

# Chlamydia trachomatis infection in pregnant women: an important risk to maternal and infant health.

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## ABSTRACT

Chlamydia trachomatis is currently, the major cause of bacterial sexually transmitted infections (STIs) worldwide. Infection prevalence peaks in women younger than 25 years. There is increasingly more evidence that infection with Chlamydia trachomatis can cause adverse pregnancy and infant health outcomes (stillbirth, premature rupture of membranes, puerperal infections, miscarriage, ectopic pregnancy, neonatal pneumonia and neonatal conjunctivitis). In spite of these data, few countries have a routine pregnancy screening program that would guarantee a decrease of the aftermath caused by untreated infections. The aim of this article is to review and discuss the current literature about Chlamydia trachomatis epidemiological data, screening and treatment in pregnant women. We think that the majority of these cases could be identified with the implementation of screening programs focusing this target group.

**Keywords:** Chlamydia trachomatis, pregnancy, pregnant women, parturient women, asymptomatic women

## INTRODUCTION

*C. trachomatis* is the most prevalent sexually transmitted bacterial infection worldwide<sup>[1]</sup>. According to European Centre for Disease Prevention and Control (ECDC), in 2014, 396 128 cases of *C. trachomatis* from 26 EU/EEA Member States, were reported and a total of 187 cases per 100 000 population were notified<sup>[2]</sup>. These infections continue to infect lots of people and the exact magnitude of this is still unknown<sup>[3,4]</sup>.

The greatest challenge to control the infection is that as many as 85% -90% of both men and women are asymptomatic, so a large reservoir of infected individuals, are capable of transmitting the infection to their sexual partners. In women not diagnosed and not treated, the infection can cause several sequelae, including chronic pelvic pain, PID (pelvic inflammatory disease) and tubal factor infertility<sup>[5]</sup>. Adverse pregnancy outcomes, including preterm birth, ectopic pregnancy (EP), low birth weight, premature rupture of

membranes (PROM), stillbirth, miscarriage as well as a neonatal disease<sup>[6]</sup>.

Protective immunity to *C. trachomatis* is considered to be short-lived<sup>[7]</sup> and recurrent genital chlamydial infection is common<sup>[8,9]</sup>. The highest incidence of *C. trachomatis* occurs in the group of fewer than 25 years of age and gradually decreases with increasing age<sup>[9,10]</sup>. Knowledge concerning the impact of infection during pregnancy can significantly improve through information strategies and treatment of infected pregnant women as a preventive health measure.

## REVIEW METHODS

Data from and inclusive of 2000 to 2016 were sought. The search process was conducted using the electronic databases Pubmed/NCBI, Cochrane and Google Scholar. The terms

"*Chlamydia trachomatis*" and "*Chlamydia trachomatis* infections" were combined with "stillbirth", "miscarriage", "preterm birth", "premature rupture of membranes", "ectopic pregnancy" or "intrauterine fetal and neonatal infection". We also searched reference lists of articles to identify supplementary information. Citations were limited to studies including pregnant women, and we did not include papers that assessed outcomes after surgical instrumentation. Our initial literature search yielded 739 unique citations. After a critical evaluation, based on study design, a total of 26 articles was selected, for review (Table 1).

## CLINICAL MANIFESTATION IN WOMEN

As obligate intracellular pathogen with an ability to exist in resting and infectious forms within human epithelial host cells, *C. trachomatis* has the capability to evade host detection and elimination, contributing to cause adverse outcomes among women<sup>[11]</sup>.

When women suffer clinical manifestations, these include increased vaginal discharge, dysuria, vaginitis, cervicitis, urethritis, or occasional postcoital bleeding and, in more severe infections, endometritis and PID. Some studies have reported a present infection on both the cervix and the urethra in 50-60% of symptomatic women, and 30% of them have only cervical infection<sup>[12,13]</sup>. *C. trachomatis* infections cause severe tubal immunopathology despite the absence of symptoms, and in over 50% of women with tubal occlusion, previous history of PID has not been reported<sup>[13-15]</sup>.

### Infections in pregnant women

During pregnancy, marked changes take place due to hormonal levels and *Lactobacillus spp* replacement occurs, making the vaginal pH less acid. This medium favors the proliferation of different pathogens, which are often difficult to eradicate, resulting in cervicovaginal infections, a common disorder during gestation. The pregnancy increases the risk of *C. trachomatis* colonization alters the immune response.

The pathogenesis of *C. trachomatis* is still not well understood. Chlamydial infection may lead to adverse pregnancy outcomes by infecting the fetus, by stimulating a fetal immunogenic response with cytokine release or causing and excessive maternal immunogenic response due to the homology of the human and chlamydial 60kDa heat shock proteins (CHSP-60)<sup>[16,17]</sup>. It is also thought that these inflammatory reactions to CHSP-60, could cause tubal damage that may lead to tubal infertility and EP<sup>[18,19]</sup>.

*C. trachomatis* infection can origin a number of complications during pregnancy, based on WHO definitions: stillbirth (fetal death at 28 or more weeks of gestation) miscarriage (pregnancy that ends spontaneously before the fetus has reached a viable gestational age of 24 weeks), preterm birth (birth before 37 weeks' gestation), as well as, PROM, EP and intrauterine fetal and neonatal infection<sup>[11,20]</sup>.

In the last few years, numerous epidemiological studies have aimed to determine the prevalence of *C. trachomatis* infection in pregnant women and its potential adverse effect, but data are influenced by setting, age, risk factors, as well as, the diagnostic method used and the type of specimen tested. Concise information is essential and could contribute to the design of appropriate infection control programs in different geographical locations. With the purpose of avoiding these complications, pregnant women should be appropriately screened, especially younger women and those with risk

factors, and if they are positive for *C. trachomatis* infection or other STIs, should be treated properly.

### Stillbirth

A high number (about 2.6 million) of stillbirths occurs yearly, 98% of these deaths take place in low-income and middle-income countries, but stillbirths also continue to affect wealthier nations, with around 1 in every 300 babies stillborn in high-income countries<sup>[21]</sup>.

Maternal infections are thought to be an important cause of stillbirth in low and middle-income countries as well as in high-income countries<sup>[11,22,23]</sup>. Although syphilis is a major contributing factor for stillbirths, some studies have found a possible association between *C. trachomatis* infection and stillbirths, but data are scarce. One Australian retrospective study<sup>[24]</sup> found the highest risk of stillbirth between women with chlamydial infection before to birth (aOR 1.40, 95%, CI 1.00 to 1.96). Another one, conducted in Finland<sup>[25]</sup>, compared the prevalence found in serum specimens. Women with stillbirth after the 21st gestational week, with preterm delivery between gestational weeks 23 and 29 and cord blood from consecutive liveborn deliveries, were studied. It was proved that *C. trachomatis* IgG antibodies are frequently detected in sera from mothers with stillbirth.

### Miscarriage

Miscarriage is one of the most common ongoing studies in adverse outcomes. In the majority of cases, women's health effects of a miscarriage may be unreported. In the most severe cases, symptoms that may occur include pain, bleeding and a risk of hemorrhage. Grief is also common, and the affected can suffer psychologically<sup>[26]</sup>.

Persistent asymptomatic *C. trachomatis* infection that it extends to the endometrium or the fetal tissue could induce spontaneous abortion. During *C. trachomatis* primary infection miscarriages are not frequent, which explains the absence of an association between this event and levels of IgA. Several patients exhibited *C. trachomatis* positive serologic results with negative detection of *C. trachomatis* DNA. These data suggest an association between miscarriage and damage induced by persistent *C. trachomatis* antibodies or a precedent of chlamydial infection that can interact with embryonic antigens<sup>[27]</sup>. *C. trachomatis* has been studied extensively and a lot of data are available for this infection from over three decades of research. Nevertheless, the literature shows different results giving rise to contradictory evidence regarding the role of *C. trachomatis* in miscarriage, perhaps because of different study design.

Many studies show a potential association of miscarriage and *C. trachomatis* infection<sup>[27-32]</sup>. Authors demonstrate positive results from products of conception and placentas by anti-chlamydial IgG and IgA antibodies and the detection of chlamydial DNA/antigen. One study performed in Switzerland<sup>[27]</sup>, found that women with positive chlamydial serology were more likely to have miscarriages than control groups (aOR2.3, 95% CI1.1-4.9). Also, detection of *C. trachomatis* DNA was more frequent in the placenta of women with miscarriage than females belonging to the control group (4% vs. 0.7%,  $p=0.026$ ). Similarly, other studies such as in Iran and the Slovak Republic, have suggested that chlamydial infection during pregnancy can increase the possibilities of miscarriage (OR=2.41; 95% CI 1.32-3.35,  $p<0.01$ ) and (OR=2.198, CI 95%: 1.058-4.56.), respectively<sup>[29,30]</sup>.

### Preterm birth and/or premature rupture of membranes

Preterm birth, an important determinant of neonatal mortality and morbidity with long-term adverse consequences for health, occurs in 9.6% of all births worldwide. The causes are multifactorial, with 30% being related to PROM<sup>[33]</sup>. Inflammatory cells or histological chorioamnionitis produced by *C. trachomatis* infections are implicated in the weakening of the fetal membranes among pregnant women thus causing PROM and preterm birth, especially at early gestational ages<sup>[34]</sup>.

Late sequelae associated with preterm birth are not infrequent. These premature children are more likely to suffer cerebral palsy, sensory deficits, learning disabilities and respiratory illnesses compared with children born at term. It results in avoidable psychological and economic costs<sup>[33]</sup>. Some studies show an increase in preterm birth when maternal chlamydia infection is produced before 32 weeks of gestation. These authors found chlamydial DNA in a high percentage of samples belonging to these women<sup>[35-37]</sup>. One of them<sup>[36]</sup> reported a fourfold increased risk of early preterm delivery in mothers with *C. trachomatis* infection.

In 2003, information regarding chlamydia infection was added to the Washington State birth certificate, allowing for an opportunity to assess the risks of adverse pregnancy outcomes in women with chlamydia infection. These results raise the possibility that *C. trachomatis* is still an important agent associated with PROM and preterm delivery. Data showed a significantly increased risk of PROM in women with *C. trachomatis* infection compared with those without infection (RR 1.50, 95% CI 1.03 to 2.17)<sup>[38]</sup>.

Other studies have identified similar correlations between preterm labor, premature preterm rupture of membrane (PPROM), or prematurity and infection with *C. trachomatis*<sup>[39,40]</sup>. One of them, a non-interventional and prospective analysis, performed in Holland<sup>[39]</sup> found that *C. trachomatis* detected by Nucleic Acid Amplification Test (NAATs) was significantly associated with prematurity before 35 weeks of pregnancy, this risk being higher before 32 weeks, suggesting that chlamydia contributes more to early than too late prematurity.

### Ectopic pregnancy

Ectopic pregnancy occurs when the blastocyst attaches to an area outside of the uterus endometrial cavity (in the fallopian tubes, ovaries or abdomen). In Western countries EP is estimated to occur in about 1–3% of pregnancies<sup>[41, 42]</sup>. More than 95% of all EPs are located in the Fallopian tube<sup>[43, 44]</sup>. An association between *C. trachomatis* infections and EP have been supported by several studies with different designs and it is considered to be the most important etiological agent<sup>[14,45-48]</sup> although others<sup>[49,50]</sup> pointed out recently that the evidence has been mostly descriptive. Past chlamydial PID is associated with increased risk of EP, but contradictory results have also been reported from Denmark, where women with at least one positive *C. trachomatis* result had a lower rate of EP than women with negative results<sup>[51]</sup>. Moreover, women with EP are at an increased risk of repeat EP and infertility<sup>[52]</sup>.

The primary cause of EP and tubal infertility is prior silent salpingitis caused by *C. trachomatis*, that which can lead to the formation of peritubal adhesions, hydrosalpinx, and intramural fibrosis. Some epidemiological studies have shown a possible association between the development of EP and chlamydial antibodies like antibodies specific to *C. trachomatis* and chlamydial heat shock protein (CHSP-60) as well as antigenic

material and histological data. These findings were found more frequently from women with ectopic pregnancies vs. controls<sup>[19,20]</sup>. Furthermore, some authors have suggested that genital *C. trachomatis* infections could increase the risk of developing EP, three or four times<sup>[11,41,42]</sup>.

### CHLAMYDIA TRACHOMATIS AND ADVERSE INFANT OUTCOMES

The risk for vertical transmission of *C. trachomatis* is between 60% and 70% and follows the infant's passage through the birth canal, which can increase the risk for neonatal sepsis. One study from Brazil demonstrated that *C. trachomatis* could contribute to the development of both severe infection and early neonatal death<sup>[52]</sup>. However, there is some evidence that vertical transmission can also occur in uterus, since newborns delivered by cesarean sections have also been born infected and with intact membranes<sup>[37]</sup>.

It is estimated that approximately 50–70% of infants born to mothers with the untreated genital chlamydial infection will become infected. About 30–50% of them will develop conjunctivitis and 10–20% pneumonia<sup>[11,54]</sup>.

### Neonatal conjunctivitis

The ocular *C. trachomatis* infection manifests as an inclusion conjunctivitis. During intracellular development cycles, the metabolically active reticulate bodies of the pathogen, are accumulated in the endosomes of host cells turning them into cytoplasmic inclusions. The inflammatory response causes granulocytes accumulation at the site of infection, which appears clinically in different forms.

The majority of chlamydial conjunctivitis develops 5–14 days after birth and heals spontaneously. However, if left untreated, symptoms ranging from mild to severe. Mild conjunctival injection gives rise to scant and watery secretions while more serious symptoms include mucopurulent discharge with chemosis, eyelid edema, and pseudomembrane formation.<sup>[55,56]</sup> Due to the slowly progressive nature of the untreated condition it can be only occasionally diagnosed in infants after two months<sup>[57]</sup>. Chlamydial conjunctivitis cannot be prevented by ocular instillation of antibiotics or silver nitrate unlike gonococcal conjunctivitis<sup>[11,54,56]</sup>.

The knowledge of the etiology in neonatal conjunctivitis cases is essential to apply initial therapy, preventing further complications. *C. trachomatis* has been regularly reported as a leading agent of neonatal conjunctivitis in several studies. In the Netherlands, where prenatal screening and treatment for *C. trachomatis* are not standard practice, a retrospective/prospective study showed high rates (61%) of *C. trachomatis* detection in infants presenting neonatal conjunctivitis to a pediatric hospital<sup>[57]</sup>. In New Delhi, one study of the infants from different pediatric departments demonstrated that *C. trachomatis* was responsible for 24% of all cases of neonatal conjunctivitis<sup>[58]</sup>.

Also, an incidence of neonatal chlamydial conjunctivitis of 4 per 1000 live births was observed in Hong Kong over a 12-month period<sup>[59]</sup>. From a major Irish regional teaching hospital, was demonstrated an incidence of Chlamydia conjunctivitis of 0.65 per 1000 live births, with an annual rising trend [60]. Others authors provide comparable data in Argentina and Chile<sup>[61,62]</sup>. The results of these studies reflect that the distribution of Chlamydia neonatal conjunctivitis is clearly associated with the prevalence of genital *C. trachomatis* among pregnant women. It has been demonstrated that prophylaxis does not significantly reduce the incidence of

neonatal chlamydial conjunctivitis. For this reason, the best method of preventing neonatal infection is by treating positive *C. trachomatis* mothers before delivery.

### Neonatal pneumonia

Pneumonia caused by *C. trachomatis* usually onset between 2 and 19 weeks typically around 6 weeks of age. These babies, generally have a low-grade fever with an increased respiratory rate and often a persistent cough. Diffuse infiltrates and hyperinflation can be seen clearly on the chest X-ray<sup>[63]</sup>. In younger infants, especially in the premature, chlamydial pneumonia can be more severe presenting initially with respiratory distress followed by apnea and may require hospitalization in 25% of cases<sup>[65]</sup>. Furthermore, untreated infants are at increased risk of developing the chronic pulmonary disease, including asthma and late chronic lung disease in old age<sup>[55,64]</sup>.

Several authors have suggested the involvement of *C. trachomatis* in the development of lower respiratory tract infection in infants, being a pathogen frequent but unacknowledged. In one observational study conducted in children from Massachusetts<sup>[65]</sup>, human strains of *C. trachomatis* were isolated from the lungs of patients with the chronic respiratory disease. On the other hand, studies from Brazil<sup>[66]</sup> and The Netherlands<sup>[67]</sup> found that Brazilian infants born to mothers with chlamydial infection had more frequent respiratory symptoms during the first 2 months of life. Also, *C. trachomatis* infection was detected in 7% of Dutch infants less than 6 months of age, with respiratory tract infection.

### TREATMENT CHLAMYDIA TRACHOMATIS INFECTIONS IN PREGNANCY

In pregnancy, the recommended antibiotics are azithromycin, amoxicillin, and erythromycin. The current first-line option is azithromycin taken in one single oral dose of 1g. Gastrointestinal adverse effects are most common with erythromycin, additionally, in pregnant women, liver clearance of this drug is increased, which could reduce its plasma concentration, resulting in treatment failure. Due to the possible adverse effects on pregnancy course and the possibility of neonatal transmission, a cure test, (preferably by NAAT), is recommended 3-5 weeks after the end of treatment, in all pregnant women with a positive result of screening, to ensure clearance of the infection. Moreover, a further test at 3 months also must be performed, to exclude reinfection<sup>[68,69]</sup>.

In pregnant women with risk factors, such as those aged < 25 years or with several sexual partners or a new sexual partner, an additional test should be performed in the third trimester of pregnancy, to prevent maternal postnatal complications and chlamydial infection in the infant<sup>[1,70,71]</sup>. Tetracyclines and fluoroquinolones are contraindicated in these women. On the other hand, the management of *C. trachomatis* infection requires control of contact tracing to prevent transmission within the community which reduces the possibility of reinfection of sexual partners<sup>[72]</sup>.

### IMPORTANCE OF AN ASYMPTOMATIC INFECTION IN PREGNANCY.

The majority of *C. trachomatis* genital infections in females are asymptomatic and without clinical evidence of complications at the time of diagnosis. Undiagnosed and untreated *C. trachomatis* infections during pregnancy can not only create

serious sequelae in women but also increase the possibility of neonatal transmission.

Investigators in the field, have demonstrated an *in vitro* state of chlamydial persistence viable but non-cultivable. This condition includes a morphological enlarged non-dividing, aberrant RB which is reversible to infectious EB. This process, which is capable of producing a persistent infection in eukaryotic host cells *in vitro*, can also occur *in vivo*. Amoxicillin, clavulanic acid, carbenicillin, ampicillin, piperacillin and penicillin V are antibiotics commonly dispensed during pregnancy that can induce the chlamydial aberrant RB phenotype. These RB can persist for weeks and even months under continued antibiotics exposure and can reorganize and mature into infectious EB once the penicillin is removed<sup>[73]</sup>.

Because of concerns about the relationship between previous exposure to penicillin-class antibiotics and persistence of *C. trachomatis* infection, which has been demonstrated in different studies, amoxicillin is now not considered a first-line therapy in pregnant women<sup>[74,86]</sup>. Clinical experience and published papers suggest that azithromycin is an antibiotic safe with mild side effects. It has effectiveness for over 94% of urogenital infections, being able to attain and maintain high tissue concentrations following a single dose which facilitates adherence to treatment. These are the reasons why this antibiotic must be used primarily, in these women<sup>[75-78, 86]</sup>.

Furthermore, a recent study found that  $\beta$ -lactam-induced persistent *C. trachomatis in vivo* is less susceptible to azithromycin *in vitro*, due to their slowed metabolism<sup>[79,80]</sup>. Therefore, the question arises whether the marked increase in the use of  $\beta$ -lactam antibiotics in recent years<sup>[81]</sup>, have had an impact on the persistence of *C. trachomatis* infection as well as lower response to first-line antibiotic used on pregnancy.

### PREVENTING CHLAMYDIA TRACHOMATIS ADVERSE PREGNANCY AND INFANT OUTCOMES

There are two factors that negatively influence the worldwide prevention of adverse pregnancy and neonatal outcomes from *C. trachomatis*: lack of progressive targeted screening/treatment recommendations for pregnant women and lack of an effective human vaccine, prevention through vaccination is not yet feasible. The complex antigen structure of this pathogen and still insufficient knowledge of the protective *C. trachomatis* antigens involved in the immune response have proven to be a barrier to the development of effective vaccines.

In most countries, the prevalence of *C. trachomatis* infection in pregnant women is not well characterized. Prevalence rates varying from 1 to 10% with even higher rates among pregnant teenagers have been described. These results are influenced by various associated risk factors for infection including in particular; age and socioeconomic status, sitting of the population tested, risk factors, etc<sup>[82-85]</sup>.

Given the strong association between *C. trachomatis* in pregnancy and adverse pregnancy outcomes, screening of pregnant women at the first prenatal visit is recommended by the Centers for Disease Control and Prevention, US Preventive Services Task Force and ACOG (American College of Obstetricians and Gynecologists)<sup>[86-88]</sup>. Additionally, these organizations suggest testing pregnant women at increased risk a second time, during the third trimester. For this motive, early detection and eradication of this bacterium without recurrent or persistent infection during pregnancy may serve for defining healthy strategies focused on prevention.

## CONCLUSIONS

Infections caused by *C. trachomatis* have shown a progressive increase in the past decade in Europe and others parts of the world<sup>[89]</sup>. Several studies showed the highest prevalence among women younger than 25 years and there is increasingly more evidence that *C. trachomatis* infection can cause important complications during pregnancy. For this reason, screening during antenatal care could reduce the rate of adverse outcomes of pregnancy. Furthermore, it has been shown that screening is cost-effective at the prevalence of 3.1-10% and cost saving (over testing symptomatic women) at a prevalence as low as 1.1%, if age was chosen as a selection factor and DNA-based test were used. There are some studies<sup>[90-92]</sup> that showed vaginal swabs as an optimal specimen for *C. trachomatis* detection and there is a study that demonstrated that, even during pregnancy, non-invasive chlamydial screening is feasible in the community<sup>[93]</sup>.

Although *C. trachomatis* genital infection is currently a public health problem worldwide because of the adverse effects on women's reproductive health and in pregnancy, neither pregnant women are screened for *C. trachomatis* infection nor it is not a notifiable disease in most countries. Young pregnant women could be tested easily because these females usually make use of antenatal care in the routinely diagnostic test for HIV, hepatitis B, and syphilis. Implementation of this approach could increase chlamydia screening rates. The CDC has recommended screening for all women at the first antenatal visit with rescreening in the third trimester in women aged  $\leq 25$  years and those who have a new or more than one sexual partner, as these are the women at highest risk<sup>[86]</sup>.

Chlamydia treatment should be provided promptly for all pregnant women testing positive for infection. Several data demonstrate that  $\beta$ -lactam antibiotics commonly prescribed during pregnancy, induce *C. trachomatis* persistent infection at clinically relevant concentrations<sup>[79,80]</sup>. For this reason, currently, azithromycin is considered first-line treatment in pregnant women. Moreover, clinical experience and published studies suggest that this antibiotic is safe and effective<sup>[75,76]</sup>.

On the other hand, repeated infection with *C. trachomatis* increases the risk for serious sequelae. A substantial proportion of women treated is reinfected by an untreated male sex partner in the first several months after treatment. Effective strategies designed at preventing reinfection and interrupting disease transmission, therefore, must provide timely treatment to all potentially infected sex partners are needed. To reduce maternal disease, adverse pregnancy outcomes, and neonatal disease, health systems should consider additional focus on *C. trachomatis* infection in younger women. A better understanding of the natural history of this bacterium is necessary to enhance the control efforts.

## COMPETING ON INTEREST

All authors declare that they have no competing interests. JAB is a researcher from ISCIII/FICYT.

## CONTRIBUTORSHIP STATEMENT

P.M.L., P.S.L., and J.A.B. participated in the planning of the study and wrote the first draft of the manuscript, revised it critically and approved the final version.

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**TABLE 1:** studies from *Chlamydia trachomatis* and adverse pregnancy and infants health outcomes

REFERENCE (YEAR)	COUNTRY	METHODS AND FINDINGS
<b><i>Chlamydia trachomatis</i> and stillbirth</b>		
B Liu <i>et al</i> (2013) [24]	Australia	Among 354 217 women, 1.0% (n=3658) had a chlamydia notification prior to birth and 0.6% of them had a stillbirth. Among pregnant women with CT infection, the risk of stillbirth was higher (aOR 1.40, 95%, CI 1.00 to 1.96)
Gencay <i>et al</i> (2000) [25]	Finland	Serum specimens from 72 mothers with stillbirth after the 21st gestational week were studied for antibodies to CT immunotypes CJHI, GFK and BED by microimmunofluorescence test. The prevalence of CT antibodies Ig G (33.3%) was highest in mothers with stillbirth. In mothers with preterm delivery was 18.8% and the prevalence found in cord blood was 10.4% .
<b><i>Chlamydia trachomatis</i> and miscarriage</b>		
Baud D <i>et al</i> (2011) [27]	Switzerland	Prospectively collected serum, cervico vaginal swab specimens, and placental samples were recovered from 386 women with and without miscarriage. Prevalence of immunoglobulin G against CT was higher in the miscarriage group than in the control group (15.2% vs. 7.3%; p = 0.018). Association between CT positive serologic results and miscarriage remained significant after adjustment for age, origin, education and number of sex partners (odds ratio 2.3, 95% confidence interval 1.1–4.9). CT DNA was more frequently amplified from products of conception or placenta from women who had a miscarriage (4%) than from controls (0.7%) ( p = 0.026).
<a href="#">Rastogi S</a> <i>et al</i> (2000) [28]	India	CT antigen was detected in endometrial curettage tissue by EIA in seventy seven spontaneous abortion females (6-24 weeks gestation). The detection rate was 15.6% (12/77). High prevalence of CT was found in multigravidae and parous spontaneous abortion patients, compared with that in primigravidae and nulliparous Chlamydia-negative spontaneous aborters (75.0% vs 25.0%; 66.7% vs 33.3%, respectively). The prevalence of Chlamydial antigen in patients with no prior history of spontaneous abortion was 16.1% (10/62) compared with 18.1% (2/11) in women with one prior abortion.
Visnovsky J <i>et al</i> (2013) [29]	Slovak Republic	316 women in first trimester of pregnancy were enrolled in the study. Prevalence of miscarriage was significantly higher in group with positive cultivation of CT infection 67.3% vs. 36.0%. Authors did not find a significant difference between the detection of chlamydial infection using conventional cultivation, ELISA or PCR. Association between a CT positive diagnostic test and miscarriage remained significant (OR=2.41; 95% CI 1.32-3.35, p<0.01)
A. Ahmadi <i>et al</i> (2013) [30]	Iran	PCR test was conducted for detection of CT in 109 women with spontaneous abortion with gestation age between 10-20 weeks (cases) and 109 women with normal pregnancy with gestation age between 20-30 weeks (controls). The number of cases with CT infections was 22.9% in the case group and 11.9% in control group, respectively. Association between chlamydia infection and spontaneous abortion was statistically significant (OR=2.198, CI 95%: 1.058-4.56).
Wilkowska-Trojnieł M <i>et al</i> (2009) [31]	Poland	CT infection diagnosis was performed by PCR among 76 women with one miscarriage and 44 women with ≥ two miscarriages. In women with one miscarriage, CT was detected in 11.8% of cases (p=0.029), in women with ≥two miscarriages in 9.1% (p=0.198) and in the comparative group in 2.2%.
H. Zeighami <i>et al</i> (2008) [32]	Iran	CT was detected, in endocervical smears by PCR, in 31 out 145 (21.37%) women with abortion and in 3 out 75 (4%) healthy women. The different was statistically significant (p<0.05)

CT: *Chlamydia trachomatis*, EIA:enzyme immunoassay

TABLE 1: CONTINUED

REFERENCE (YEAR)	COUNTRY	METHODS AND FINDINGS
<b><i>Chlamydia trachomatis</i> and preterm delivery and/or premature rupture of membranes</b>		
Andrews WW <i>et al</i> (2000) [35]	USA	CT infection was determined with a ligase chain reaction assay of voided urine samples collected at 24 weeks' gestation and 28 weeks'. Case patients (spontaneous preterm birth at <37 weeks' gestation; n = 190) and control subjects (delivery at ≥37 weeks' gestation, matched for race, parity, and center; n = 190) were defined among 2929 pregnant women. After adjustment for risk factors, women with CT infection reported two- to three-fold increased risk of preterm delivery before 35 weeks gestation than among the control women.
Rours <i>et al</i> (2011) [36]	Netherlands	4055 pregnant women attending a participating midwifery practice or antenatal clinic were studied. Urine samples, tested by PCR, were analysed for CT infection. The CT prevalence was 3.9%. After adjustment for potential confounders, CT infection was associated with preterm delivery before 32 weeks (OR 4.35 [95% CI 1.3, 15.2]) and 35 weeks gestation (OR 2.66 [95% CI 1.1, 6.5])
Folger AT <i>et al</i> (2013) [37]	USA	A retrospective cohort study was conducted among 3354 women with documented CT infections. Infected women whose infections were detected after 20 weeks gestation or persistent during the pregnancy represented the reference group. Those women with CT infections detected and eradicated at or before 20 weeks gestation were the intervention group. The relative risk for moderate to late spontaneous preterm birth (32–36 weeks gestation) was higher 0.54 (95% CI 0.37–0.80) for women in the intervention group who were 19 years of age and younger.
<a href="#">M M Blas</a> <i>et al</i> (2007) [38]	USA	851 women diagnosed with CT infection were tested. After adjusting for age and education, CT infected women were at an increased risk of preterm delivery (RR 1.46, 95% CI 1.08 to 1.99) and premature rupture of membranes (RR 1.50, 95% CI 1.03 to 2.17) compared with non-infected women.
Rours <i>et al</i> (2011) [39]	Netherlands	Placental histology and clinical data were prospectively obtained from 304 women. CT was detected in 76 (25%) placentas. Histological evidence of placental inflammation was present in 123 (40%) placentas: 41/76 (54%) with CT vs 82/228 (36%) without CT infection (OR 2.1, 95% CI 1.2-3.5).
<b><i>Chlamydia trachomatis</i> and ectopic pregnancy</b>		
Machado <i>et al</i> (2007) [14]	Brazil	CATs in tubal occlusion or previous ectopic pregnancy were tested from 55 women with tubal damage and 55 parous women. CAT was measured using the whole-cell inclusion immunofluorescence test and cervical chlamydial DNA was detected by PCR. The prevalence of chlamydial antibodies and antibody titers in women with tubal occlusion or previous ectopic pregnancy was significantly higher (p<0.1) than in parous women
Barlow RE <i>et al</i> (2001) [45]	UK	The prevalence of chlamydial DNA was determined by PCR and in-situ hybridisation (ISH) in fresh tissue specimens (endometrium, fallopian tube and ovary). Thirty three women presenting with ectopic pregnancy (EP) and 50 control patients from the UK and the West Indies, were investigated. In the UK EP group, chlamydial DNA was detected by PCR in 56% of patients; similar results were found in the Trinidad EP group (67%).
Shaw JLV <i>et al</i> (2011) [46]	UK	Fallopian tube biopsies were screened for current chlamydial infection by PCR. Past CT infection was determined by an enzyme-linked immunosorbent assay. Expression levels of PROKR2 mRNA were higher in fallopian tube from women with serological evidence of past CT infection, compared with women with no serological evidence of past infection.
Bakken <i>et al</i> (2007) [47]	Norway	Prospectively collected CT laboratory data (1990-2003) to EP hospital data (discharge and outpatient registries) in a nested case-control study was made. Six hundred sixteen women with CT test before first EP were eligible as cases. Three controls were matched to each case for year of birth, age at first test, and number of prior tests. Previous CT infection was associated with elevated EP risk (odds ratio [OR], 1.4; 95% confidence interval [CI], 1.0-2.0). In stratified analysis, the association was only significant for the youngest women (born 1970-1984) who had a nearly complete CT testing history (OR, 2.1; 95% CI, 1.3-3.2).

CT: *Chlamydia trachomatis*, EP: ectopic pregnancy, CAT: serum *Chlamydia* antibody titres

REFERENCE (YEAR)	COUNTRY	METHODS AND FINDINGS
		<b><i>Chlamydia trachomatis</i> and ectopic pregnancy: continued</b>
Rantsi <i>et al</i> (2011) [48]	Finland	A total of 800 cases of ectopic pregnancy were included. Equal number of pregnant women without the outcome diagnosis served as controls. Anti-chlamydial IgG antibodies were associated with EP. Positive antibody levels were found in 21.0% of cases and 14.6% of controls ( $p = 0.001$ ; odds ratio, 1.56; 95% confidence interval, 1.20-2.03). Previous exposure to CT, as indicated by serum antibodies, doubled the risk of EP within age and was highest among women 35 years or older.
Low N <i>et al</i> (2006) [50]	Sweden	Data from 43 715 women, aged 15-24 year, were analyzed in Uppsala. The cumulative incidence of PID by age 35 years was 3.9% (95% CI 3.7% to 4.0%) overall: 5.6% (4.7% to 6.7%) in women who ever tested positive for CT, for EP 2.3%
<b><i>Chlamydia trachomatis</i> and infants outcomes</b>		
<b>Neonatal conjunctivitis</b>		
Rours <i>et al</i> (2008)[57]	Netherlands	Two cohorts of infants <3 months of age presenting with conjunctivitis were studied, one retrospectively and one prospectively. Laboratory diagnosis was based on bacterial culture and polymerase chain reaction for CT. CT was detected in 27 (64%) of 42 retrospectively studied infants and 14 (61%) of 23 prospectively studied infants.
Mobile <i>et al</i> (2002) [58]	India	Conjunctival specimens from 70 newborns with conjunctivitis were subjected to bacterial culture and sensitivity testing, monoclonal antibody based CT antigen detection test and species-specific Chlamydia antibody detection in the sera of babies and their mothers, by micro-immunofluorescence assay. CT antigen was detected in conjunctival smears of 17 (24%) babies. Six babies and their mothers tested positive for <i>C. trachomatis</i> Ig G antibodies. At follow-up after 14 weeks, 6 (35.29%) of the Chlamydia antigen-positive babies were found to have developed recurrent conjunctivitis. CT was responsible for almost a quarter of all cases of neonatal conjunctivitis, with recurrences in 35% of cases.
Yip TPP <i>et al</i> (2007) [59]	China	Consecutive patients with neonatal conjunctivitis were investigated separately for CT by polymerase chain reaction, direct immunofluorescent assay, and cell culture. An incidence of neonatal chlamydial conjunctivitis of 4 per 1000 live births in Hong Kong over a 12-month period from 2004 to 2005 was demonstrated.
Quirke <i>et al</i> (2008) [60]	Ireland	All cases of conjunctivitis caused by CT in neonates under 30 days, were analyzed at Cork Hospital. CT was detected by PCR. There were 18 cases of neonatal conjunctivitis during the study. The overall annual incidence of neonatal conjunctivitis in this region was 0.65/1000 live births.
Di Bartolomeo <i>et al</i> (2005) [61]	Argentina	45 out of 571 (7.8%) conjunctival samples were positive for CT by EIA. It was no observed no change about CT prevalence since 1995
C. Valencia <i>et al</i> (2000) [62]	Chile	In 162 newborns, coming from 14 Primary Health Centers from Santiago de Chile, CT was detected by indirect fluorescence and PCR. Those patients with positive indirect fluorescence and PCR were defined as infected. The prevalence of CT was 8%, and the distribution of the positive cases was similar in the different Health Centers

CT: *Chlamydia trachomatis*, EP: ectopic pregnancy, PID: pelvic inflammatory disease, EIA: enzyme immunoassay

TABLE 1: CONTINUED

REFERENCE (YEAR)	COUNTRY	METHODS AND FINDINGS
<b>Pneumonia</b>		
WC Webley <i>et al</i> (2009) [64]	USA	BALF samples obtained from 182 children undergoing bronchoscopy for clinical reasons, were assayed using: PCR analysis, in vitro tissue culture and immunofluorescence staining for the presence of CT. Seventy nine (43.40%) patients were CT positive
A de Borborema <i>et al</i> (2013) [66]	Brazil	Eighty seven newborns were studied, 16 (18.4%) presented respiratory symptoms. Of these newborns, eight (50%) were born to CT-positive mothers evidencing a RR of 7.7. Moreover, neonates born to positive mothers were more likely to develop respiratory symptoms such as nasal obstruction (RR = 6.7), coryza (RR = 7.7), cough (RR = 27.0) and dyspnea (RR = 15.4) (CI 95%)
Rours <i>et al</i> (2009) [67]	Netherlands	The presence of CT in infants less than 6 months of age who presented with respiratory complaints to the Erasmus MC-Sophia hospital was evaluated. Respiratory specimens, primarily nasopharyngeal swabs, were tested for CT. From 148 (94%) infants, 187 respiratory specimens (184 nasopharyngeal aspirates and three BALF were available for CT testing. The mean age of the infants was 67 (SD 49) days. CT was detected in 10 (7%) infants. One (10%) CT positive infant was also infected with RSV

CT: *Chlamydia trachomatis*, RSV: respiratory syncytial virus and BALF: bronchoalveolar lavage fluid

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