Pravara Med Rev; September 2022, 14 (03), 32 - 39
DOI: 10.36848/PMR/2022/70100.510230

**Review article**

# Prevalence of Chlamydia infection in infertility and management: Review

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**Abstract:**
The prevalence of ureaplasmaurealyticum, mycoplasma hominis, chlamydia trachomatis and neisseria gonorrhoeae infections, and the rubella status of patients undergoing an initial infertility evaluation.The infection panel included in the protocol for infertility evaluation should include chlamydia screening or not for both male and female partners and its utility and cost effectiveness. Vaccination could be substantially more effective than other biomedical interventions in controlling epidemics of *Chlamydia* infection. Currently, the best public health intervention available is increasing the rate of screening and treating infected individuals. Administrating a protective vaccine to adolescents before their first sexual experience could induce a significant reduction in prevalence which could not be obtained by screening teenagers, even with a coverage of 100 per cent . Unfortunately, no protective vaccines, either fully or partially, are available although there have been many attempts to develop one. The immunological characteristics of the genital tract and the tropism of *Chlamydia* for mucosal epithelial cells emphasize that a *C. trachomatis* vaccine must induce both mucosal and systemic protective responses. Present review highlights prevalence of chlamydia in infertility and its management.

**Keywords:** Ureaplasmaurealyticum, mycoplasma hominis, chlamydia trachomatis

## Introduction

The prevalence of ureaplasmaurealyticum, mycoplasma hominis, chlamydia trachomatis and neisseria gonorrhoeae infections, and the rubella status of patients undergoing an initial infertility evaluation. The infection panel included in the protocol for infertility evaluation should include chlamydia screening or not for both male and female partners and its utility and cost effectiveness.

Chlamydia trachomatis is an obligate intracellular parasite bacterium that can infect both genital and non genital sites including the cervix, rectum and eyes[1-3]. Genital C. trachomatis infection is a leading cause of bacterial sexually transmitted disease, responsible for more than 131 million emerging infections worldwide, and may manifest as mucopurulent cervicitis with a watery or purulent discharge and easily induced bleeding with a swab[4].

C. trachomatis has a biphasic life cycle comprising a metabolically active noninfectious reticulate body (RB) and an infectious environmentally resistant elementary body (EB). The RB replicates by binary fission within the confines of the inclusion and differentiates into EBs at the end of the infectious replication cycle, while the EBs are closely followed by releasing from the cell to initiate new infection via cytolysis or endocytosis[5,6].Various factors such as antibiotic treatment, host immunological response, or nutrient starvation disturb the C. trachomatis developmental cycle, and under such conditions, the EBs can convert to enlarged noninfectious aberrant bodies (ABs). This so-called “viable but non-cultivable growth stage” is associated with chronic and repeat



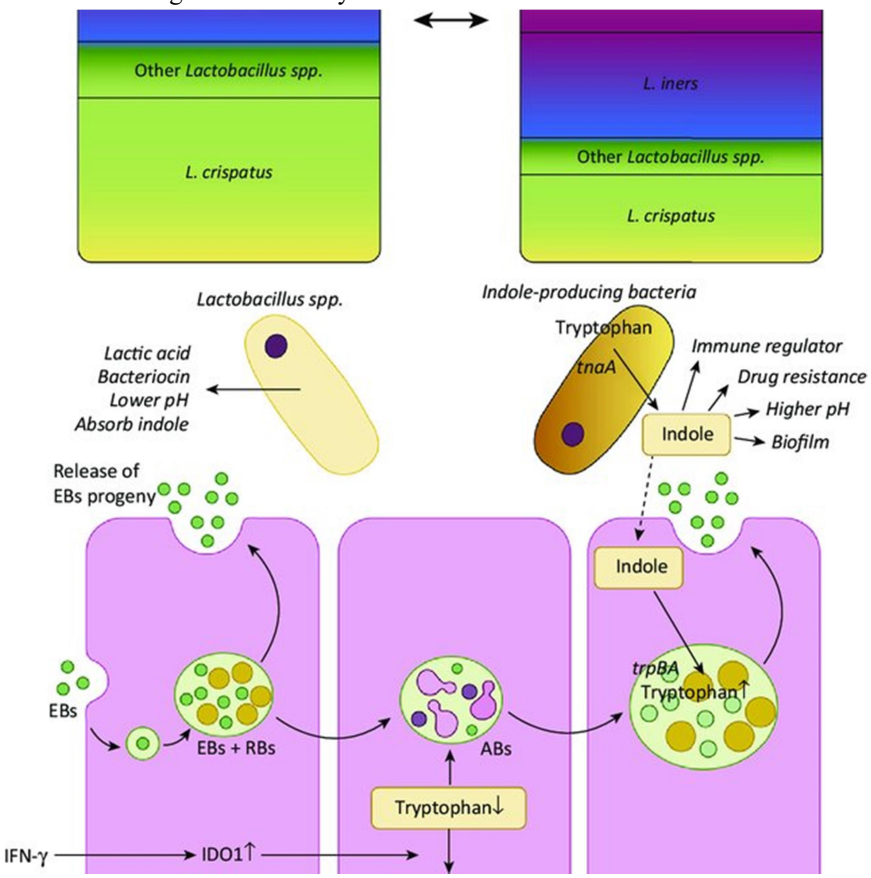
PMR P ISSN: 0975-0533, E ISSN: 0976-0164

infections that can lead to serious complications in women, including obstructive infertility, ectopic pregnancy, and preterm birth[7,8]. Besides, persistent C. trachomatis infection enhanced the expression of C. trachomatis Hsp60 (cHsp60), capable of activating mononuclear cells or monocyte-derived macrophages producing E-selectin, intercellular adhesion molecule (ICAM)-1, and vascular cell adhesion molecule (VCAM)-1 and amplifying the ongoing inflammatory process by secreting pro-inflammatory cytokines[9,10]. Moreover, this infection could also provoke the release of human heat shock protein (HSP)60, very similar to chlamydial heat shock protein (cHsp)60, which was firstly produced by early-stage embryos. In this regard, cross-reactive cHsp60 peptides elicited an immune response that can recognize the human hsp60 and increase the pathogenesis of genital chlamydial infection[11,12].

**PATHOGENESIS:**

Lactobacillus-dominated vaginal microbiota is considered a marker of health status for healthy women[13,14] owing to its ability to produce lactic acid and multiple bacteriostatic and bactericidal compounds to protect against extraneous pathogenic bacteria[15-17].women infected with C. trachomatis were hypothesized to undergo an alteration in their vaginal microbiota dominated by Lactobacillus iners or by diverse anaerobic bacteria[18.] However, the vaginal microbiota varies greatly among individuals due to host intrinsic factors such as age, diet, ethnicity, menstrual cycle, and external factors such as geographic location and genital diseases[19].

L. iners is incapable of downregulating histone deacetylase 4 and does not sufficiently reduce cell proliferation to protect against C. trachomatis infection[20,21]. Conversely, other species of the genus Lactobacillus such as L. jensenii, L. crispatus, and L. gasseri are capable of producing Dlactic acid, bacteriocins, and other antimicrobial compounds to protect against sexually transmitted pathogens, including C. trachomatis, Neisseria gonorrhoeae, and HPV[22,23].



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C. trachomatis is an intracellular pathogen that generally triggers a strong host T-helper 1 (Th1) cell and IFN-g response by the release of chemokines upon infection, and in turn, this could magnify the inflammatory response by recruiting Chlamydia-specific immune cells[24,25]. Therefore, it is not surprising that women with tubal infertility who were C. trachomatis-positive had significantly higher vaginal levels of IFN-g.

Women with tubal infertility and C. trachomatis infection are prone to have an L. iners- rather than L. crispatus-dominated vaginal microbiota and have a decrease in Lactobacillus, Bifidobacterium, Enterobacter, Atopobium, and Streptococcus, which could be restored with varying degrees by azithromycin treatment.

**Risk factors for chlamydia infection:**

The factors that best predicted self-reported chlamydia among females were number of partners, age, and having been reimbursed for sex**.**

Among males, the number of partners and alcohol consumption were the strongest predictors.

Increasing number of partners up to 10 during the past 12 months was the most important predictor for both genders.

There is no clear evidence that chlamydia is associated with type of partners, contraceptive use, or age at first intercourse.

**Age:** Younger age is shown consistently to be associated with increased risk of chlamydial infection among the sexually active population.There are a number of reasons why adolescents are at greater risk for genital chlamydial infection than older people. A higher risk in adolescent females may be associated with certain aspects of physical development that make this group more vulnerable to sexually transmitted infections, including the persistence of columnar epithelium on the cervix, which supports the growth of *C trachomatis*, and changes in vaginal flora and mucus production[26,27]. As well, older women may have acquired partial immunity after initial or serial infections in the past[28]. Differences in the prevalence of infection between adolescents and adults are also often attributed to differences in sexual behaviours.

**Race and/or ethnicity and socioeconomic status**

The relationships among race, socioeconomic status (SES) and genital chlamydial infection are not clear[29].

**Number and type of partners**

Multiple partnerships may increase the likelihood of encountering a sexually transmitted pathogen through the increased probability of choosing a partner with infection, while having new or casual sexual contacts may be related to increased risk because of a reduced familiarity between partners[30]. the relationship between the number of recent partners (in the past one, two, three or six months), type of sex partners (new, casual or regular) and genital chlamydia is not consistent across the studies for males or females.

**Contraceptive use :**

The relationship between the use of condoms and other barrier contraceptives (diaphragm or cervical cap), and genital chlamydial infection is inconsistent across the studies. Use of a barrier method was shown to be associated with reduced risk of infection compared with the use of other methods of contraception in two of five studies in females[31-35].

There are three possible reasons for these inconsistencies. First, individuals may have become infected before barrier use and started to use barriers after their symptoms appeared. Second, individuals may over-report barrier contraceptive use. Third, it is unclear how best to measure consistent and correct barrier use[36].

**Age at first intercourse :**

Age at first intercourse may be causally related to sexually transmitted infections. Four of seven studies that looked at this risk factor found a higher risk of infection in women who had early age of sexual debut in single factor analysis, but none of these studies demonstrated a significant relationship in multivariate analysis.

**Other risk factors :**

Addiss et al[37] found that women with one child or no children were at five times greater risk for chlamydia than women with two or more children. This may be due to involuntary infertility following 'silent' chlamydial PID.

**Clinical course in patients :**

**Chlamydial infection in men:**

1. Asymptomatic ≈ 50 %.
2. Non specific urethritis .

The role of *C. trachomatis* in the development of urethritis, epididymitis and orchitis in men is widely accepted. Though the role of this organism in prostatitis is controversial, but up to 35- 50 per cent incidence has been reported in patients with prostatitis[38].



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Strong association with : Infection of the testes and the prostrate is implicated in the deterioration of sperm (decrease sperm motility, increase proportion of sperm abnormalities, significant reduction in sperm density, sperm morphology and viability and increased likelihood of leucocytospermia) affecting fertility. Chlamydial infection may also affect the male fertility by directly damaging the sperm as sperm parameters, proportion of DNA fragmentation and acrosome reaction capacity are impaired. However, the role of *C. trachomatis* in male infertility is not yet proven.

Chlamydial infection in women: Studies on the natural course of untreated C. trachomatis lower genital tract infections in women show spontaneous clearance rates of 30 –50% in the first 2–3 years[39-41].

1. Cervicitis and pelvic inflammatory disease: Our studies indicated a risk for tubal infertility after chlamydia infection in the range up to 4.6%, which corresponds with assumptions made in most economic analyses reporting a risk of PID after chlamydia infection up to 30% and a risk of developing infertility after PID of 10–20%:
2. Exposure to antibiotics and interferon-gamma results in persistence infection.
3. Tubal factor infertility and ectopic pregnancy :For tubal tissue damage to occur, prolonged exposure to chlamydia is considered a major predisposing factor, either by chronic persistent infection or by frequent reinfections[42,43]. It has been hypothesized that this prolonged or repeated exposure of the host to the micro-organism evokes a chronic low-grade auto-immune response which leads to chronic inflammation and subsequent tissue damage[44].The risk of developing tubal infertility after PID is estimated at 10–20%, and from this it can be concluded that the risk to test-positive women of developing tubal infertility ranges between 0.1 and 6%[45].

**Investigations:**

The main focus is on PID and tubal infertility, with the aim to propose more accurate estimates of these risks, which can be used in patient counselling and inserted in future cost-effectiveness analyses of different screening strategies.

Various test and their sensitivity and specificity in assessing genital chlamydia infection are as follow :

| Test | Sensitivity (%) | Specificity (%) | Detection limit (no. of microorganisms) |
|---|---|---|---|
| NAAT[a] | 90-95 | >99 | 1-10 |
| DFA[b] | 80-85 | >99 | 10-500 |
| EIA[C] | 60-85 | 99 | 500-1000 |
| DNA-probe[d] | 75-85 | >99 | 500-1000 |
| Cell culture | 50-85 | 100 | 5-100 |
| POC[e] | 25-55 | >90 | >10 000 |

[a] Nucleic Acid Amplification Test. DNA-based: PCR Amplicorassay , LCR , currently BD ProbeTec. RNA-based: TMA, AMP-CT, current system from Gen-Probe is named TIGRIS; NASBA.
[b]Direct Fluorescence Assay.
[c] Enzyme Immuno Assay. .
[d]DNA-based: hybrid capture assay, Ampliprobesystem; RNA-based: PACE 2 .
[e] Point of care test (Biorapid Chlamydia Ag test , QuickVue Chlamydia test ).

In conclusion, when comparing the performances of chlamydia detection assays, taking the above mentioned discussion points into account, NAAT is most sensitive (90–95%) and highly specific, followed by the new generation DNA-probe assays which are more or less equally sensitive (up to 85%), followed by culture (up to 80%), and finally the POC or rapid tests, which are quite insensitive (25 –55%).

Chlamydia IgG antibody testing in serum is applied in reproductive medicine in the fertility work-up on a large scale, but it has no place in early diagnosis of chlamydia infections. Among women with clinical signs and symptoms of mild to moderate PID, antibodies to C. trachomatis were



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shown to be associated with reduced pregnancy rates. In fertility clinics CAT was introduced as a screening test for tubal infertility[46,47] after it had become evident that an association exists between chlamydia IgG antibodies in serum and tubal pathology[48]. The most accurate tests for CAT have a sensitivity of 60% for tubal pathology, whereas their specificity is 85 –90%[49].

**Role of screening:**

There are no randomized trials that show effectiveness of opportunistic chlamydia screening on PID-incidence in non-pregnant women.

The efficacy of prophylactic treatment has been studied in women undergoing induced abortion. A meta-analysis showed that postabortion infection could be reduced by half and that prophylaxis is to be preferred over a screen-and-treat strategy. In a randomized study comparing prophylaxis against chlamydia, gonorrhoea and bacterial vaginosis versus a screen-and-treat strategy, antibiotic prophylaxis was concluded to be at least as effective as a screen-and-treat policy in minimising post-abortion infections and to be more cost-effective[50,51]. A disadvantage of universal prophylaxis is that infected women remain unnoticed and cannot be offered the benefits of partner notification and treatment. Therefore, a third strategy has been proposed, involving prophylaxis at the time of abortion followed by screening for gonorrhea and chlamydia to ensure adequate follow-up of treatment results and partner notification[52].

**Treatment:**

**Uncomplicated genital chlamydia[53]**

For people with uncomplicated genital chlamydia, the WHO STI guideline suggests one of the following options:

- azithromycin 1 g orally as a single oral dose
- doxycycline 100 mg orally twice a day for 7 days

or one of these alternatives:

- tetracycline 500 mg orally four times a day for 7 days
- erythromycin 500 mg orally twice a day for 7 days
- ofloxacin 200–400 mg orally twice a day for 7 days.

*Conditional recommendation, moderate quality evidence*

Compared with the conventional therapy, azithromycin has advantage of having better compliance being administered in the physicians' chamber. All the other regimens have similar cure rates and adverse effect profiles. Patients should be instructed to abstain from sexual intercourse for seven days after the treatment initiation. Both the partners should be treated simultaneously in order to prevent re-infection of the index patient. Patient need not be re-tested after completing the treatment, unless the symptoms persist or re-infection is suspected.

*Chlamydial infection with PID*: Recurrent chlamydial infection increases the risk for developing ectopic pregnancy and PID. PID can be treated on an outpatient basis unless indicated (accompanied by severe illness, nausea, vomiting, high-grade fever, tubo-ovarian abcess or intolerance or unresponsiveness to oral therapy). The CDC has recommended ofloxacin 400 mg orally (bd) or levofloxacin 500 mg orally once a day (od) with or without metronidazole 500 mg orally (bd) for two weeks. In case of intolerance to the above mentioned regimen, ceftriaxone 250 mg intramuscular (im) or cefoxitin 2 g (im) as a single dose with concurrent probenicid 1 g orally in single dose plus doxycycline 100 mg orally (bd) with or without metronidazole 500 mg orally (bd) for two weeks[54].

**Multidrug resistant and heterotypic resistant *Chlamydia trachomatis***

The characteristics of antibiotic resistance of *C. trachomatis* differ significantly from those of other bacteria in several ways.

First, because chlamydiae are intracellular pathogens, antimicrobial susceptibility must be determined by their ability to proliferate within a host cell in the presence of varying concentrations of antibiotic.

Second, unlike the case for most bacteria, when *C. trachomatis* organisms are found to be resistant to typically effective antibiotics such as tetracycline, the resistance is not absolute. In fact, *C. trachomatis* displays what is known as "heterotypic resistance" *in vitro*; that is, the chlamydial population contains both susceptible and resistant organisms. Thus, although it is possible that all organisms within a population may be capable of expressing resistance, only a small proportion does so at any one time. Testing for the MCC (defined as lowest concentration of drug that permitted no inclusions to be formed on passage on an antibiotic free medium) may allow the small percentage of organisms that were resistant to the



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first exposure to antibiotic (MIC) to then multiply and form inclusions[55]. Heterotypic resistance exhibited by some *C. trachomatis* strains, therefore, may be missed unless both MIC and MCC testing is done. In strains that exhibit heterotypic resistance, many aberrant inclusions are seen, and the proportion of atypical to typical inclusions gradually increases along with a decrease in the overall number of inclusions until all inclusions become aberrant or absent, which is reinforcing the fact that the resistance exhibited by individual organisms within the chlamydial population is heterogenous (defined as heterotypic resistance). The mechanisms underlying heterotypic resistance in *C. trachomatis* is not known.

It is hypothesized that multidrug resistance in *C. trachomatis* is phenotypic in nature rather than genotypic. Also, heterotypic resistance may be a by product of some undefined alteration of the growth rate or life cycle, resulting in a longer phase or intermediate stage that is more refractory to the antimicrobial agents. Alternatively, it may be mediated by some kind of mechanisms that exclude the drug from cell wall or chlamydial inclusion (*e.g.* efflux pump). Further studies are required to prove these hypotheses.

There are no data regarding management of clinically resistant *C. trachomatis* infection. *In vitro* data suggest that resistance to ofloxacin imparts resistance to other fluoroquinolones, such as ciprofloxacin. Although many of the newer quinolones, including trovafloxacin, sparfloxacin, grepafloxacin and tosufloxacin have equal or greater MICs for *C. trachomatis*, these need to be tested against an ofloxacin-resistant strain[56,57]. Perhaps a prolonged course of therapy with a standard agent such as doxycycline or azithromycin would be effective against resistant *C. trachomatis* disease, because such therapy has been efficacious against C. pneumoniae infection in cases of relapse[58].

Azithromycin 1 g immediately and doxycycline 100 mg twice daily have shown good antimicrobial activity against *C. trachomatis* and studies have demonstrated >95 per cent microbiological cure at 2-5 wk, with antimicrobial resistance being hardly reported[59]. However, there are evidences of multidrug resistance to *C. trachomatis* in women with high bacterial load but not in men who had been sexually inactive after treatment.

**Vaccines**

Vaccination could be substantially more effective than other biomedical interventions in controlling epidemics of *Chlamydia* infection. Currently, the best public health intervention available is increasing the rate of screening and treating infected individuals. Administrating a protective vaccine to adolescents before their first sexual experience could induce a significant reduction in prevalence which could not be obtained by screening teenagers, even with a coverage of 100 per cent[60]. Unfortunately, no protective vaccines, either fully or partially, are available although there have been many attempts to develop one. The immunological characteristics of the genital tract and the tropism of *Chlamydia* for mucosal epithelial cells emphasize that a *C. trachomatis* vaccine must induce both mucosal and systemic protective responses[61].

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PMR P ISSN: 0975-0533, E ISSN: 0976-0164