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Review Article

A comprehensive review on prevalence and its adverse outcome of *Chlamydia trachomatis* on female genital tract

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ABSTRACT

One of the most prevalent bacterial infections acquired through sexual contact is Chlamydia trachomatis. The age group of 16-19 years old (young sexually active individuals) is where females are most susceptible to contracting this virus. Most of the time they are asymptomatic, but if they are not treated, they might have serious side effects including pelvic inflammatory disease (PID). Chylamdia can be diagnosed using a variety of diagnostic methods; however, recent groundbreaking research using NAAT has made the diagnosis and treatment of the condition two times simpler. Key words such as 'chlamydia,' 'pelvic inflammatory disease' 'cervicitis,' 'sexually transmitted infection,' 'vaginal discharge' were used in a systematic search of the electronic databases PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus to find studies published between January 2009 and December 2023. Overall, this review helps to clarify the effects of Chylamdia on the female reproductive system, which in turn helps to clarify some of the problems and basic care associated with it. In general, the review's goal is to shield the public from serious health problems and make them more equipped to deal with them in case they acquire them.

Keywords: Chlamydia, Pelvic inflammatory disease, Cervicitis, Sexually transmitted infection

INTRODUCTION

Chlamydia trachomatis is the most common bacterial sexually transmitted infection (STI), and it is linked to a greater likelihood of pelvic inflammatory disease (PID), ectopic pregnancy, tubal infertility,

and susceptibility to human immunodeficiency virus infection.[1,2] PID is hypothesized to happen when germs climb from the lower genital tract and infect and inflame the uterus, fallopian tubes, and ovaries.[3] Although the microbiological cause of PID is unknown, *C. trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, and microbes associated with bacterial vaginosis are frequently isolated from PID women's lower and upper genital tracts.[4]

C. trachomatis is a gram-negative obligate intracellular pathogen that infects the ocular, genital, and respiratory tissues. *Chlamydial serovars* exhibit distinct tropisms for different mucosal locales, which is intriguing, but the molecular mechanisms governing these activities are not fully known. *C. trachomatis* is divided into 15 variants (genovars).[5] *C. trachomatis* infects the cervix and urethra first, resulting in vaginal discharge and dysuria. If the infection is not detected and treated, it can spread to the fallopian tubes, causing pelvic inflammatory diseases such as cervicitis, endometritis, and salpingitis.[6] *C. trachomatis* infections are asymptomatic in 80-90% of cases.[7,8] The young sexually active female population has been found to have the highest prevalence of *C. trachomatis* infection, serving as a reservoir for future transmission.[9]

Trachomatis serovars D-K is the world's top cause of bacterial sexually transmitted infection (STI). C. trachomatis serovars A-B, on the other hand, produces trachoma in endemic locations, primarily in Africa and the Middle East. Trachoma is a primary cause of preventable blindness globally.

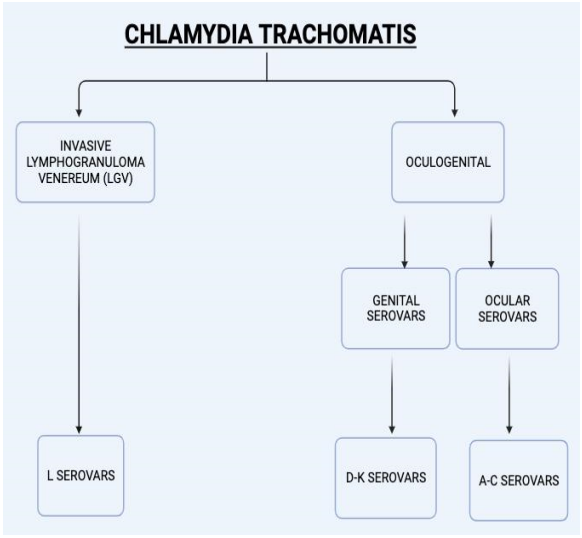

Figure 1: The *Chlamydia trachomatis* serovars have been shown here.

Note: Created with BioRender.com.

For 2012, the WHO projected a global prevalence of chlamydia at 4.2% (95% CI: 3.7-4.7) among women aged 15-49 years.[17] Approximately 8% of US women and 15% of Swedish women have had a PID diagnosis at some point in their lives.[11,12] The majority of illnesses are found in the Western Pacific and the Americas regions.[13] The majority of infected men and women are asymptomatic or only mildly symptomatic, and diagnosis happens after screening or when a contact is ill. The prevalence is relatively high when compared with other bacterial STIs because asymptomatically infected individuals may not seek treatment, and repeat infection after single dose therapy is common. Infection is more frequently reported in young women than young men.[13,14]

Chlamydia has a distinct biphasic developmental cycle that includes the conversion of the extracellular, infectious EBs (elementary bodies) to the intracellular, non-infectious RBs (reticulate bodies), the division of RBs, and the reorganization of RBs back into EBs. The recurring cycle appears to be the norm. Chlamydial persistence is defined as a long-term relationship between chlamydiae and their host cells during which these bacteria remain alive but culture-negative.[15,16]

It has been difficult to define a spectrum of virulence for C. trachomatis strains in the setting of genital tract infection. It is difficult to identify clinical characteristics that predict ascending infection and disease development in vulnerable people because PID can be asymptomatic.[17] The genetic propensity of an infected individual also influences disease outcome (40%). Genome research and novel approaches to characterizing infection kinetics and host response may be beneficial, while genetic manipulation of strains will provide a direct method for investigating the contribution of putative virulence loci to infectivity, transmission, immunopathology, or cancer.[18]

METHODS

When searching through comprehensive databases like PubMed, Embase, LitCovid, MedRxiv, BioRxiv, Google Scholar, EBSCO MEDLINE, CINAHL, and Scopus, terms like 'Chlamydia,' 'Pelvic Inflammatory Disease,' 'cervicitis,' 'sexually transmitted infection,' and 'vaginal discharge' were used to find studies published between January 2015 and December 2023.

The title and abstract of studies published in English were checked to facilitate data extraction and analysis. Then, a few complete texts of accepted papers were chosen. For each particular subject, systematic reviews that included meta-analysis were first included. Recent RCTs that had been published but had not yet been covered by systematic reviews were also included.[19] We also included different study designs, like primary research studies, including cross-sectional studies, case-control studies, cohort studies, and clinical trials. The studies involved sexually active females of reproductive age (15-49 years) in both community and clinical settings.

Exclusion criteria

Review articles, case reports, and studies with insufficient data or inappropriate methodologies were excluded. Also Studies relying on non-laboratory-confirmed diagnostic methods or self-reported Chlamydia trachomatis status, studies lacking relevant outcome measures or studies with insufficient detail on adverse outcomes associated with *Chlamydia trachomatis*, and studies published in languages other than English due to potential language barrier issues were not included.

Demographic factors

Young age (20 years) is the most common demographic correlate of chlamydial infection in women.[20] This could be explained by anatomic differences in the cervix in younger women, where the squamo-columnar junction, a key host target for *C. trachomatis*, is everted and thus more exposed.[21] Also, more risk-taking and unhealthy sexual practices, with less consistent use of condoms, can add to this increased risk. In accordance with the results of the preventive screening conducted in the Netherlands, examination of urine samples revealed that the prevalence of *C. trachomatis* was highest in the age group of 18 to 25 years (5.3%). In the age group of 26 to 30 year-old women, the prevalence was 3.4%, and there were no cases found in the age group of 31 to 40 year-old women.[22]

Different racial groups have variable rates of chlamydial, gonococcal, or both STIs (sexually transmitted infection) (coinfection). The Black Caribbean race was found to have the highest prevalence of both gonorrhea and Chlamydial infections. Co-infection was less likely in white people than in black people.[23] The Northern California (US) research of 18-29-year-old women found that CI (chlamydial infection) was more prevalent among black

and Asian individuals (4.2%) than among white subjects (1.4%).[24] According to epidemiological studies, the main risk factors for the prevalence of CI are frequent sexual relationships, failure to use barrier contraception during sexual contact or inconsistent use of it, cervical ectopy, a negative attitude toward condom use on the part of adolescent females and their partners, concurrent STIs, and unemployment. Between 2.9% and 6.4% of pregnant women who are asymptomatic have CI, according to studies conducted in the Netherlands across various time periods.[25]

Regional differences

The prevalence rates in high- and low-income nations differ.

Wealthy nations in high-income countries, a strong healthcare infrastructure frequently makes better detection and reporting possible.

Countries with low and middle incomes

Underreporting may occur in certain low- and middle-income countries due to limited access to diagnostics and healthcare services. Socio-economic variables, cultural norms, and healthcare policies all have an impact on regional variances.[26]

Some research don't support this claim as the probability of developing CI is correlated with socioeconomic class, the use of contraception, the number of sexual partners in the previous six months, or the number of new partners in the recent two months.[27]

Thus, a complicated interaction between demographic, age-related, and geographic factors accounts for the global incidence of *Chlamydia trachomatis*. Understanding these variances is essential for creating focused prevention and intervention strategies on a worldwide level as efforts to address this STI continue.

CLINICAL MANIFESTATION

Since up to 70% to 80% of infected women and 50% of infected males remain asymptomatic, the clinical picture of individuals with chlamydial infection may be deceiving. The typical vaginal discharge of a female with an uncomplicated chlamydial infection is mucoid, odorless, and free of pruritis.[21]

Some patients may show signs of a urinary tract infection, such as frequent urination and dysuria.[27] Endometritis and salpingitis can develop as a result of infection that may rise from the cervix. Chlamydial PID may manifest as pelvic or lower stomach discomfort together with cervical motion tenderness, uterine or adnexal tenderness, or even without any symptoms at all (up to and including upper genital tract infection, according to some studies).[28,29]

Cervicitis with a yellow, hazy, mucoid discharge is visible from the os upon examination. When the cervix is scraped with a spatula or brush, it frequently bleeds freely. The presence of >5 WBC/HPF (high power field), which is symptomatic of urethritis, can be detected by urinalysis.[30]

Clinically, chlamydial infections cannot be separated from other urethral infections. Chlamydial infections can be distinguished from other lower genital tract infections using the amine test, which involves a considerable release of odor when KOH is added to the vaginal fluid, however it has a low specificity.[21]

In a high-risk group, between the time a patient tested positive for *C. trachomatis* and the time they returned for treatment, 2% to 5% of untreated women experienced PID.[31,32]

Having a *C. trachomatis* genital tract infection can harm a pregnancy as well. A higher risk of ectopic pregnancy is linked to prior chlamydial infection.[33,34] Infection with *C. trachomatis* has been linked to spontaneous abortion, stillbirth, and preterm delivery.[35-37] Chlamydia-infected pregnant women are more likely to experience negative pregnancy outcomes and postpartum PID. There have been recorded sequelae such as stillbirth, low birth weight, neonatal death, shorter gestation periods, preterm delivery, and premature rupture of membranes (PROM).[38]

During delivery, *C. trachomatis* can also be transferred to a newborn through contact with infected cervical tissue and secretions, infecting the eye, oropharynx, urogenital tract, and rectal mucous membranes. In some areas, infection could be asymptomatic. The most typical presentation is conjunctivitis caused by *C. trachomatis*, which appears 5-12 days after birth.[39] Although *C. trachomatis* can also cause a subacute, afebrile pneumonia that starts in children as young as one to three months old.[40]

C. trachomatis has been suggested as a potential risk factor for cervical cancer in addition to major reproductive implications such infertility, ectopic pregnancy, and persistent pelvic pain. Although the human papillomavirus (HPV) is a known cause of cervical cancer, this disease is not always brought on by HPV exposure. Consistent, high-risk HPV infections are more likely to develop into squamous cell carcinoma (SCC) or invasive cervical cancer (ICC) in the presence of known cofactors such smoking, behavioural variables, age, genetic background, and individual immunological variance.[41] Based on research linking the presence of anti-CT antibodies with risk for ICC or SC and the discovery of chlamydial DNA in HPV-associated lesions, chronic cervical infection by *C. trachomatis* has been postulated as a cofactor.[42,43] These infections are frequently symptomatic, in contrast to *C. trachomatis*, and are linked to genital tract infections. A fever is frequently present, and symptoms include anorectal pain, discharge, tenesmus, rectal bleeding, and constipation. Strictures and extensive scarring could develop as a result of non-treatment.[44]

DIAGNOSTIC PROCEDURES

Chlamydiae are labile bacteria, and it is possible to maintain viability by keeping specimens cool and reducing the amount of time between specimen collection and laboratory processing.[45] Patients with urogenital, anorectal, and ophthalmic symptoms, those with STIs other than chlamydia, those who have had sexual contact with someone who has a STI, and those who are scheduled for chlamydia screening should all get tested for the infection.[46]

Both direct and indirect techniques are used in diagnostic procedures to find CT infections. Assays for direct pathogen identification, such as culture, antigen tests like Enzyme immunoassay (EIA), direct fluorescent antibody (DFA), immunological chromatographic and rapid diagnostic tests (RDTs), nucleic acid hybridization, and amplification tests, were often used to assess localized infections. For the diagnosis of chronic or invasive infection (PID, LGV), indirect techniques such as sexually acquired reactive arthritis (SARA) rely on the identification of antibodies against *C. trachomatis*.[47]

Swabs from many anatomical locations, including the endocervix, urethra, anal canal, and conjunctivae, can be used as culture specimens, but only with specialized tools and transport medium.[48] After 48-72 hours, samples are spun onto a confluent cell monolayer and stained with Giemsa, iodine, or fluorescence-labeled antibodies to chlamydial antigens (LPS or MOMP) to look for the appearance of distinct intracytoplasmatic inclusions. Since detection is very specific when MOMP-specific antibodies are used for labelling cell culture, it has long been thought of as the standard test for CT detection.[49]

The most accurate test to find chlamydia is nucleic acid amplification test (NAAT). These tests have a high specificity that is equivalent to culture, however unlike culture, they don't require living pathogens, making specimen transit easier. As a result, NAATs are now the preferred test for chlamydia and have supplanted culture as the preferred method of diagnosis. Due to inadequate diagnostic accuracy, antigen tests (EIA, DFA, RDTs) are no longer advised for chlamydia testing.[48,50]

In addition to the chlamydia tests' adequate diagnostic precision, the turnaround time for results generation and reporting is crucial for starting treatment on schedule. NAATs are often conducted in a centralized laboratory, requiring the transfer of test specimens and the communication of test findings to the doctors. Since NAAT-based diagnoses need a second visit from patients, if they do not return, therapy may be delayed or discontinued altogether, which may contribute to the high prevalence of infection. Since RDTs (Rapid diagnostic tests) enable near-patient (point-of-care) testing and deliver findings in a few minutes, they are independent of these logistical demands and enable patients to start receiving antibiotic medication right away when they test positive. The majority of RDTs employ lateral-flow immunochromatographic techniques to detect chlamydia LPS antigen in urine or vaginal swabs.[47]

Given that chlamydia antibodies can only be detected after several weeks, that antibody titers may be low, and that many serologic tests are unable to distinguish between antibodies against various chlamydia species, testing for chlamydia antibodies in various chlamydia species is not helpful in the diagnosis of local epithelial infections of the lower genital tract. However, serology can be useful in the identification of invasive and persistent infections (PID, LGV, SARA). The germs are typically not detected in urine or anogenital swabs in these situations, although a causal chlamydia infection can be determined using serologic data. Negative serology most certainly rules out the involvement of chlamydia as chronic CT infections and problems from ascending infections are typically accompanied by a positive antibody response. Positive serology, on the other hand, does not always indicate an associated chlamydia infection.[47]

PREVENTION

Latest study indicates that rather than single infections, *C. trachomatis* tubal damage may often be the consequence of repeated infections.[51,52] So it stands to reason that untreated sex partners rather than freshly acquired sex partners may be the most typical source of reinfection among women. Recurrence happens soon after the first infection, according to a number of studies and according to Blythe et al 38% of recurring cases did not report finding new partners for sex.[53,54] Referring the partner(s) to a clinic for treatment by the doctor via the index woman is the most popular current approach for the management of sex partners of women with chlamydia infection.[55]

Partner notification by a healthcare professional is another strategy for partner therapy. Disease intervention specialists (DIS) commonly carry out this in the US. Although partner notification for syphilis has typically been found to be effective, it is still unknown if this strategy is effective for controlling chlamydia, but it can still be given another look as a potential solution. Additionally, it requires a lot of labor and could offend some ethnic groups.[56,57]

Effective ways to prevent Chlamydia trachomatis infections

Most important is safe sexual practices-promoting the regular and appropriate use of condoms during intercourse. Encouraging partners to speak candidly about sexual health. Sexual education program putting in place thorough sex education initiatives in communities and schools to raise awareness of STIs, including *Chlamydia trachomatis*. Frequent screening initiatives-putting in place regular screening programs, particularly for high-risk groups like young adults who are sexually active and those who have several sexual partners. Healthcare

services that are accessible-facilitating simple access to private, cost-effective healthcare services, such as primary care physicians and sexual health clinics. Research on vaccinations-encouraging the development of vaccines to protect against *Chlamydia trachomatis* as a preventative step.

TREATMENT

The management of chlamydia is based on the patients and the infected partners. The first foremost important step in management would be treat those who are infected in the sexual network.

The introduction of single-dose treatment has been the other important breakthrough in the management of chlamydial infection, aside from NAATs. Patients are now identified and treated with the highest level of convenience and dependability as a consequence. The macrolides, tetracyclines, quinolones, and penicillins are antimicrobial classes that are effective against *C. trachomatis*.[58]

Macrolides

Erythromycin, roxithromycin, azithromycin, and clarithromycin are among the antibiotics in the macrolide class. Macrolides work well against various gram-negative bacteria as well as gram-positive bacteria (with the exception of enterococci).[59] The macrolide is an azalide with a long half-life, excellent tissue penetrability, and resistance to stomach acid. For the treatment of simple urethral, cervical, or rectal chlamydial infections, one dosage of 1 g azithromycin is adequate.[60]

The microbiological and clinical cure rates of a single dose of azithromycin and a seven-day treatment of doxycycline are comparable. It is important to remember that azithromycin is a category B medication that is not approved for use during pregnancy. Observational information, however, points to the safety of its usage during pregnancy.[61,62]

Macrolides have a risk of common side effects such as nausea, vomiting, abdominal discomfort, and diarrhoea, much like any other antibiotic. The main cause of abdominal complaints is that macrolides are motilin agonists, which raise the likelihood of gastrointestinal problems and adverse effects.[63] Although uncommon, severe side effects, including Stevens-Johnson syndrome and toxic epidermal necrolysis, are a possibility and should be taken into consideration when giving these medications.[64]

In general, macrolides are a safe class of antibiotics to use; however, because of their side effect profile and potential for medication interactions, there are certain relative contraindications. Although macrolides have arrhythmogenic properties, they should be avoided by patients with extended QT intervals on electrocardiograms. Additionally, these medications should not be taken by those who have congenital diseases, including long QT syndrome type 2.

Macrolides should be avoided by patients using class Ia and class III antiarrhythmic medications, as both of these drug classes lengthen the QT interval and cause arrhythmias.[65]

Tetracyclines

The first-line antibiotic for the treatment of chlamydial infections also includes tetracycline (TET). Tetracycline (TET) or a TET derivative, however, is the main medication used to treat chlamydial infections in both people and animals. The Centers for Disease Control and Prevention advise treating patients with either a single dose of azithromycin or a 7-day course of doxycycline (a TET derivative).[66]

Tetracyclines have long been the go-to therapy for chlamydial infection. Poor compliance may result from their negative effects and lengthy course of treatment. More than 90% of patients who take 100 mg of doxycycline twice a day for 7 days will be cured. Tetracyclines shouldn't be taken when expecting.[58]

Quinolones

It has been demonstrated that the quinolones ofloxacin and ciprofloxacin are active against these bacteria both in vitro and in vivo. The therapy of C. trachomatis cervical infection, which is regarded as the first sign of pelvic inflammatory disease (PID), is particularly well suited for ofloxacin. The anti-chlamydial medication ofloxacin 400 mg twice a day for 7 days is quite effective.[67]

Quinolone-resistant they may no longer be used in the future due to the discovery of *C. trachomatis in vitro*. Also, quinolones are contraindicated in pregnancy.[58]

Prospective pathways and research deficits: domain for upcoming studies

Vaccine creation ongoing investigation and creation of a potent vaccine against *Chlamydia trachomatis*. Best practices for screening looking into the best and most affordable methods for screening for *Chlamydia trachomatis*, particularly in environments with low resources.

Comprehending the immune response investigating the human immunological response to *Chlamydia trachomatis* in order to guide the creation of vaccines and therapeutic approaches. Antimicrobial resistance's effects evaluating the development, effects, and treatment-related ramifications of *Chlamydia trachomatis* antibiotic resistance. Interventions behavioral investigating the role that behavioral treatments play in lowering the spread of *Chlamydia trachomatis* and encouraging safe sexual conduct.

Possible interventions and public health approaches

Internet services and telemedicine increasing the availability of internet and telemedicine services for private *Chlamydia trachomatis* testing and consulting. Interventions in the community putting community-based strategies into practice to promote testing, lessen stigma, and raise awareness.

International cooperation encouraging global cooperation for uniform data gathering, reporting, and exchange of best practices on the prevention of *Chlamydia trachomatis*. Personalized instruction for at-risk populations creating focused teaching efforts that take socioeconomic and cultural aspects into account for those at high risk.

CONCLUSION

Female genital *C. trachomatis* infection is a complicated, multidimensional problem with far-reaching effects. It has been discovered to make HIV infection easier to get and spread. It has to be addressed holistically, encompassing individuals, legislators, educators, and healthcare professionals. To lessen the frequency and effects of this illness on women's reproductive health and general well-being, early identification, prompt treatment, and a dedication to safe sexual practices are crucial. In conclusion, protecting women's reproductive health requires managing *Chlamydia trachomatis* infections. Preventive measures are essential and include frequent screenings, education, and safe sexual behaviours. Controlling the infection's spread mostly involves partner notification, prompt identification, and efficient management. In order to improve preventative and treatment efforts, future research should concentrate on developing vaccines, developing the best screening techniques, and comprehending the immune response. Globally, women's reproductive health will be improved and *Chlamydia trachomatis*-related difficulties will be reduced as a result of the combined application of these tactics and continuing research projects.

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