract infection. One recent randomized controlled trial has provided strong evidence that intervention with selective screening for chlamydial infection. These include single-dose therapy using azithromycin, utilization of NAAT, and the use of FVU specimens for the diagnosis. However, it remains to be seen whether such intervention will also have a significant effect on the incidence of tubal factor infertility. The Swedish experience strongly suggests that screening efforts to reduce Chlamydia trachomatis infection and PID result in a decline of ectopic pregnancies. In the past few years there has been a 40% decrease in ectopic pregnancies in Sweden (Egger, 1996; Kamwendo et al., 1998), the decline being most striking in young women. The risk of ectopic pregnancy decreased concurrently with the decline in chlamydial infection in young women, whereas in older women the association was less striking (Egger et al., 1998).

Socio-economic studies linking secondary prevention of C. trachomatis infection and infertility and adverse pregnancy outcome are needed to convince public health authorities of the need for, and benefit of, such programmes. Rates of C. trachomatis infection still remain high both in developed and developing countries, which suggests that the traditional STD control programmes are not effective against Chlamydia trachomatis. The current practice of detection of C. trachomatis infection in most clinical settings is presumptive and expectant, and screening programmes have not been implemented extensively. Screening will contribute to the early detection of chlamydial infections because most infections are asymptomatic or minimally symptomatic, and has been shown to be cost-effective even in low-prevalence populations (Paavonen et al., 1998b). Compared with a symptom-driven no-screening situation, a universal C. trachomatis screening programme using the PCR test would save money, in terms of direct cost, when the baseline prevalence of C. trachomatis infection exceeds 3.9%. The validity of the decision tree can be judged by considering whether the probabilities of final outcomes produced by the model among infected patients in the baseline situation are in accordance with what is known of the occurrence of these outcomes in practice on the basis of research findings or clinical experience. As shown in Table III, these figures approach a 50% reduction in long-term sequelae, which corresponds to previous clinical findings (Scholes et al., 1996). This suggests that a relatively simple baseline cost–benefit analysis of C. trachomatis screening strategy is valid and useful, and can help decision makers in the allocation of health care resources.

References


Received on March 22, 1999; accepted on June 24, 1999.