



Original article

The association between *Chlamydia trachomatis* in late pregnancy and the development of premature rupture of membranes (PROM)

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ABSTRACT

Background: Premature rupture of membrane (PROM) is considered an important cause of perinatal morbidity and mortality with increased maternal and neonatal risks. The etiology of PROM is known to be multifactorial, however, genital infections such as *Chlamydia trachomatis* is a possible contributing factor to its occurrence. The aim of this study was to assess the incidence rate of *Chlamydia trachomatis* infection in pregnancy and its role in the etiology of PROM. **Methods:** Two groups of patients were included; study and control groups. The study group included twenty full term pregnant women with the diagnosis of recent premature rupture of membranes with a duration of less than twelve hours while the control group included ten normal cases having the same criteria but with intact membranes. All patients were admitted to El Shatby Maternity University Hospital and an informed written consent was taken. Serum samples were collected in red top vacutainer for all women to detect *Chlamydia trachomatis* Immunoglobulin M (IgM) and Immunoglobulin G (IgG). In addition, endocervical swabbing was performed to detect *Chlamydia trachomatis* antigen using ELISA technique. **Results:** The study showed no significant association between PROM and *Chlamydia trachomatis* infection. However, the prevalence of *Chlamydia trachomatis* cervicitis in women with PROM was higher as compared to the control group; 45% compared to 20% by chlamydial antigen. **Conclusion:** The fact that this infection statistically increases the risk of PROM could not be confirmed.

Introduction

Chlamydia trachomatis is the most common sexually transmitted bacterial infection all over the world. As per European Centre for Disease Prevention and Control, 26 EU states noted around 400,000 cases of *Chlamydia trachomatis* in 2014, for a total of 187 cases per one thousand hundred people [1].

Numerous people are still being infected by these organisms, and the extent of this infection is yet unclear [2,3]. A significant reservoir of infected people can spread the infection to their sexual encounters because up to 90% of infected men and women are asymptomatic. This creates difficulties for infection control [4]. Undiagnosed and/or

untreated infections in women can result in a number of consequences, including tubal infertility, chronic pelvic pains, and pelvic inflammatory disease [5].

Preterm birth, ectopic pregnancy (EP), low birth weight, premature membrane rupture (PROM), stillbirth, and miscarriage are just a few of the negative pregnancy outcomes that the bacteria can cause, in addition to neonatal illness [5].

Protective immunity to *Chlamydia trachomatis* is not lifelong and the recurrence is common [6]. The group of women under 25 years old have the highest infection rates, which steadily decline with age [7]. By using the right informational techniques and treating infected pregnant women as a preventive step, the impact of infection during pregnancy can be significantly reduced [8].

During pregnancy, the vaginal pH becomes more alkaline, and this helps the multiplication of many pathogens resulting in cervicovaginal infections. Thus, pregnancy changes the body's immune defense and raises the likelihood of *Chlamydia trachomatis* infection [8].

Chlamydial infection may cause troubles during pregnancy by infecting the fetus, inducing an overactive maternal immune response due to the homology between human and Chlamydial 60 kilodalton heat shock proteins, or by causing a fetal immunogenic reaction with cytokine release. Additionally, it was observed that these inflammatory responses can injure the tubes, which can cause tubal infertility and EP. Many epidemiological studies have attempted to figure out the frequency of Chlamydial infection among pregnancy and its potential effects in recent years, but the results have been influenced by age, risk factors, as well as the methodology used and type of specimen used to test for the infection [9, 10].

Information gathering is crucial and could aid in the creation of effective infection control plans for various regions. Pregnant women must be thoroughly checked, particularly younger women and those who are at risk. If they test positive for *Chlamydia*, they should also receive treatment [10].

In 9.6% of all births all over the world, preterm birth and/or PROM are among the significant infant death and morbidity risks with long-term detrimental impacts on health [11]. Particularly at early gestational ages, inflammatory cells or histopathological chorioamnionitis brought on by *Chlamydia trachomatis* infections may be blamed for the weakening of the fetal membranes that results in

PROM and preterm birth [11,12] Preterm birth can have late complications, which is not unusual. When there is Chlamydial infection prior to 32 weeks of gestation, some studies indicate an increase in preterm birth [13].

The aim of this study was to evaluate the incidence rate of cervical *Chlamydia trachomatis* infection at term pregnancy and its role in the etiology of PROM, which may affect the mode of delivery and the perinatal outcome.

Patients and Methods

The study group included twenty full-term pregnant women within the age group of 25 to 40 years, at or above 37 weeks gestation, the parity was three or less and were admitted to the emergency room of El Shatby Maternity University Hospital with recent premature rupture of membranes less than twelve hours. The control group included ten normal full-term pregnant women with the same criteria of the study group but with intact membranes. The exclusion criteria included women with pre-gestational or gestational diabetes mellitus, history of vaginal examination in the week preceding PROM, cases with intrauterine fetal death (IUFD), history of PROM in previous pregnancies and fever with elevated body temperature above 37.5°C.

All women who participated in the study were informed and a written consent was obtained from each one of them. The diagnosis of PROM was confirmed through a sterile speculum with a trickle of fluid from the external os of the cervix or a pool of fluid at the posterior vaginal fornix. All patients were subjected to thorough history taking, complete general and abdominal examinations and ultrasound assessment of the fetal condition. Laboratory investigations to detect *Chlamydia trachomatis* infection were performed through:

i- A cotton-based swab obtained from the endocervix by rolling across it under sterile conditions, then, samples analyzed using the ELISA technique for detection of *Chlamydia trachomatis* antigen. ii- serum samples collected in a red top vacutainer to detect *Chlamydia trachomatis* immunoglobulin M (IgM) and immunoglobulin G (IgG) by ELISA.⁽¹³⁾ All women were followed till delivery with perinatal outcome evaluation.

Statistical analysis of the data

The data were analyzed and studied statistically through: i- Chi-square test, ii- Fisher's Exact or Monte Carlo correction, iii- Student t-test, and iv- Mann Whitney test.

Results

Twenty percent of the control group showed a positive result for *Chlamydia trachomatis* antigen while 45% of the study group showed the same result. Despite the fact that the incidence of *Chlamydia trachomatis* infection by antigen detection was higher in the case group, this failed to prove a difference that is statistically significant with $p=0.246$.

Regarding detection of *Chlamydia trachomatis* infection by IgM, 30% of the control group showed positive results while 20% of the study group showed the same result with statistically insignificant difference where $p=0.657$. Seropositivity for IgG was noted in 20% of the control group and 40% of the study group with no statistically significant difference where $p=0.419$ (Table 1).

Anti-chlamydial immunoglobulin M (IgM) was positive in all women of the control group who

showed positive chlamydial antigen while in the study group this correlation was evident in only one-third of women who showed positive chlamydial antigen.

Anti-chlamydial immunoglobulin G (IgG) was positive in 50% of women of the control group who showed positive chlamydial antigen while in the study group this correlation was evident in 75% of women with positive chlamydial antigen.

This means that some of the women with positive *Chlamydia trachomatis* antigen had negative IgG or IgM and vice versa.

All women of the control and study groups were followed till delivery to evaluate the mode of delivery, fetal outcome and occurrence of puerperal infection (Table 2).

Table 1. Comparison between the two studied groups according to *Chlamydia trachomatis* detection tests.

<i>Chlamydia trachomatis</i> detection tests	Control (n = 10)		Study (n = 20)		χ^2	FE p
	No.	%	No.	%		
Antigen						
Negative	8	80.0	11	55.0	1.794	0.246
Positive	2	20.0	9	45.0		
IgM						
Negative	7	70.0	16	80.0	0.373	0.657
Positive	3	30.0	4	20.0		
IgG						
Negative	8	80.0	12	60.0	1.200	0.419
Positive	2	20.0	8	40.0		

χ^2 : Chi square test

FE: Fisher Exact

p: p value for comparing between the studied groups (significant p value ≤ 0.05)

Table 2. Comparison between the two studied groups according to the results of follow-up.

Follow-up	Control (n = 10)		Study (n = 20)		χ^2	FE p
	No.	%	No.	%		
Mode of delivery						
NVD	6	60.0	9	45.0	0.600	0.439
C.S	4	40.0	11	55.0		
Condition of the fetus at delivery based on 5 min Apgar score						
Normal	7	70.0	13	65.0	0.327	MC p 1.000
Moderately depressed	2	20.0	5	25.0		
Severely depressed	1	10.0	2	10.0		
Puerperal infection						
Yes	1	10.0	4	20.0	0.480	0.640
No	9	90.0	16	80.0		

p: p value for comparing between the studied groups (significant p value ≤ 0.05).

Discussion

There is still a controversy between studies correlating between *Chlamydia trachomatis* infection during pregnancy and adverse pregnancy outcomes. Whereas some studies suggesting that chlamydial infection during pregnancy is associated with increased risk of adverse pregnancy outcomes while other studies failed to prove a positive correlation between this infection and the occurrence of PROM [14,15].

The present study aimed to compare the prevalence of *Chlamydia trachomatis* cervicitis between women who experience an early membrane rupture and normal pregnant women at term. According to this study, there is no significant association between PROM and *Chlamydia trachomatis*. This result is consistent with what **Silva et al.** [16] found in a sizable meta-analysis, they reported that PROM was more common in pregnant women infected with *Chlamydia trachomatis*. However, the fact that *Chlamydia trachomatis* infection increases the risk of PROM, could not be confirmed statistically. Moreover, in order to determine the incidence of chlamydial infection in pregnant women and the relationship between a positive chlamydial infection and the occurrence of premature membrane rupture, **Angelova et al.** [17] undertook a prospective cohort research and they found that there is no statistically significant relationship between positivity for *Chlamydia trachomatis* infection and premature rupture of the membranes.

Again, in case-control research done on pregnant women in their 3rd trimester, **Nakubulwa et al.** [18] didn't find any association between PROM and *Chlamydia trachomatis*. Also, **Yalti et al.** [19] who performed a prospective cohort study, revealed 1.2% *Chlamydia* prevalence among all pregnant women, and no statistically significant association between *Chlamydia trachomatis* and preterm birth or PROM was discovered. On the other hand, in contrast to the results of the present study, **He et al.** [14] did a meta-analysis that included fifty studies. They concluded that *Chlamydia trachomatis* infection during pregnancy was associated with a higher risk of preterm premature rupture of the membranes (PPROM). Another meta-analysis done by **Olson-Chen et al.** [20] showed an overall association between *Chlamydia trachomatis* and PROM in ten publications with statistically significant results.

Tang et al. [15] conducted a global systematic review and meta-analysis with a sample size of 6882 patients and showed an increased prevalence of PROM in *Chlamydia trachomatis* patients with a very low level of certainty as the design and conduct were biased in each study.

Blas et al. [21] did a population-based retrospective cohort study using Washington State birth certificate data. They showed that PROM and *Chlamydia trachomatis* infection were positively correlated. Similar results were shown in a case-control study that was done in California to assess the relationship between *Chlamydia trachomatis* infections identified during pregnancy and adverse perinatal birth outcomes [21,22].

In the present study, there is no statistically significant difference between study and control groups as regard mode of delivery, while **Ibishi et al.** [23] showed that PROM has increased the rate of cesarean section delivery. Our result might be explained in that we have the potentials to deal with such cases of PROM through induction and acceleration of labor together with strict fetal monitoring. Thus, the rate of cesarean is not increased significantly particularly in the tertiary leading hospitals like El Shatby University Hospital.

The present study showed a discrepancy in the results between *Chlamydia trachomatis* antibodies detection and *Chlamydia trachomatis* cervical antigen detection. This discrepancy is attributed to the fact that enzyme immunoassay (EIA) tests used for *Chlamydia trachomatis* antigen detection can produce inaccurate positive results because of cross-reactions between antichlamydial antibodies used in the EIA tests and the lipopolysaccharide (LPS) of other microorganisms from the vagina.

Conclusion

Statistically, there was no significant association between PROM and *Chlamydia trachomatis* infection during pregnancy. The antigen detection of *Chlamydia trachomatis* in pregnant individuals diagnosed with PROM was 45% as compared to the control group was 20% which was statistically insignificant.

Recommendations

Further randomized control studies on a larger sample size are needed to assess the association between *Chlamydia trachomatis* infection and the occurrence of PROM. Also, further studies are needed to assess the role of co-infection

with *Chlamydia trachomatis* and other sexually transmitted infections in women with premature rupture of membranes.

Limitations

The relatively small number of the study and control cases was a limitation in this study.

Moreover, the study was conducted at term pregnancy, which might be a limitation, and hence the selection of other cases at different gestation with preterm labor and PROM to reveal any possible association with such infection might be considered in future research.

Conflicts of interest: The authors report no conflicts of interest.

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References

- 1-**European Centre for Disease Prevention and Control.** Chlamydia control in Europe: literature review. Stockholm: ECDC; 2014.
- 2- **Urdea M, Penny L, Olmsted S, Giovanni M, Kaspar P, Shepherd A, et al.** Requirements for high impact diagnostics in the developing world. *Nature* 2006; 444 (1):73-9.
- 3-**Ward B, Plourde P.** Travel and Sexually Transmitted Infections. *J Travel Med.* 2006;13(5):300-17.
- 4-**Stamm W.** Diagnosis of *Chlamydia trachomatis* genitourinary infections. *Intern J Gynecol Obstet.* 1989;28(2):196-7.
- 5-**Brunham R, Rey-Ladino J.** Immunology of *Chlamydia* infection: implications for a *Chlamydia trachomatis* vaccine. *Nat Rev Immunol.* 2005;5(2):149-61.
- 6-**Hosenfeld C, Workowski K, Berman S, Zaidi A, Dyson J, Mosure D, et al.** Repeat Infection With *Chlamydia* and Gonorrhea Among Females: A Systematic Review of the Literature. *Sex Transm Dis J* 2009;36(8): 478-89.
- 7-**Batteiger B, Tu W, Ofner S, Van Der Pol B, Stothard D, Orr D, et al.** Repeated *Chlamydia trachomatis* Genital Infections in Adolescent Women. *J Infect Dis* 2010;201(1):42-51.
- 8-**Jolly AM, Moffatt ME, Fast MV, Brunham RC.** Sexually transmitted disease thresholds in Manitoba, Canada. *An Epidemiol* 2005; 15(10):781-8.
- 9-**Rours G, Duijts L, Moll H, Arends L, de Groot R, Jaddoe V, et al.** *Chlamydia trachomatis* infection during pregnancy associated with preterm delivery: a 13. population-based prospective cohort study. *Eur J Epidemiol* 2011;26(6):493-502.
- 10-**Folger AT.** Maternal *Chlamydia trachomatis* infections and preterm birth: The impact of early detection and eradication during pregnancy. *Matern Child Health J* 2014;18(8):1795-802.
- 11-**Beck S, Wojdyla D, Say L, Pilar Bertran A, Meraldi M, Harris Requejo J, et al.** The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. *Bull World Health Organ.* 2010;88(1):31- 8.
- 12-**Mercer BM.** Preterm premature rupture of membranes: current approaches to evaluation and management. *Obst Gynecol Clin North Am* 2005; 32(3):411-28.
- 13-**Habib Z, Morteza S, Shahin N, Ali M.** Detection of *Chlamydia trachomatis* in Endocervical Smears of Women with Abortion by PCR. *Res J Biol Sci.* 2008; 3(3):342-4.
- 14-**He W, Jin Y, Zhu H, Zheng Y, Qian J.** Effect of *Chlamydia trachomatis* on adverse pregnancy outcomes: a meta-analysis. *Arch Gynecol Obstet* 2020; 302(3):553–67.
- 15-**Tang W, Mao J, Li KT, Walker JS, Chou R, Fu R, et al.** Pregnancy and fertility-related adverse outcomes associated with *Chlamydia trachomatis* infection: a global systematic review and meta-analysis. *Sex Transm Infect* 2020; 96(5):322–9.

- 16-Silva MJ, Florêncio GL, Gabiatti JR, Amaral RL, Eleutério Júnior J, Gonçalves AK. Perinatal morbidity and mortality associated with chlamydial infection: a meta-analysis study. *Braz J Infect Dis* 2011; 15(6):533-9.
- 17-Angelova M, Kovachev E, Tsankova V, Koleva I, Mangarova S. Role and Importance of *Chlamydia trachomatis* in Pregnant Patients. *Open Access Maced J Med Sci* 2016;4(3):410-2.
- 18-Nakubulwa S, Kaye DK, Bwanga F, Tumwesigye NM, Mirembe FM. Genital infections and risk of premature rupture of membranes in Mulago Hospital, Uganda: a case control study. *BMC Res Notes* 2015;8(1):573.
- 19-Yalti E, Ersoy GS, Tanir M. Prevalence of *Chlamydia trachomatis* infection in pregnant women with preterm labor, PROM, and abortion. *Firat Tıp DergFirat Med J* 2015; 20(3): 143-
- 20-Olson-Chen C, Balaram K, Hackney DN. *Chlamydia trachomatis* and adverse pregnancy outcomes: Meta-analysis of patients with and without infection. *Matern Child Health J* 2018;22(6):812–21.
- 21-Blas MM, Canchihuaman FA, Alva IE, Hawes SE. Pregnancy outcomes in women infected with *Chlamydia trachomatis*: a population-based cohort study in Washington State. *Sex Transm Infect* 2007;83(4):314–8.
- 22-Chow JM, Kang M-S, Samuel MC, Bolan G. Assessment of the association of *Chlamydia trachomatis* infection and adverse perinatal outcomes with the use of population-based Chlamydia case report registries and birth records. *Public Health Rep* 2009;124 Suppl 2:24–30
- 23-Ibishi VA, Isjanovska RD. Prelabour Rupture of Membranes: Mode of Delivery and Outcome. *Open Access Maced J Med Sci* 2015; 3(2):237-40.