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Chlamydia trachomatis screening in preterm labor: A systematic review and meta-analysis

Tomi T. Kanninen[a], Johanna Quist-Nelson[b], Giovanni Sisti[c], Vincenzo Berghella[b,*]

[a] Department of Obstetrics and Gynecology, Richmond University Medical Center, Staten Island, NY, USA
[b] Department of Obstetrics and Gynecology, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA
[c] Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, Bronx, NY, USA

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ABSTRACT

Objective: Spontaneous preterm labor (PTL) is responsible for approximately half of all preterm births with intrauterine infection being an important risk factor for PTL. *Chlamydia trachomatis* infections have been associated with preterm prelabor rupture of membranes (P-PROM) and preterm birth, but its impact on PTL has not previously been specified. The aim of this study was to evaluate the overall prevalence of *Chlamydia trachomatis* infections in pregnant women with threatened PTL compared to those not in threatened PTL.

Study design: A literature search was performed in electronic databases using combinations of: "*Chlamydia*", "vaginal cervical infection" and "preterm labor." Cohort and case-controlled studies examining threatened PTL and *Chlamydia trachomatis* infection demonstrated by culture or NAAT methods at time of diagnosis of threatened labor. The Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for reporting of observational studies for systematic reviews was used. Bias was assessed with the Methodological Index for Non-Randomized Studies (MINORS) score. Meta-analysis was performed using a random effects model.

Results: Four studies were identified. A total of 591 women were included, 309 in the threatened PTL, and 282 controls not in threatened PTL. Women presenting in PTL had an increased risk of screening positive for *Chlamydia trachomatis* compared to the control group (27/308 (9%) vs 3/282 (1%); OR 7.74, 95% CI 2.64–22.71).

Conclusions: The incidence of *Chlamydia trachomatis* in women with threatened PTL is approximately 9%, and significantly increased compared to asymptomatic controls. Women with threatened PTL should be considered for screening for *Chlamydia trachomatis.*

Introduction

About ten percent of pregnancies in the United States are affected by preterm birth and subsequently increased infant morbidity and mortality [1]. Spontaneous preterm labor (PTL) is responsible for approximately half of all preterm births [2]. Research focused on exploring the etiology of preterm birth remains inconclusive, likely because of its multifactorial nature.

Intrauterine infection is an important risk factor for PTL [3]. Studies examining the colonization of the maternal genital tract by several specific organisms, such as gonorrhea, trichomonas and bacterial vaginosis, have consistently showed associations with preterm birth [4,5]. *Chlamydia trachomatis* is the most common bacterial sexually transmitted infection (STI) in the United States. In the US in 2016 there were more than 1.59 million infections reported to the Centers for Disease Control (CDC) [1]. Genital *Chlamydia trachomatis* infections in women are generally asymptomatic. In pregnant women, *Chlamydia trachomatis* infections have been associated with preterm prelabor rupture of membranes (PROM) and preterm birth, though the results are conflicting [6,7]. This has also been true of newer studies using sensitive DNA amplification techniques [8,9]. To date, studies have shown that treatment of *Chlamydia trachomatis* in pregnancy leads to a decrease in the incidence of PPROM and low birth-weight but its impact on PTL has not previously been specified [10,11].

The aim of this study was to evaluate the overall prevalence of *Chlamydia trachomatis* infections in pregnant women with

* Corresponding author at: Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Thomas Jefferson University, 833 Chestnut Street, First Floor, Philadelphia, PA 19107, USA.
E-mail address: Vincenzo.Berghella@jefferson.edu (V. Berghella).

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threatened PTL compared to those who do not have threatened PTL through systematic review and meta-analysis.

Material and methods

Data sources

The review was designed *a priori* and followed the Meta-analyses of Observational Studies in Epidemiology (MOOSE) guidelines for reporting of observational studies established for systematic reviews [12]. We searched Medline, ClinicalTrials.gov, Embase, Science direct, the Cochrane Library at the CENTRAL Register of Controlled Trials from establishment until May 2018. Search items used were combinations of: "*Chlamydia*", "vaginal cervical infection" and "preterm labor". Language or geographic location restrictions were not applied. Electronic searches and the eligibility of the studies were independently assessed by two authors (TK, GS). The study was not submitted to PROSPERO the international prospective register of systematic reviews.

Main outcomes measures and eligibility criteria

Studies were included if they screened women in threatened PTL (including both women with cervical change and those with uterine contractile activity but no cervical change) compared to those without threatened PTL, screened with culture and/or NAAT for *Chlamydia trachomatis*. Threatened PTL was defined as per each individual trial. Exclusion criteria were studies that screened women with *Chlamydia trachomatis* only by other methods (e.g. serum antibodies) as these methods have been shown to be less sensitive and specific [13]. Additional exclusion criteria were studies including patients with multiple gestations, or lethal anomalies, or if the control group was not screened for *Chlamydia trachomatis*. Preterm PROM was not considered to be an exclusion criteria. The primary outcome was the incidence of *Chlamydia trachomatis* following PTL as compared to controls. Additionally, we examined the incidence of gonorrhea, urinary tract infections, group B *Streptococcal* colonization. A subgroup analysis of the incidence of *Chlamydia trachomatis* following PTL as compared to controls without PPROM was planned if an adequate number of studies examining this outcome were available.

To assess the risk of bias, the criteria outlined in the methodological index for non-randomized studies (MINORS) score was used [14]. In each included trial we assessed twelve domains as follows: was the study purpose clearly stated, consecutive patients included, prospective data collection, appropriate endpoints, unbiased assessments, appropriate follow-up length, loss to follow-up less than 5%, prospective sample size calculation, adequate controls, contemporary groups, similar groups at baseline and adequate analysis.

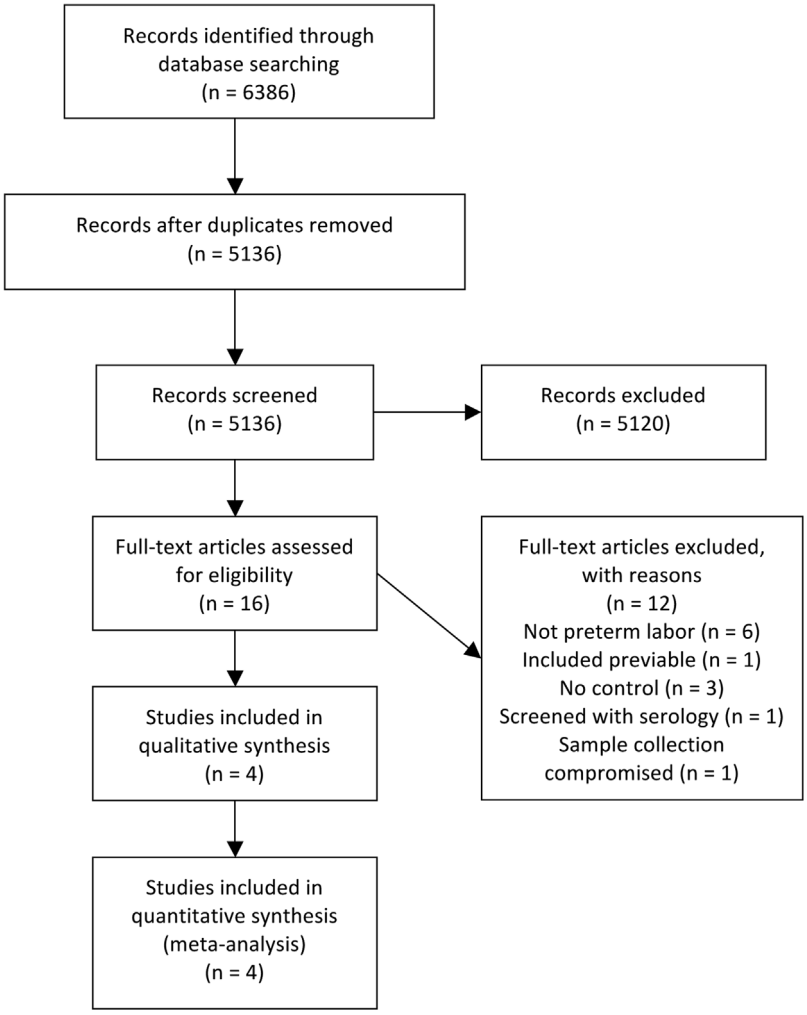

Fig. 1. PRISMA flow diagram.

The review authors categorized each study on each criteria as "reported and adequate," "reported and inadequate," or "not reported" of bias. If the total number of included studies in the analysis of a priority outcome was >10, we also planned to test for potential publication bias by visual inspection of a funnel plot.

Authors (TK, GS) independently assessed inclusion criteria, risk of bias, and data extraction in accordance with the MOOSE guidelines. Disagreements were resolved by discussion by consulting a third reviewer (VB).

Data collection and analysis

Review Manger 5.3 (Copenhagen, Denmark: The Nordic Cochrane Centre, Cochrane Collaboration) was used for data analysis. Higgins I^2 was used to assess heterogeneity across the studies with >80% considered to be high level of heterogeneity. Random effects model was used to analyze the studies. The results were reported as odds ratio (OR) with 95% confidence interval (CI).

Ethical approval

Ethical committee and institutional review board approval was not required for this systematic review and meta-analysis.

Results

General characteristics of the studies

Articles for 16 studies were assessed for eligibility and we identified four studies screening for *Chlamydia trachomatis* in women with threatened PTL (Fig. 1). Six studies examined women not in PTL. One study included women prior to 24 weeks gestation. Three studies had no controls. One study screened with serum antibodies. One study used a compromised method of sample collection with a thorough saline wash conducted prior to sample collection.

The characteristics of the four included studies are summarized in Table 1 [15–18]. Studies were conducted in Cameroon, Washington (USA), Finland and the United Kingdom. None of the studies included randomized comparisons between women. There were a total of 591 women, 309 in the threatened PTL screening group, and 282 in the no threatened PTL screening. Screening occurred in general in the late second and early third trimester, between 20–36 weeks (Table 1). Screening occurred by Cyclo-heximide treated McCoy cells in three studies and with PCR in the remaining one [15–18].

Demographics evaluated in the four studies were in general similar when reported (Table 2), except for in the Martius et al. study there was a significant difference with a larger percentage of patients <20 years of age, with a history of preterm birth, premature rupture of membranes (PROM), intra and post partum fever in the PTL groups

Table 1
Characteristics of included studies.

	Lamont (1986)	Martius (1988)	Ngassa (1994)	Kurkinen-Raty (2001)
Location of study	United Kingdom	USA	Cameroon	Finland
Number of included patients	98 (72 vs 26)	212 (97 vs 115)	126 (63 vs 63)	155 (77 vs 78)
Type of study	Case controlled	Case controlled	Case controlled	Case controlled
Gestational age of inclusion (weeks)	26 + 0 to 34 + 0	20 + 0 to 36 + 0	28 + 0 to 34 + 0	22 + 0 to 32 + 0
Characteristics of control group	Undergoing cesarean delivery at similar GA	Uncomplicated pregnancies between the 20th and 36th gestational weeks	Routine and high-risk clinic patients	Antenatal clinic matched for gestational age, parity, maternal age
Inclusion criteria	Patients with PTL with or without preterm PROM from 26-33	Patients with PTL with or without preterm PROM from 20-36	Regular, painful uterine contractions once every 10 min accompanied by any degree of cervical effacement and/or dilatation irrespective of whether the membranes were ruptured or not	Symptoms (contractions) or because of cervical changes (shortening, opening or softening of the cervix) detected by manual examination
Exclusion criteria	Lethal congenital anomalies	<16 years of age, antibiotic use within 2 weeks, diabetes mellitus, chronic heart disease, renal disease, chronic hypertension, pregnancy-induced hypertension, cervical cerclage, placenta abruption or previa, multiple gestation, congenital malformations	Antepartum hemorrhage, intra-uterine death, polyhydramnios, history of cervical incompetence, absence of US dating of pregnancy in cases of discrepancy	PROM and ongoing preterm delivery
Definition of PTL	Regular, painful and palpable contractions occurring $\geq$ 2 in 10 min.	Two or more regular, painful contractions within ten minutes, lasting longer than two hours, at less than <37 wks	Regular, painful contractions at least once every 10 min. with any degree if cervical effacement and/or dilatation with or without PPROM	Contractions or cervical changes (shortening, opening or softening of the cervix) by manual exam
History of preterm delivery	NR	Unknown	12/63 (19%) vs 4/59 (6.8%)	19 (25%)/3(4%)
Chlamydia screening test used	Cyclo-heximide treated McCoy cells	Cyclo-heximide treated McCoy cells	Cyclo-heximide treated McCoy cells	PCR

Data are presented as total number (n experimental / control) as number (percentage) or as mean ± standard deviation.
Abbreviations: PROM, premature rupture of membranes; PTL, preterm labor; USA, United States of America; US, ultrasound; GA, gestational age; wks, weeks; PPROM, preterm premature rupture of membranes; PCR, polymerase chain reaction.

Table 2
Patient demographics.

	Lamont (1986)	Martius (1988)	Nagassa (1994)	Kurkinen-Raty (2001)	Total
Age (years)	NR	Patients <20 yrs of age: 25 vs 10	23.6±5.3 *vs* 24.6±5.6	29.9±6.3 vs 30.8±6.0	26.8 vs 27.7
Avg gestational age at screening (weeks)	NR	NR	30.90±1.87 vs 31.06±1.98	NR	–
Avg gestational age at delivery	NR	NR	NR	NR	–
Preterm rupture of membranes	Included*	81/97(83%) vs 12/115 (15%)	Included*	Excluded	–
Chorioamnionitis	24/43 (56%) vs 2/21 (10%)	NR	NR	NR	–

Data are presented as n experimental / total in experimental group (%) vs n control/ total control group (%) or as mean ± standard deviation.
Abbreviations: NR, not reported; Avg, average; Yrs, years.
* Breakdown not reported.

as compared to the controls [17], and in the Kurkinen-Raty et al. study the study group had a greater history of preterm delivery, hospital admissions, and a lower gestational age at delivery [18]. Mode of delivery was not reported by any of the included papers.

Synthesis of the results

The number of positive *Chlamydia trachomatis* cultures ranged from 0 to 18% in four studies (Table 3). The number of positive patients in the control group ranged from 0 to 3%. Women presenting in threatened PTL had a significantly increased risk of screening positive for *Chlamydia trachomatis* (27/308, (9%) vs 3/282 (1%); OR 7.74, 95% CI; 2.64 to 22.71) compared to controls (Table 3). Women in the preterm labor group were significantly more likely to be colonized with GBS (45/246 (18%) vs 21/219 (10%); OR 2.08, 95% CI; 0.36 to 12.09), but not in being affected by UTIs (10/159 (7%) vs 2/104 (2%); OR 3.20, 95% CI; 0.68 to 15.03) (Table 3) in women with threatened PTL compared to controls. We were unable to perform a subgroup analysis of patients excluding PROM given the insufficient number of studies with data in this regard (Table 3). Heterogenity was low for the primary outcome (Higgins $I^2 = 0\%$). Publication bias was not assessed as there were an inadequate number of studies to properly assess a funnel plot.

Bias and the methodological quality within our studies were assessed with the MINORS score (Fig. 2) [14]. Overall, the risk of bias in our studies was judged to be adequate. Baseline characteristics were judged to be adequate in the Martius et al., Lamont et al., and Kurkinen-Raty et al. studies, they were reported and judged as inadequate in Ngassa et al. study. Selection, detection and performance bias was judged to be low as culture and NAAT results were not known at the time of collection in the study and control groups. Reporting bias was judged to be low.

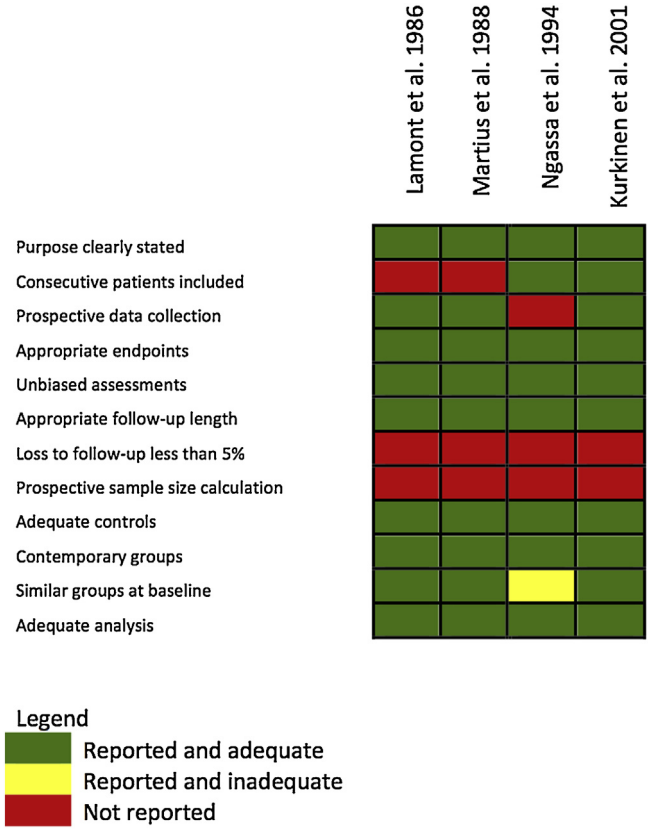

Fig. 2. MINORS score for evaluation of bias and the methodological quality within studies.

Comment

Chlamydia trachomatis infections during pregnancy have been associated with PROM and premature delivery [6–9]. Treatment of *Chlamydia trachomatis* in pregnancy leads to a decrease in the incidence of preterm PROM and low birth-weight; however, its impact on symptoms of PTL remains unclear [10,11]. There have been no randomized trials to examine if universal or risk based screening in pregnancy improves outcomes. This is likely because the deleterious nature of this bacterium in women and neonates makes any randomized control trial ethically complex. However, societies continue to

Table 3
Incidence of *Chlamydia trachomatis* and other infections.

	Lamont (1986)	Martius (1988)	Nagassa (1994)	Kurkinen-Raty (2001)	Total	OR (95% CI)
Chlamydia trachomatis	5/71 (7%) vs 0/26 (0%)	17/97 (18%) vs 3/115 (3%)	5/63 (8%) vs 0/63 (0%)	0/77 vs 0/78	27/308 (9%) vs 3/282 (1%)	7.74 (2.64-22.71)
Gonorrhea	2/72 (3%) vs 0/26 (0%)	NR	NR	NR	2/72 (3%) vs 0/26 (0%)	–
UTI	4/72 (6%) vs 1/26 (4%)	NR	NR	6/77 (8%) vs 1/78 (1%)	10/149 (7%) vs 2/104 (2%)	3.20 (0.68-15.03)
GBS	4/72 (6%) vs 0/26 (0%)	35/97 (36%) vs 11/115 (10%)	NR	6/77 (8%) vs 10/78 (13%)	45/246 (18%) vs 21/219 (10%)	2.08 (0.36-12.09)

Data are presented as n experimental / total in experimental group (%) vs n control/ total control group (%).
Abbreviations: GBS, group B streptococcus, NR, not reported, UTI, urinary tract infection.

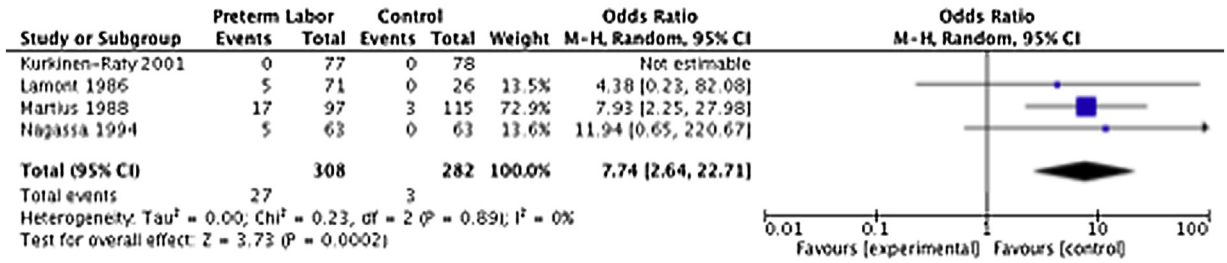

Fig. 3. Forest plot of Odds Ratio of *Chlamydia trachomatis* infection in patients with preterm labor as compared to controls.

recommend screening. This is true of American College of Obstetricians and Gynecologists and the Center of Disease Control and Prevention that recommend screening for *Chlamydia trachomatis* in all pregnant women [19,20]. It is of particular interest to understand if screening provides any beneficial effect for women during pregnancy. Though treatment seems to improve outcomes in pregnancy in regard to rates of preterm PROM and low-birth weight infants, the current prevalence of *Chlamydial trachomatis* infection during pregnancy is unclear. In this regard, the majority of studies (Martius et al., Lamont et al., and Ngassa et al.) included in this review indicate that a substantial portion of women with symptoms of PTL, 18%, 7% and 8% respectively, were positive for *Chlamydia trachomatis* [15–18]. Overall, women in threatened PTL were over seven times at risk for screening positive for *Chlamydia trachomatis* than controls (Fig. 3). Though PTL is not synonymous with preterm birth, it is responsible for significant medical interventions with attached health costs and it can be indicative of pregnancies that then go on to deliver prematurely. These results lend more support to current screening strategies. Screening strategies in general depend on the prevalence of disease in the populations examined. In this regard, populations with a low prevalence of disease risk having an increased rate of false positives on screening tests and the positive predictive value of a screening will suffer. This may be true of Finnish population in the study of Kurkinen-Raty et al., which had no positive *Chlamydia trachomatis* results [18]. Overall, the portion of pregnant women with symptoms of PTL in these studies supports current screening strategies.

Strengths and limitations

The four studies included in this review are limited by a small number of patients and incompletely defined study and control groups (Table 1). In addition, screening techniques differed between studies with culture and NAAT techniques being utilized. Though specificity is similar between NAAT and cultures, sensitivity is largely accepted as greater with the NAAT technique [13]. Importantly, two of the studies provided data indicating that the study group had a higher rate of a history of preterm birth, thereby potentially influencing the data. Additionally, we were unable to perform a subgroup analysis of patients excluding PROM given the insufficient number of studies with data in this regard. *Chlamydia trachomatis* has been shown to be associated with PROM and the presence of PROM in the study population of this meta-analysis may have influenced the results. Further larger studies in the future are needed to better define the overall prevalence of these infections in PTL controlling for the presence of PROM within the study population. However, the currently reviewed studies support a continued screen of *Chlamydia trachomatis* as it is associated with symptoms of PTL.

Conclusion

PTL is responsible for approximately half of all preterm births with intrauterine infection being an important risk factor for PTL. *Chlamydia trachomatis* infections have been associated with PROM and preterm birth, but its impact on PTL has not previously been specified. Four studies screening for *Chlamydia trachomatis* in women with threatened PTL were identified. The incidence of *Chlamydia trachomatis* in women with threatened PTL is approximately 9%, and significantly increased compared to asymptomatic controls. Screening for *Chlamydia trachomatis* should be considered in women with threatened PTL.

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Declaration of Competing Interest

The authors report no conflict of interest.

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References

[1] Centers for Disease Control and Prevention. Sexually transmitted disease surveillance. Atlanta: U.S. Department of Health and Human Services; 2016 2017.
[2] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.
[3] Romero R, Sirtori M, Oyarzun E, Avila C, Mazor M, Callahan R, et al. Infection and labor. V. Prevalence, microbiology, and clinical significance of intraamniotic infection in women with preterm labor and intact membranes. Am J Obstet Gynecol 1989;161:817–24 Review.
[4] Watts DH, Krohn MA, Hillier SL, Eschenbach DA. The association of occult amniotic fluid infection with gestational age and neonatal outcome among women in preterm labor. Obstet Gynecol 1992;79:351–7.
[5] Cunnington M, Kortsalioudaki C, Heath P. Genitourinary pathogens and preterm birth. Curr Opin Infect Dis 2013;26:219–30.
[6] Andrews WW, Klebanoff MA, Thom EA, Hauth JC, Carey JC, Meis PJ, et al. Midpregnancy genitourinary tract infection with Chlamydia trachomatis: association with subsequent preterm delivery in women with bacterial vaginosis and Trichomonas vaginalis. Am J Obstet Gynecol 2006;194:493–500.
[7] Harrison HR, Alexander ER, Weinstein L, Lewis M, Nash M, Sim DA. Cervical Chlamydia trachomatis and mycoplasmal infections in pregnancy. Epidemiol Outcomes JAMA 1983;250:1721–7.
[8] Andrews WW, Goldenberg RL, Mercer B, Iams J, Meis P, Moawad A, et al. The preterm prediction study: association of second-trimester genitourinary chlamydia infection with subsequent spontaneous preterm birth. Am J Obstet Gynecol 2000;183:662–8.
[9] Rours GI, Duijts L, Moll HA, Arends LR, de Groot R, Jaddoe VW, et al. Chlamydia trachomatis infection during pregnancy associated with preterm delivery: a population-based prospective cohort study. Eur J Epidemiol 2011;26:493–502.
[10] Ryan Jr GM, Abdella TN, McNeeley SG, Baselski VS, Drummond DE. Chlamydia trachomatis infection in pregnancy and effect of treatment on outcome. Am J Obstet Gynecol 1990;162:34–9.
[11] Martin DH, Eschenbach DA, Cotch MF, Nugent RP, Rao AV, Klebanoff MA, et al. Double-blind placebo-controlled treatment trial of chlamydia trachomatis endocervical infections in pregnant women. Infect Dis Obstet Gynecol 1997;5:10–7.
[12] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting.

Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–12.
[13] Meyer T. Diagnostic procedures to detect *Chlamydia trachomatis* infections. Microorganisms 2016;4:25.
[14] Slim K, Nini E, Forestier D, Kwiatkowski F, Panis Y, Chipponi J. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712–6.
[15] Lamont RF, Taylor-Robinson D, Newman M, Wigglesworth J, Elder MG. Spontaneous early preterm labour associated with abnormal genital bacterial colonization. Br J Obstet Gynaecol 1986;93:804–10.
[16] Ngassa PC, Egbe JA. Maternal genital Chlamydia trachomatis infection and the risk of preterm labor. Int J Gynaecol Obstet 1994;47:241–6.
[17] Martius J, Krohn MA, Hillier SL, Stamm WE, Holmes KK, Eschenbach DA. Relationships of vaginal Lactobacillus species, cervical Chlamydia trachomatis, and bacterial vaginosis to preterm birth. Obstet Gynecol 1988;71:89–95.
[18] Kurkinen-Räty M, Ruokonen A, Vuopala S, Koskela M, Rutanen EM, Kärkkäinen T, et al. Combination of cervical interleukin-6 and -8, phosphorylated insulin-like growth factor-binding protein-1 and transvaginal cervical ultrasonography in assessment of the risk of preterm birth. BJOG 2001;108:875–81.
[19] American Academy of Pediatrics and. American college of obstetricians and gynecology. Guidelines for perinatal care. 7th ed. Washington, DC: American College of Obstetricians and Gynecology; 2012.
[20] Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines. 2015.