Commentary

**Chlamydia trachomatis & infertility**

Genital *Chlamydia trachomatis* infection is the leading cause of curable bacterial sexually transmitted diseases (STDs) worldwide, especially among young in industrialized countries. According to WHO\(^1\), globally, new cases of *C. trachomatis* infection have been estimated as 92 million, including 43 million in South East Asia. Estimates of the global prevalence and incidence of these infections depend on quantity and quality of data available from the different regions and require well designed epidemiological studies.

In India, a study conducted in female sex workers (FSWs) and married contacts, attending a STD clinic in Mumbai, found that 23.2 per cent were chlamydia-positive\(^2\). The prevalence of *C. trachomatis* in asymptomatic and symptomatic women attending a Gynaecology clinic at Delhi was 4 and 30.4 per cent respectively\(^3\). A community based study in Delhi detected this infection in 4000 women, both in symptomatic with vaginal discharge (2.9%) and asymptomatic (1.5%) (our unpublished observations). While a previous study\(^4\) in a community of urban and rural adult population of Tamil Nadu determined the prevalence of *Chlamydia* as 3.9 per cent, 28.7 per cent in an urban slum in Delhi were found to harbour this infection in another report\(^5\).

The magnitude of morbidity associated with sexually transmitted chlamydial infection is enormous. *C trachomatis* is responsible for a wide spectrum of diseases in men and women including urethritis and mucopurulent cervicitis, with a variety of sequelae viz., salpingitis, endometritis, pelvic inflammatory disease (PID), ectopic pregnancy (EP), tubal factor infertility (TFI), epididymitis and proctitis. Like other STDs, the brunt of the infection is on women, who suffer from its damaging consequences. In contrast to gonorrhoea, another major cause of infertility, most individuals infected with *Chlamydia* are asymptomatic or minimally symptomatic and therefore diagnosis is made either after screening of the individual or when a symptomatic partner is diagnosed.

Chlamydial PID, a major reproductive health-care issue in women, is the most important preventable cause of infertility and adverse pregnancy outcome. The sharp worldwide increase in the incidence of PID during the past two decades resulted in secondary epidemics of TFI and EP\(^6\). According to available evidence, approximately 20 per cent of women with chlamydial lower genital tract infection will develop PID, 4 per cent chronic pelvic pain, 3 per cent infertility and 2 per cent adverse pregnancy outcome\(^6\). After a single episode of PID, the risk for TFI is approximately 10 per cent, each repeat episode doubling the risk\(^7\). The intense and chronic inflammation elicited and maintained by re-infection or persistent infection with *C. trachomatis* leads to the damaging sequelae such as infertility\(^8\), and it can apparently cause more severe tubal immunopathology than other agents, in spite of the absence of overt symptoms\(^9\). PID and its chronic sequelae are associated with chlamydial IgG antibody formation, and a correlation between serum antibody titres and the presence of tubal factor subfertility has been established\(^10\). A trend was observed in some countries, where women postpone pregnancy and the doctor is consulted for
the first time because of infertility. Subclinical salpingitis was found to be more common than symptomatic PID. Persistent tubal infections by *C. trachomatis* are common in spite of administration of antibiotics and microbiological cure. Differences in host factors, such as genetic polymorphism in cytokine response and human leukocyte antigen type, may play a role in the outcome of PID\textsuperscript{11}.

In a recent study, in STD clinic attendees of a UK hospital\textsuperscript{12}, *C. trachomatis* was detected in 44 per cent of male contacts of females with endocervical chlamydiae, using polymerase chain reaction (PCR), emphasizing the fact that both partners should be treated to avoid recurrent infections. *C. trachomatis* IgG antibodies in the man of the infertile couple can cause decreased pregnancy rates and presence of IgG antibodies in the woman. There was a high prevalence of asymptomatic persistent infections among infertile couples\textsuperscript{13}. *C. trachomatis* can significantly affect the function of human spermatozoa, resulting in subfertility in infected individuals by a route that is independent of any damage to the reproductive epithelium. In addition, undiagnosed *C. trachomatis* infection could contribute to poor outcome in assisted conception techniques such as *in vitro* fertilization\textsuperscript{14}.

Although the role of *Chlamydia* in TFI has been proved convincingly in developed countries, there are not enough data to establish the association between *C. trachomatis* infection, salpingitis and tubal infertility. Antichlamydial IgG antibodies were present in 68 per cent of women with infertility, 50 per cent with bad obstetric history and 10 per cent of healthy fertile women, in Amritsar, India\textsuperscript{15}. *Chlamydia*-specific IgG antibody was significantly higher (70\%) in women with TFI than in healthy fertile women (35\%) and infertile women with causes other than TFI (55\%)\textsuperscript{16}. The article by Malik *et al*\textsuperscript{17} in the current issue, using cell culture and antigen detection techniques to confirm the presence of *C. trachomatis* in women presenting with primary and secondary infertility, is an important contribution to the Indian literature.

Early diagnosis is one of the most cost-effective means of preventing the long-term sequelae of chlamydial infections. Acute infections have been diagnosed by cell culture, direct immunofluorescence, enzyme immunoassay, direct DNA hybridization and more recently by nucleic acid amplification tests (NAATs), having high sensitivity. Because of its high specificity (100\%), cell culture is the only standard test in cases with legal implications such as rape or sexual abuse. PCR and ligase chain reaction (LCR) are the two most commonly used alternatives to conventional methods and have proved useful for the detection of *C. trachomatis* in cervical and urethral samples, both in symptomatic and asymptomatic women\textsuperscript{18}. With increasing use of these tests, more infected persons and their partners will be identified and treated, and the chance of reduction of transmission may increase. A comparative study of cell culture and NAAT\textsuperscript{19} observed the latter to be significantly (*P*<0.0001) more sensitive and recommended NAAT to be considered the new "gold standard". In contrast, a commercial transcription-mediated amplification (TMA) assay in endocervical swab specimens failed to identify all chlamydia positive patients, diagnosed by a ‘gold standard’ culture assay\textsuperscript{20}. Testing of first-void urine (FVU) specimens with NAAT has shown similar sensitivity as tests with endocervical swab cultures, offering the opportunity to screen for infections in asymptomatic subjects\textsuperscript{17}. Self collection of an introital specimen was advocated in large-scale settings in developing countries for detection of *C. trachomatis*\textsuperscript{21}. Although the use of urine samples for the diagnosis of *C. trachomatis* infections was effective, a study conducted in women and men attendees of a STD clinic showed that urine samples should be additional to conventional swab(s), instead of replacing them. Similar sensitivity and specificity of culture and NAAT, using swabs were observed\textsuperscript{22}. Laboratory to laboratory variation in *Chlamydia* cell
culture sensitivity accounts for part of the substantial variability in published evaluations of the sensitivity of nonculture *Chlamydia* diagnostic tests.  

In chronic or persistent chlamydial infections, the level of *Chlamydia* is very low and bacteria are often not viable. This results in continuing positive NAATs but only intermittent isolation of viable *Chlamydia* and positive assays for chlamydial protein antigen. In the study by Malik *et al* only 28 per cent infertile women could be confirmed by culture and antigen detection. This could be because laboratory tests, having less sensitivity in chronic infections were used. An earlier study also found chlamydial antigen and antibody in 42.8 and 25 per cent of PID cases and 27.2 and 16.6 per cent of infertility cases, respectively.

As most infections are asymptomatic and only a few with symptoms attend STD clinics and are diagnosed, screening for *C. trachomatis* infection remains an essential component for control. *Chlamydia* serology was found to be an inexpensive, noninvasive test for TFI that matches or surpasses the predictive value of most standard infertility tests. The use of NAATs associated with serology test was found to be the best diagnostic strategy. High levels of chlamydial IgA and IgG antibodies detected in various biological materials such as follicular fluid samples in patients with fertility disorders, could display association between *Chlamydia* infection and infertility, mainly as its organic cause. In subfertile women with tubal pathology, serological markers of persistent *C. trachomatis* infections are significantly more common as compared to women without tubal pathology. *C. trachomatis* IgG-positive subfertile women with slightly elevated (< 10 mg/l) C reactive protein levels are at highest risk of persistent *C. trachomatis* infections and tubal pathology. Significant associations were also detected, recently, between *C. trachomatis*-specific heat shock protein (hsp) antibodies and secondary infertility.

The variety of acute and chronic manifestations of genital chlamydial infections poses a considerable public health challenge to many developing nations, including India. Antibiotics are effective against the organism, when properly diagnosed. However, clinical presentation of complications are often the first evidence of an infection as asymptomatic infections are highly prevalent, as highlighted in this study. To limit the scourges of *C. trachomatis* infection in the population, a well planned disease-management strategy from STD-care providers, using highly sensitive and specific diagnostic techniques (appropriate to the resources and technical expertise available) and specific antibiotics for treatment of the patient and his/her partner, according to standard treatment regimens, are mandatory. This should be complemented with strong public health measures to promote the diagnosis and treatment of disease symptoms, in the absence of laboratory support. Emphasis should be given to simple cost effective testing strategies such as serology for screening of high risk asymptomatic women for treatment and prevention of the various sequelae. Research in the direction of designing a simple and inexpensive laboratory test for the specific diagnosis of chlamydial infections and generation of up-to-date laboratory based incidence/prevalence data needs encouragement. An effective prophylactic vaccine may be the best approach to protect the human population from the most severe consequences of these infections, especially as recent research has shown some promise.

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**References**


