***Review Article***

# PREVALENCE AND IMMUNOGENETIC ASPECTS OF *CHLAMYDIA TRACHOMATIS* INFECTION ASSOCIATED WITH CONJUGAL INFERTILITY


## ABSTRACT

*Chlamydia trachomatis* is a mandatory intracellular bacterium whose only natural host is humans. It is the main cause of sexually transmitted bacterial infections worldwide and is most prevalent in young women and men (14-25 years) probably due to its asymptomatic course, inadequate treatment of the partner and delayed development of protective immunity. *Chlamydia trachomatis* infects squamocolumnar or transition epithelial cells, causing cervicitis in women and urethritis in men. Symptoms are mild or absent. Infection by *Chlamydia trachomatis* exacerbates the host's inflammatory response to support its mandatory intracellular developmental cycle. Infertility is the most relevant sequel and affects 15% of couples of reproductive age. The factors responsible for infertility are dominated by *Chlamydia trachomatis*, which can cause serious complications, such as tubal obstructions, ectopic pregnancy, epididymitis, and total irreversible azoospermia. Infertility remains neglected or underdiagnosed in Angola and in most sub-Saharan African countries**.** The present study aims to estimate the prevalence of *Chlamydia trachomatis* and its impact on the reproductive health of couples worldwide, particularly in Sub-Saharan Africa. This review was performed by searching the relevant literature using keywords in the databases MEDLINE, PubMed and Uptodate without language or year restrictions, including Marital Infertility, *Chlamydia trachomatis*, and Angola. The prevalence of *Chlamydia trachomatis* infection is high, and the impact on human reproduction in Africa lacks screening programs and studies of greater scientific relevance.


***Keywords****: Conjugal infertility, Chlamydia trachomatis, Diagnosis, Angola*

## 1. INTRODUCTION

The World Health Organization (WHO) [1] states that sexually transmitted infections (STIs) are among the top five categories in the world for which people seek medical care due to the profound repercussions on sexual and reproductive health. *Chlamydia trachomatis* is the second most common STI in the world and the most common in young women [2]. A critical characteristic of the infection is that immunity is not long-lasting, and reinfection or persistent infection is common [3]. Further, the consequences of *Chlamydia trachomatis* make it the most expensive nonviral STI in the world [4].

The global prevalence is variable, and the data revealed by the U.S. Centers for Disease Control and Prevention (CDC) [4] show that approximately 3 million new infections are diagnosed each year in the United States [5,6].

Several studies have shown that *Chlamydia trachomatis* is a gram-negative bacterium that parasitizes eukaryotic cells, which are found most frequently in the uterine cervix, with serious consequences for the health of women. It is considered a pathogen of high virulence, containing more than 20 serotypes. The bacterium has an affinity for squamocolumnar or susceptible transitional epithelial cells, leading to cervicitis in women and urethritis in men [7]. The transition zone is the probable initial site of infections, according to Reis-Góes et al. [8]. The symptoms are usually mild or absent, but the ascending infection in some women can lead to pelvic inflammatory disease (PID), resulting in reproductive sequelae, such as ectopic pregnancy, infertility and chronic pelvic pain. Complications of infection in men include epididymitis and reactive arthritis. In sexually active women, dyspareunia may reduce sexual satisfaction [9,10,11]. Herkenhoff et al. [12] reported that no sexually transmitted disease has outperformed *Chlamydia trachomatis* in terms of frequency. It is, therefore, the most referenced in Europe, and its detection is common in women with tubal lesions, in which surgical interventions have not proved fruitful, often determining permanent infertility. Its actual prevalence is unknown because it is often asymptomatic [13].

The diagnosis includes a detailed clinical history, to exclude other related pathologies, with the use of highly complex laboratory techniques such as polymerase chain reaction (PCR), whose identification sensitivity has been shown to be superior to those of culture examination. PCR also promotes the detection of nucleotide-specific sequences [11]. Although there are antibiotics that can be used, antimicrobial treatment does not improve the disease after it is established. Drug resistance is rare, but treatment failures have been described. The development of an effective vaccine that protects against diseases of the upper tract or that limits continuous transmission is an important goal for its eradication [7].

This review of the literature aimed to estimate the global prevalence of *Chlamydia trachomatis* infection worldwide, in sub-Saharan Africa and particularly in Angola. There is a need to

conduct permanent epidemiological studies on the infectious diseases prevalent in Angola, as it will allow a global view of the multiple pathologies existing in the country, some of which have been poorly studied and others neglected. Studies that promote knowledge of the factors associated with prevalence, the various circulating *Chlamydia trachomatis* serotypes and their phylogenetic species will be of high relevance and social impact. In Angola, there is little scientific data available on this subject, and studies refer mainly to the impact of the disease on the reproductive health of couples. The clarification of these issues will allow the definition of strategies or policies to assist the affected cases, with a greater focus on the juvenile layer. There is a consensus that the greatest challenge in controlling *Chlamydia trachomatis* infection lies in the fact that 70 to 80% of women and 50% of infected men are asymptomatic, making them the reservoirs of infection for their partners.

## 2. BASIC THEORETICAL FRAMEWORK

The testimonies on *Chlamydia trachomatis* infection date back to 1907, when Ludwig Halberstaedter and Stanislau von Prowazek described, for the first time, an intracellular bacterial genus of Chlamydia infecting orangutans. They performed conjunctival smears of patients with trachoma and subsequently observed granulomas characteristic of trachoma in the conjunctiva of orangutans. Shortly thereafter, inclusions similar to those found in orangutan trachoma were observed in the conjunctival cells of European newborns [14].

From this perspective, *Chlamydia trachomatis* has been characterized as a gram-negative bacterium that is very virulent and has more than 20 serotypes that parasitize eukaryotic cells. Thus, it causes problems in humans, most frequently in the cervix, with serious consequences to the health of women. It presents two morphologically distinct forms, one highly infectious, called elementary corpuscles (CEs), and the noninfectious metabolically active reticulated corpuscles (RCs) [8,15].

The course of the disease can be silent or subacute, leading to nonperception by the patient or nonsuspicion by the health professional. However, the most characteristic clinical sign of *Chlamydia trachomatis* is mucopurulent cervical discharge, which flows from the external cervical orifice and is not always observed [6,16].

Infection by *Chlamydia trachomatis* is considered one of the major problems for human reproductive health and is one of the most referenced infections in the world. It is, for all intents and purposes, a silent epidemic and a mandatory reporting disease because it is responsible for high rates of asymptomatic infections in women, being associated with PID, which eventually causes bridging and adhesions in the pelvic cavity, causing Curtis-Fitz-Hugh (CFH) syndrome. In addition, several authors, such as Bonetti and Silva [17], described other deleterious outcomes, highlighting chronic pelvic pain, dyspareunia, infertility, and ectopic pregnancy, all resulting in reduced quality of life for and sexually active women [18].

The female sex has a higher infectious risk for some STIs, such as *Chlamydia trachomatis*, because the cervical columnar epithelium, after puberty, is more exposed to the vaginal environment, with greater cervical ectopy, and is usually present in 60-80% of sexually active adolescents [18].

In men, untreated *Chlamydia trachomatis* infection may serve as an important reservoir, resulting in repeated transmission of the infection to their partners. The agent is able to bind to the sperm, eventually functioning as a disease vector for the female genital system. By this mechanism, it can cause occlusion of the male genital tract, causing lesions in the cells involved in spermatogenesis and inducing the production of anti-sperm antibodies, impairing their motility and causing premature death and male infertility [12,20,21,22].

Infertility caused by this infection has become a global public health problem, affecting approximately 8-10% of couples, especially young men and women. Thus, 30% of infectious causes of infertility are of female origin, 30% of male origin and 30% of mixed origin. It is estimated that in 10% of cases, it is not possible to determine the causes.

Assis et al. [23] define infertility as a process resulting from organ failure due to dysfunction of the reproductive organs or gametes and characterized by the absence of pregnancy after 12 months of regular sexual intercourse without the use of barrier methods. Fonseca [24] considers infertility as a life crisis and, as in all crises, contends that it produces changes in the emotional balance that cause a downwards cascade of self-esteem such as disorganization, sadness, loss of hope and feelings of guilt.

The pathophysiological aspects and the mechanism of infertility, described by several authors, coincide. Infertility is associated with the presence of autoantibodies induced by repetitive silent infections of *Chlamydia trachomatis*, which induce the release of tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and interferon gamma (IFN)-γ, resulting in apoptosis of epithelial cells and macrophages. Thus, repeated infections by this agent contribute to the increase in lesions and the level of immune response by specific antibodies such as anti-Hsp60. The extent of the lesion seems to be a determinant for the establishment of tubal impermeability [25].

## 3. GLOBAL PREVALENCE OF *CHLAMYDIA TRACHOMATIS*

In a study of a sample of households in the United States conducted from 2007 to 2012 as part of the National Health and Nutrition Examination Survey (NHANES), the prevalence of *Chlamydia trachomatis* was 1.7% among participants aged 14 to 39 years old; this corresponded to 1.8 million infections. The highest prevalence was approximately 14% in African-American women [26].

Data from several authors, such as Santos et al. [27], Moraes [18], and Bonetti and Silva [17], revealed that *Chlamydia trachomatis* has been known since the 1980s as a bacterial infection

and the most common cause of avoidable infertility. It is frequently identified in large urban centres. Although it affects both sexes, it is often treated only in women, since the manifestations and consequences have a greater impact on their reproductive health.

Pereira [28] reported that Sweden was the first country in the world to consider *Chlamydia trachomatis* as a severe infection and to adopt screening programs [29]. Subsequently, other countries, such as the United States, Canada, England and Scotland, also adopted programs with the same objectives and obtained satisfactory results. Data released by the CDC regarding a managed care study showed that STI screening programs, especially for *Chlamydia trachomatis,* can reduce the incidence of (PID) by approximately 60% and reduce the expenditure of public resources [27].

Studies show that the prevalence of infection in young women in the United States has ranged from 2 to 7% among college students, from 4 to 12% among women seen in family planning clinics and from 6 to 20% among all women seen in sexually transmitted disease clinics, which suggests that STIs have greater relevance associated with *Chlamydia trachomatis* [15].

Fernandes et al. [30] showed a prevalence of 10.9% in women aged 20 to 47 years in their study; however, these rates varied according to the type of population studied, the size of the sample collected and the testing policies used for diagnosis, the sensitivity of the diagnostic tests, and the population's access to health services [30].

The WHO [1] reported that STIs are extremely endemic and constitute a public health challenge in the African region, as well as worldwide, and it is estimated that 357 million new cases of the four main curable STIs emerge annually at the global level in individuals ages 15 to 49. These STIs in descending order of frequency are trichomoniasis 142 million, chlamydia 131 million, gonorrhoea 78 million and syphilis 6 million. Most infections were observed in the Western Pacific and the Americas. Infection by *Chlamydia trachomatis* was the most common among the infections with mandatory reporting in the United States [31].

There is a consensus among researchers that there is a need for more studies on *Chlamydia trachomatis* due to its high prevalence. It is estimated that approximately 92 million new cases of infection occur each year*,* reaching almost 37% of STI cases; most are observed in developing countries, affecting mainly adolescents and young people in approximately 8-40% of all cases [32]. The WHO [1] reports that this microorganism infects approximately 90 million people per year through sexual intercourse and that 50-60% of cases progress to infertility, especially of the tubal type. *Chlamydia trachomatis* can exist in the host asymptomatically and cause devastating, irreparable and disabling damage. It is a silent epidemic [21,22,32,33].

In Colombia, in 2011, 1,313 cases were diagnosed; in 2010, 1,525 and in 2009, 1,538 people were diagnosed with *Chlamydia trachomatis* infection [34]. The authors were unanimous in

stating that approximately 5 to 14% of young people aged 16 to 20 and 3 to 12% of women from 20 to 24 years of age were infected with *Chlamydia trachomatis* [35].

A meta-analysis conducted by Roshani et al. [36] in Iran showed that the prevalence of women infected with *Chlamydia trachomatis* reached 15%. The study by Lewis et al. [37] in Australia estimated the prevalence of infection among indigenous women under 25 years of age was 22.1%. In women subjected to assisted fertilization, the prevalence was 40%, which is indicative of the importance of controlling and preventing the sequelae caused by this infection [32].

In the United States, infections by this agent are the most commonly reported STI, and health costs exceed USD $500 million per year. According to North American data from the CDC, this disease was the most often reported STI from 1994 to 2008 [33].

The North American studies showed an infection rate of 6.8% among sexually active women in the age group 14 to 19 years. The National Screening Program for *Chlamydia trachomatis* in England provides molecular screening for all individuals under 25 years of age who are sexually active [28].

Table 1 shows the prevalence of *Chlamydia trachomatis* infection across the various continents, ranging from 45.1% to 12.5%. The rate of detection was high in the 1980s and 1990s, most likely due to the efforts of governments to adopt infection screening programs in response to reports of its high prevalence worldwide the high transmissibility and the repercussions on the health. A high prevalence was found on the Asian and African continents, of 16.3% and 16.5%, respectively, in adults (94.2%; CI = 89.2-97.3%) and adolescents (82.9%; CI = 66, 4-93.4%). The diagnosis was essentially made by immunofluorescence, and the biological samples used were the blood of the study participants (48.7%; CI = 48.8-51.7%) and cervical-vaginal smears (15.1%; CI = 14.8-15.5%).

**Table 1. Specific prevalence of *C. trachomatis* exposure and infection**

| Period | No. | Prevalence | 95% CI |
|---|---|---|---|
| 1980-1990 | 510 | 45.1 | 40.7-49.5 |
| 1991-2000 | 4.675 | 26.3 | 25.1-27.6 |
| 2001-2010 | 10.548 | 14.2 | 13.5-14.9 |
| 2011-2017 | 30.637 | 12.5 | 12.1-12.8 |
| Continent | | | |
| America | 24.966 | 13.9 | 13.5-14.4 |
| Europe | 2.191 | 6.9 | 5.9-8.0 |
| Asia | 13.102 | 16.3 | 15.7-17.0 |
| Africa | 6.111 | 16.5 | 15.6-17.5 |
| **Age group** | | | |
| Adolescents | 35 | 82.9 | 66.4-93.4 |

| | | | |
|---|---|---|---|
| Youth | 34.828 | 13.0 | 12.6-13.4 |
| Adults | 158 | 94.2 | 89.2-97.3 |
| **Diagnostic Test** | | | |
| Molecular (Amplification of Nucleic Acids | 43.724 | 13.5 | 13.2-13.9 |
| Immunofluorescence | 108 | 43.8 | 40.8-46.8 |
| Immunoenzymatic | 1.175 | 23.1 | 20.6-25.5 |
| Cultivation | 391 | 29.2 | 24.7-33.9 |
| **Sample** | | | |
| Cervical-vaginal smear | 38.161 | 15.1 | 14.8-15.5 |
| Urine | 706 | 6.4 | 5.8-7.8 |
| Serum-Blood | 1.149 | 48.7 | 48.8-51.7 |

**Source:** Lozano et al. [34]

In Portugal, adolescents aged 15 to 19 years are the age group with the highest rate of infection. According to the Report of the European Centres for Disease Control, 116 and 167 cases in this age group were reported in 2017 and 2018, respectively. This is a relevant public health concern due to the high rates among the young population, with multiple sexual partners, poor sex education, and high rates of reinfection. The asymptomatic course of infection hinders diagnosis as well as epidemiological control [19].

The rates of STIs have increased, even with the general awareness of the population and the implementation of new diagnostic techniques. Crosby et al. [39] attributed the increase in these rates to the trend of early onset of sexual activity among young people, involving multiple sexual partners, running the risk of not only being infected by *Chlamydia trachomatis* but also by other STIs, as shown in the map in Fig. 1.

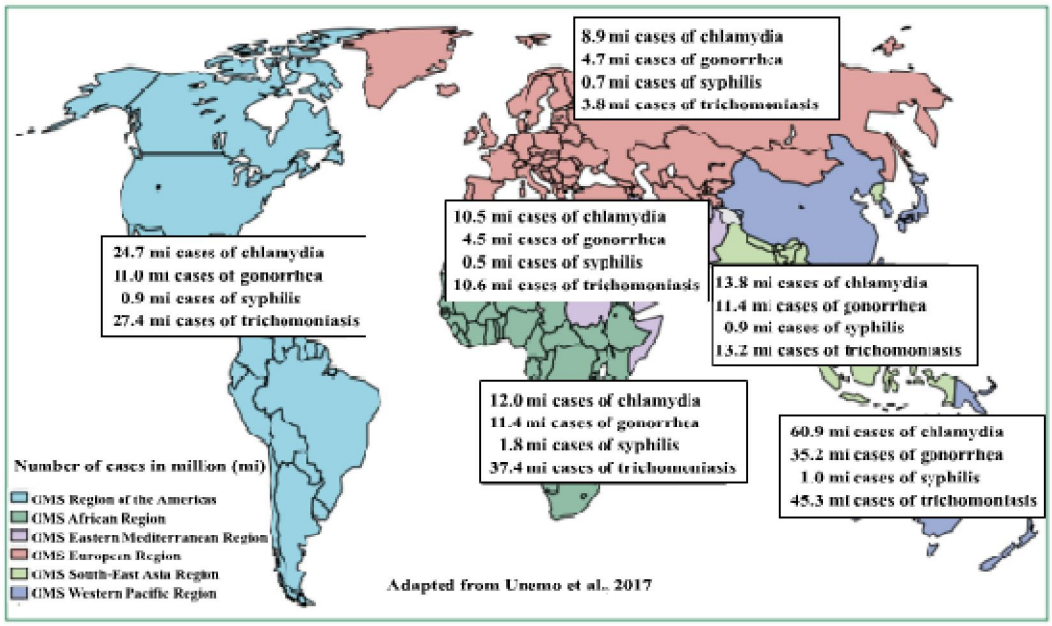


**Fig. 1. Global estimate of new cases of four curable STIs per region in males and females aged 15 to 49 years [39]**

In a systematic review, 25 studies from several countries were analysed in which the prevalence of urogenital *Chlamydia trachomatis* in women ranged from 1.1% to 10.6% and for men from 0.1% to 12.1%. The mean prevalence of infection was variable between countries and was higher in women than in men, and the highest prevalence was found in younger age groups (<25 years). The absence of symptoms of infection was common in both men and women, with a mean of asymptomatic patients of 88.5% and 68.3%, respectively [39].

Fig. 2 shows that the overall prevalence of *Chlamydia trachomatis* infection from data collected between 2005 and 2012 was 4.2% (95% CI: 3.7-4.7%) in females aged 15 and 49 years old, with regional prevalence ranging from 1.8% to 7.6%. In males aged 15 to 49 years, the overall prevalence was 2.7% (95% CI: 2.0-3.6%) [39].

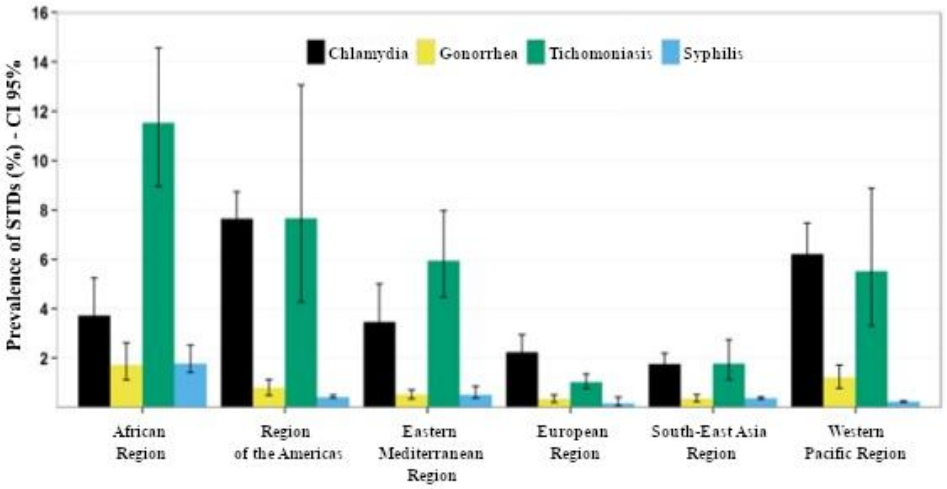


**Fig. 2. Overall estimation of the prevalence of four STIs by region in females aged 15 to 49 years [39]**

Approbato [40] emphasizes that the CDC five basic strategies for the prevention and control of STIs: (i) Education and counselling on how to avoid STIs for individuals who exhibit risky behaviours, (ii) screening for identification of asymptomatic and symptomatic carriers who do not seek health care, (iii) diagnosis and correct treatment of infected individuals, (iv) counselling and treatment of sexual partners, if they have STIs or not and finally (v) vaccination, when available, for individuals who are at risk of contracting an STI. A critical characteristic of Chlamydia organisms is that immunity to infection is not long-lasting. As a result, persistent reinfection is common.

## 4. *CHLAMYDIA TRACHOMATIS* INFECTION IN SUB-SAHARAN AFRICA AND ANGOLA

The statistics on *Chlamydia trachomatis* infection on the African continent are consistent with the clinical and epidemiological aspects of other continents because it is a cosmopolitan infection. Peters et al. [11], in a cross-sectional study on *Chlamydia trachomatis* infection in South African women, reported that the prevalence is high in Sub-Saharan Africa, with more than 10 million new cases each year. The burden of STIs in South Africa is estimated at 20% and is higher in women than in men [10,12].

Masese et al. [41], in a study on the incidence and correlation of *Chlamydia trachomatis* infection in a high-risk group of Kenyan women, reported a global incidence of infection of 92 million cases worldwide, and approximately 16 million (17%) of those cases occurred in Africa. Another study conducted with female adolescents in Uganda estimated a prevalence of

*Chlamydia trachomatis* of 4.5%, which was higher in at-risk groups, while in Nairobi, the prevalence in studies conducted with sex workers was 9% to 28.5% in Dakar-Senegal [41].

Regarding the impact of infection on human reproduction, the studies by Siemer et al. [42] and Ngandjio et al. [43] in Ghana showed that infection by *Chlamydia trachomatis* was a risk factor for infertility in women in Ghana and West Africa, with a prevalence of 3.78%. These researchers also found that most infections became undetectable due to asymptomatic patients, consequently increasing the proportion of infertile couples by approximately 11%, which also put this population at significant risk of human immunodeficiency virus (HIV) infection [42,43].

In this context, the epidemiological studies by Sturm-Ramirez et al. [44], conducted in Senegal on the molecular epidemiology of *Chlamydia trachomatis*, argued that some nonulcerative pathogens, such as *Chlamydia trachomatis,* may serve as biological cofactors for seroconversion of HIV. The explanation lies in the inflammatory reaction caused by *Chlamydia trachomatis*, which promotes the access of CD4 lymphocytes (HIV target) to the inoculation site [44,45].

A hospital-based cross-sectional study of infertile women in Mwanza (Tanzania) was conducted by Ramadhani et al. from November 2015 and April 2016 to determine the importance of *Chlamydia trachomatis* in endocervical smears of 290 infertile women with an average age of 32 ± 6.6 years using the Chlamydia rapid antigen test, with a PCR sensitivity and specificity of 87.5% and 96.5%, respectively [46].

They showed that the prevalence of *Chlamydia trachomatis* was 105/290 (36.21%, 95% CI 30.6% to 41.7%). The prevalence was significantly higher than that of young adolescents ($p < 0.001$). In addition, *Chlamydia trachomatis* was more strongly associated with primary infertility (45/104, 43.3%) than with secondary infertility (60/186, 32.2%). The difference in prevalence between the two studies suggests that *Chlamydia trachomatis* is an important factor in infertility, while the association with primary infertility indicates that it affects women at a relatively young age and concludes that the prevalence of *Chlamydia trachomatis* among infertile women in Mwanza is high. Thus, establishing the prevalence of *Chlamydia trachomatis* can be a powerful argument in favour of prioritizing interventions, such as routine screening and treatment of high-risk women [46].

Data on Angola are referenced by a study by Cappuccinelli et al. [47] conducted at the Lucrécia Paim Maternity Hospital, which sought to evaluate the incidence of *Chlamydia trachomatis* infection and concluded that infection is one of the major causes of endocervicitis/PID in women and epididymitis/deferentitis in men. The consequent conjugal infertility tends to be simultaneously a health problem and a social disadvantage in the context of African culture [47]. The same study revealed an incidence of 27-75%, and the cases presented with symptoms of pelvic pain, cervicitis, dysuria and dyspareunia, corresponding to 41.1%, 51.5%,

8% and 4%, respectively. The incidence was higher in the 20-24 age group, with approximately 25.2%, when subjected to the Indirect Immunofluorescence Test [47].

## 5. BIOLOGY OF *CHLAMYDIA TRACHOMATIS*

*Chlamydia trachomatis* is a mandatory intracellular bacterium whose only natural host is human. It develops successful mechanisms to prevent destruction by autophagy and by the host's immune system, persisting within its epithelial cells [48]. Chlamydia has a biphasic cycle, with two forms: the first is called elementary bodies (EC), which is the infectious and resistant form that survives in the extracellular environment, and the second is called reticular bodies (RCs), which is noninfectious and is the proliferative form of the disease [8].

There are several serotypes of *Chlamydia trachomatis,* and until 1999, the order *Chlamydiales* had only the genus *Chlamydia* within the family *Chlamydiaceae*, with differentiation of the four species *Chlamydia trachomatis, Chlamydia psittaci*, *Chlamydia pneumoniae* and *Chlamydia pecorum* defined by phenotypic, morphological and morphological criteria [29].

Until the 1960s, it was considered a virus due to its small size ranging from 0.2 to 1.5 µm and its mandatory intracellular parasitism, not having the ability to generate ATP to produce its own energy, depending entirely on the host for its reproduction. However, these organisms have several properties that confirm their bacterial nature, such as internal and external membranes similar to those of gram-negative bacteria, possession of DNA, RNA and ribosomes, synthesis of their own proteins, nucleic acids and lipids, and susceptibility to antibiotics [15].

The members of the order *Chlamydiales* are bacteria phylogenetically distinct from all known bacteria because they have a unique biphasic development cycle that differentiates them from all other prokaryotes [29]. The species *Chlamydia trachomatis* is divided into more than a dozen serovars, a division based on the specific immunoreactivity of OMP (outer membrane proteins), which are membrane surface proteins associated with LPS (lipopolysaccharide antigen) that have species-specific epitopes containing four regions with variable amino acid sequences among the different serovars.

The genes encoding the OMPs in the different serovars have a high degree of homology, and these regions are predominantly constant, spaced by four variable domains (VDs), grouped from I-IV, with approximately 40 to 90 bp (base pairs). There is a variation in the sequence of amino acids and in the length of the OMPs (between 372 and 375 amino acid residues); this is due to the differences observed in the VD coding sequences between the serovars of *Chlamydia trachomatis* [29].

The serovars are divided into three disease groups, which for ocular disease (trachoma) is implicated by serovars A, B, Ba and C, which are agents of follicular conjunctivitis, responsible for the blindness of neonates worldwide; the disease is preventable but has a high prevalence

in Africa, the Middle East, Asia and South America. Among those involved in sexually transmitted infections are serovars D, Da, E, F, G, Ga, H, I, Ia, J and K. The prevalence of these serovars is heterogeneous, but authors from different countries report serovars D and EF as the most often implicated; however, genotypes D, F, E, and G are significantly associated with women younger than 25 years of age, with high exposure to risk factors for STIs [29,49].

## 6. GENETICS OF *CHLAMYDIA TRACHOMATIS*

The genome of *Chlamydia trachomatis* is formed by a circular chromosome with approximately 1,045 megabases whose content is 45% guanine-cytosine and a plasmid called a cryptic plasmid of 7.5 kilobases (kb). The plasmid encodes eight proteins and is a transcriptional regulator of chromosomal genes and a virulence factor. The plasmids isolated from *Chlamydia trachomatis* are conserved, with less than 1% variation in the nucleotide sequence; these have eight phases of open reading frame (*ORF*) interspersed with four short noncoding sequences of 22 bp [50].

### 6.1 Immune response

Immune response is based on the action of Mannose Binding Lecithin (MBL), Mannose-Binding Lectin and the presence of *heat shock proteins* (Hsp60). MBL is synthesized primarily in the liver and has the function of recognizing antigens through structures arranged on their surfaces, called pathogen-associated molecular patterns (PAMPs), which in turn contain cellular receptors, pathogen recognizers (PRRs), promoters of inflammatory modulation and cell apoptosis. A state of MBL deficiency suggests that this condition predisposes patients to numerous infectious diseases, including *Chlamydia trachomatis*. Thus, there is a hypothesis that there is a defect in the first line of innate defence of the host; the variant of codon 54 of the gene, which codes for MBL, may contribute to the persistence of *Chlamydia trachomatis* in the upper female genital tract. The development of epitope immunity in Chlamydia Hsp60, which is also present in the corresponding human Hsp60, may increase the susceptibility to pregnancy failure in infected women [48]. Vinagre [51] also reported that the frequency of MBL deficiency was higher not only in women but also in partners (14% to 16%) than in controls (less than 5%).

The Hsp60 protein (CT-Hsp60) is synthesized during persistent infection and is released into the bloodstream; as a consequence, the cells that make up the body's immune system will produce anti-*Chlamydia trachomatis*-Hsp60 antibodies [39,52]. The members of the Hsp60 family are especially recognized as immunodominant antigens of some pathogens, such as *Chlamydia trachomatis*.

Infection in the upper genital tract will induce an intense tubal inflammatory response, with the action of antibodies against *Chlamydia trachomatis* Hsp60, causing tubal lesions. Some of these Hsp60 polypeptides are involved in protein folding and translocation of organelles through cell membranes, which are called molecular chaperones. The presence of Hsp60 may be

essential for cell multiplication, also developing important functions for the regulation of cell differentiation, division and apoptosis [39,48].

Although this protein is initially associated with beneficial and physiological properties, Hsp60 expression has also been associated with several pathological conditions.

Hsp60 triggers humoral and cell-mediated immune responses with intense macrophage activity. Activated macrophages release proinflammatory cytokines, and infection induces the release of tumour necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β) and interferon gamma (IFN-γ) [53].

Apoptosis of epithelial cells and infected macrophages leads to the release of more proinflammatory cytokines and exacerbates the host's inflammatory response. Thus, repeated infections by this agent contribute to the increase in lesions and the level of immune response by anti-Hsp60 antibodies, and the extent of the lesion seems to be determinant in the establishment of tubal impermeability. In this context, Valladão et al. [52] showed that 75% of women who were unable to become pregnant, who had tubal occlusion and no previous history of STI had circulating antibodies to the structural antigens of *Chlamydia trachomatis* [54].

## 7. CONCLUSION

- *Chlamydia trachomatis* is considered one of the major problems for human reproduction, and despite affecting people of both sexes, it is often treated only in women, since the manifestations and consequences have a greater impact on the reproductive health of women than men.
- The high rates of asymptomatic infections, especially in women, suggest the availability of free diagnostic tests, as well as national screening programs for *Chlamydia trachomatis*, which already exist in other countries.
- The mechanism of infertility is associated with the presence of autoantibodies induced by persistent, silent infections of *Chlamydia trachomatis* (hsp60-CT), which are released into the bloodstream, inducing the release of TNF-α, IL-1β and IFN-γ.
- Infection by untreated *Chlamydia trachomatis* in men may serve as a natural reservoir, resulting in repeated transmission of the infection because the agent is able to bind to the sperm, eventually functioning as a disease vector for the female genital system.
- In the male genital tract, it causes damage to the cells involved in spermatogenesis and induces the production of anti-sperm antibodies, impairing motility and causing premature death, which can lead to male infertility.

## COMPETING INTERESTS

The authors declare that they have no conflicts of interest or personal relationships that may have influenced the work reported in this article.

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