Review Article

Relationship between Vaginal Bacterial Infections and Pregnancy Outcomes: A Systematic Review and Meta-Analysis

Hojjat Rokni[1], Amjad Ahmadi[2], Yousef Moradi[3], Bijan Nouri[4], Daem Roshani[4]

[1]Department of Epidemiology and Biostatistics, Faculty of Medicine, Kurdistan University of Medical Sciences, Sanandaj, Iran, [2]Department of Microbiology, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran, [3]Social Determinants of Health Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran, [4]Health Metrics and Evaluation Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran

Abstract

Background: Bacterial infections are among the most serious infections worldwide. They can cause miscarriage, premature birth, stillbirth, and ectopic pregnancy in pregnant women. The aim of this study was to investigate the relationship between bacterial infections and pregnancy outcomes through a systematic review and meta-analysis. **Materials and Methods:** PubMed, Scopus, Web of Science, and Embase databases were searched from January 2000 to December 2018 using appropriate keywords to identify related articles. The final related studies were selected and evaluated using the Newcastle-Ottawa Scale (NOS). **Results:** Results of this meta-analysis based on combining case-control studies showed that the presence of bacterial infections could lead increase in the odds of all pregnancy outcomes like premature infant birth (odd ratio [OR]: 1.50; 95% Confidence Interval [CI], 1.39–1.61), preterm delivery (OR: 1.54; 95% CI, 1.39–1.70), abortion (OR: 1.16; 95% CI, 1.04–1.29), stillbirth (OR, 1.29; 95% CI, 1.12–1.49), and ectopic pregnancy (OR: 1.12; 95% CI, 1.05–-1.19). The results showed that the Risk Ratio (RR) of preterm delivery in pregnant women with vaginal infections was 1.57 (95% CI, 1.46–1.67), whereas the RR of abortion was 2.02 (95% CI, 1.72–2.38). **Conclusions:** Based on the results of this meta-analysis, the presence of bacterial infections in pregnant women can lead increase in the risk of pregnancy outcomes especially, preterm delivery, abortion, stillbirth, and ectopic pregnancy. Therefore, it is necessary for obstetricians and gynecologists to pay attention to the diagnosis of these infections in women before pregnancy and during pregnancy in order to prevent the consequences of these infections.

Keywords: *Abortion, bacterial infections, ectopic pregnancy, premature births, stillbirths*

Introduction

Pregnancy guarantees the survival of the human race.[1] Today, healthy pregnancy, as an indicator of development, has received growing attention in all healthcare systems.[2] A normal, healthy pregnancy should last between 38 and 42 weeks.[3] There is a wide range of factors and diseases that may affect the length of pregnancy. One of these challenging factors is a bacterial infection. Bacterial infections are among the most common infectious diseases, adversely affecting sexual and reproductive health worldwide.[4,5] These infections can increase the risk of ectopic pregnancy in women, leading to sudden and severe bleeding following a ruptured fallopian tube. Besides, the complications of these infections are not limited to patients. Pregnant women with such infections may suffer from consequences such as miscarriage, preterm delivery, stillbirth, ectopic pregnancy, and diseases, as well as other complications in the fetus.[6] The literature review revealed that 5% of pregnant mothers in developed countries and 25% in developing countries are at risk of preterm delivery.[7] Also, a leading cause of maternal mortality in the first trimester of pregnancy is ectopic pregnancy, in which the embryo implantation occurs outside the uterine cavity, particularly in the fallopian tubes. As a pregnancy emergency, it often requires prompt intervention. The World Health Organization (WHO) reported that 4.9% of maternal deaths are attributable to ectopic pregnancies.[8,9]

Sexually Transmitted Diseases (STDs) are mainly transmitted through sexual contact (vaginal, anal, and oral sex) and, in some cases, through contaminated blood or blood products. Most STDs, including chlamydia, gonorrhea, and syphilis, can also be transmitted from mother to infant

Address for correspondence:
Dr. Daem Roshani, Health Metrics and Evaluation Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran.
E-mail: rezaeeit93@gmail.com

Access this article online

Website: https://journals.lww.com/jnmr

DOI: 10.4103/ijnmr.ijnmr_199_22

Quick Response Code:

How to cite this article: Rokni H, Ahmadi A, Moradi Y, Nouri B, Roshani D. Relationship between vaginal bacterial infections and pregnancy outcomes: A systematic review and meta-analysis. Iran J Nurs Midwifery Res 2024;29:1-15.

Submitted: 08-Jul-2022. **Revised:** 05-Aug-2023. **Accepted:** 06-Aug-2023. **Published:** 09-Jan-2024.

during pregnancy and childbirth.[10] On the other hand, a key point regarding these diseases is that most infections remain undiagnosed and untreated, which may lead to adverse pregnancy outcomes in women.[11]

Assessing the relationship between these different infections and pregnancy outcomes can be helpful in future planning for more appropriate pre- and postnatal, and neonatal care; therefore, the findings of this study can be effective in changing and updating treatment guidelines. Due to the contradictory results on the relationship between STDs and pregnancy outcomes,[5–11] this systematic review and meta-analysis investigated and analyzed studies on vaginal bacterial infections and pregnancy outcomes.

Materials and Methods

This systematic review and meta-analysis were conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline.[1] All original published articles (case-control and cohort studies) were searched in PubMed, Scopus, Web of Science, and Embase databases. All the authors searched the databases, hand searching through the reference lists and grey literature (Google Scholar). We searched in these search engines with language limitations (English) from January 2000 to December 2018. The search protocol was developed based on four main roots of "pregnant women," "maternal outcomes," "bacterial infection," and "vaginal infection." All related components of maternal outcomes including preterm labor, spontaneous preterm delivery, premature birth, ectopic, spontaneous abortion, and stillbirth. Also, all related components of bacterial infection included *Chlamydia trachomatis, Trichomonas vaginalis, Haemophilus ducreyi,* Treponema pallidum (syphilis)*, Mycoplasma, Neisseria gonorrhoeae*, and bacterial vaginosis. The results were limited to human subjects and refined for pregnant women. In this study, Reference Manager bibliographic software was used to manage the searched citations. Duplicate entries were searched by considering the title of the published papers, authors, publication year, and specifications of the source types. We reviewed the primary search results, and after reviewing each article by title and available abstract, some of the articles were eliminated. The evaluation of the papers was based on the inclusion and exclusion criteria independently performed by two authors (HR andYM). Case-control and cohort articles in English were selected, which investigated the relationship between vaginal bacterial infections and pregnancy outcomes and contained relevant information. In the present meta-analysis, the letter to the editor, review studies, meta-analyses, case reports/case series, clinical/interventional trials, and studies with measurement indicators other than OR and Risk Ratio (RR) were excluded from the analysis.

After three steps of assessment for the titles, abstracts, and full texts, the full text of each selected article was retrieved for detailed analysis. The data were extracted using a checklist recording name of the first author, publication date, country, study subjects, patient age, gestational age, sample size, detection method, exposure types, outcome types, colonization types, sampling method, RR, OR, and control variables.

To evaluate the possible biases and the quality of studies, the Newcastle-Ottawa Scale (NOS) was used for analytical observational studies (case-control and cohort studies). Informed by the aspects of the studies (including selection, comparability, and outcome), the quality of the studies was determined using the "star" rating system. Scores ranged from 0 (worst case) to 9 (best case). Studies with scores of 0–4, 5–7, and above 7 were categorized as low quality, moderate quality, and high quality, respectively.

All analyzes were performed using STATA version 16 (StataCorp LLC, College Station, Texas, USA).[2] First, the logarithm and Standard Deviation (SD) of OR and RR logarithm and Confidence Interval (CI) 95% were calculated for meta-analysis. The effect size of the reported studies was different; thus, in case-control studies, OR was reported, and, in cohort studies, RR was reported. The random effect model was used for the analysis. To check the heterogeneity in the meta-analysis, I-square and Q Cochrane indicators were applied. According to the Cochrane criteria, if the I-square percentage is 0–25%, there will be no heterogeneity; 25–50%, heterogeneity will be low; 50–75%, heterogeneity will be high but acceptable; and 75–100%, heterogeneity will be very high. To identify the main source of heterogeneity, subgroup analysis based on important variables (the number of sexual partners, number of samples, type of studies, and geographical location) and meta-regression analysis were used. The publication bias was examined using the Egger's regression asymmetry test.[4] Sensitivity analysis was also performed using a random effect model, in which each study was excluded from the research to evaluate the effect of that study on the overall estimate.

Ethical considerations

The study protocol was approved by the Ethics Committee of Kurdistan University of Medical Sciences (IR.MUK.REC.1397.317). The authors avoided plagiarism in any form in writing the present study. Also, the researchers avoided any data fabrication and falsification while drafting this manuscript.

Results

Search results

As shown in Figure 1, 8,838 articles were identified in the initial search. After deleting duplicate data, 5,197 articles were singled out for screening. Following the review of the title and abstract, 476 articles were chosen for the full-text analysis. Accordingly, 394 papers were removed for various

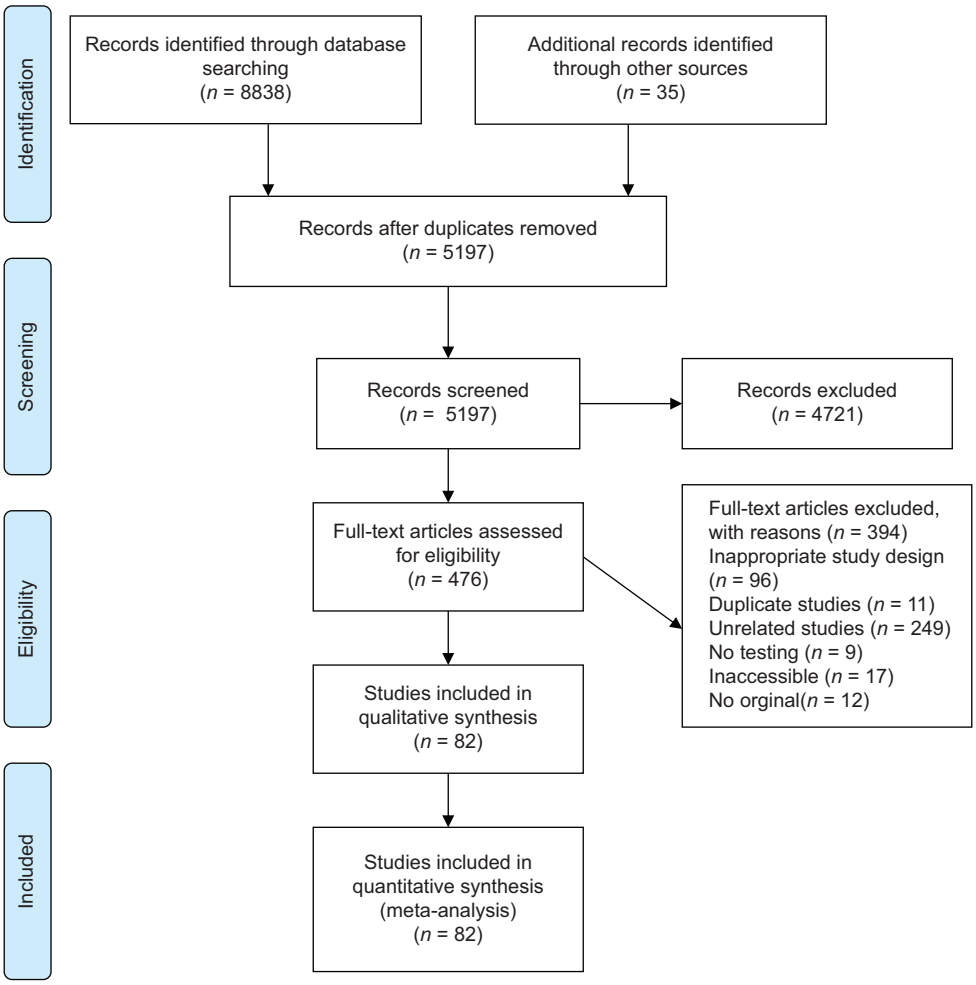

Figure 1: Flowchart of the systematic review of the relationship between genital infections and pregnancy outcomes during 2000–2018

reasons, including improper study design, irrelevance, duplication, improper testing, restricted access, and lack of originality. Finally, after the qualitative evaluation of data, 31 cohort articles [Table 1] and 52 case-control articles [Table 2] were assessed for analysis.

Analysis of case-control studies

1) Preterm births outcomes

Regarding bacterial infections and preterm delivery in pregnant women, 19 case-control studies were included in the meta-analysis. The merging case-control studies showed that pregnant women with bacterial infections (regardless of the type of infection) were 1.5 times more likely to give birth to a premature infant (OR: 1.50; 95% CI, 1.39–1.61). The heterogeneity of this meta-analysis was high (91.06%) with a significance level of 0.001. The highest and lowest ORs in these 19 case-control studies were reported by Harada *et al*. and Baud *et al*., respectively [Figure 2].[46,56] The results of publication bias are presented in Figure 3. The results of the Egger's test showed no publication bias in the effect of bacterial infections in preterm delivery in pregnant women (coefficient, 1.04; Standard Error [SE], 0.986; $p = 0.289$). In this study, the subgroup analysis was performed in case-control studies based on the type of colonization, the type of bacterial infection, and the type of bacterial infection diagnosis method. The analysis of the type of colonization showed that based on the types of samples (blood, vaginal, cervical, and urine), bacterial infections increased the odds of preterm delivery in pregnant women by 1.17 (OR: 1.17; 95% CI, 0.98–1.40), 1.98 (OR: 1.98; 95% CI, 1.76–2.24), 1.23 (OR: 1.23; 95% CI, 1.07–1.42), and 1.65 (OR: 1.65; 95% CI, 1.24–2.19), respectively [Table 3]. Depending on the type of bacterial infection, the results showed different associations, which are of paramount importance. In the case of bacterial infection, the odds of preterm delivery were 1.54 times higher (OR: 1.54; 95% CI, 1.39–1.70), whereas, in the presence of *Ureaplasma urealyticum*, the odds of infection were approximately eight times higher (OR: 7.96; 95% CI, 5.50–11.51). The odds of preterm delivery were different based on the diagnostic method, whereas according to the molecular method, this odds was estimated at 1.40 (OR: 1.40; 95% CI, 1.11–1.76) [Table 3].

2) Abortion outcomes

Regarding the relationship between bacterial infections and abortion in pregnant women, seven case-control

Table 1: The main characteristics of cohort and population-based cohort studies

Authors (Year) (Reference number)	Type of study Country Study population	Age Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
Jacobsson *et al*. (2002)[5]	Cohort Sweden Hospital-based	27 852	Bacterial vaginosis	Premature birth	2.10 (0.90–4.90)	*
Afolabi *et al*. (2016)[6]	Cohort Nigeria Population-based	30.90 46	Bacterial vaginosis	Premature birth	2.68 (1.44–4.98)	*
Aaltone *et al*. (2002)[7]	Cohort Finland Hospital-based	29.50 22	*Mycoplasma urealyticum*	Premature birth	3.34 (8.80–1.27)	*
Averbach *et al*. (2013)[8]	Cohort USA Population-based	31.50 81	*Mycoplasma genitalium*	Premature birth, abortion		*
Azargoon *et al*. (2006)[9]	Cohort Iran Hospital-based	* 1,223	*T. vaginalis* Bacterial vaginosis	Premature birth	5.99 (3.79–9.49) 0.73 (0.22–2.17)	*
Bakken *et al*. (2007)[10]	Cohort Norway Hospital-based	* *	*C, trachomatis*	Ectopic pregnancy		*
Balu *et al*. (2003)[11]	Cohort USA Hospital-based	26.20 *	Bacterial vaginosis	Premature birth	1.00 (0.70–1.50)	Maternal race and vaginal bleeding during the pregnancy
Blas *et al*. (2007)[12]	Cohort USA Population-based	* *	*C. trachomatis*	Premature birth	1.46 (1.08–1.99)	Maternal age and education
Bretelle *et al*. (2015)[13]	Cohort France Hospital-based	* *	Bacterial vaginosis	Premature birth	3.90 (1.10–-14.10)	*
Daskalakis *et al*. (2006)[14]	Cohort Greece Hospital-based	* *	Bacterial vaginosis	Premature birth	2.19 (1.21–3.98)	Age, ethnicity, height, weight, gravidity, history of miscarriage or pregnancy termination, smoking
De Borborema-Alfaia *et al*. (2013)[15]	Cohort Brazil Hospital-based	* *	*C. trachomatis*	Premature birth		*
Dingens *et al*. (2016)[16]	Cohort USA Hospital-based	* *	Bacterial vaginosis	Abortion	1.15 (0.27–4.96)	Presence of sexually transmitted infections (syphilis, gonorrhea, chlamydia, and/or genital herpes)
Donders *et al*. (2000)[17]	Cohort Belgium Hospital-based	* *	*M. urealyticum*, Bacterial vaginosis, and *M. hominis*	Abortion	5.50 (2.90–10)	NR*
Fahmy *et al*. (2015)[18]	Cohort Egypt	* *	Bacterial vaginosis	Premature birth		*
Harper *et al*. (2012)[19]	Cohort USA Hospital-based	* *	Bacterial vaginosis	Premature birth	1.10 (0.80–1.50)	*
Hollegaard *et al*. (2007)[20]	Cohort Denmark	29 NR	*C. trachomatis*	Premature birth	2.60 (1.10–-6.29)	*

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Table 1: Contd...

Authors (Year) (Reference number)	Type of study Country Study population	Age Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
Lata *et al*. (2010)[21]	Cohort India Hospital-based	26.50 *	Bacterial vaginosis	Premature birth		*
McPheeters *et al*. (2005)[22]	Cohort USA Hospital-based	* *	Bacterial vaginosis	Premature birth	2.60 (1.70–4.10)	*
Menard *et al*. (2010)[23]	Cohort France Hospital-based	29 790	*Gardnerella vaginalis*	Premature birth		*
Nelson *et al*. (2008)[24]	Cohort U.S.A Hospital-based	24.20 754	Bacterial vaginosis	Premature birth	1.03 (0.64–1.63)	*
Nelson *et al*. (2009)[25]	Cohort USA Hospital-based	24 50	*G. vaginalis*	Premature birth	1.21 (0.73–2.01)	*
Nelson *et al*. (2014)[26]	Cohort USA Population-based	23.50 483	Bacterial vaginosis	Premature birth		Baseline (t1) microbiota level measured on a continuum and body mass index
Oakeshott *et al*. (2002)[27]	Cohort United Kingdom Population-based	* 1,189	Bacterial vaginosis	Abortion	1.15 (0.7–1.87)	*
Odendaal *et al*. (2006)[28]	Cohort South Africa Population-based	20.6 343	*C. trachomatis*	Premature birth		*
Rittenschober-Böhm *et al*. (2017)[29]	Cohort Austria Population-based	* 3,643	*M. urealyticum*	Premature birth	1.40 (0.8–2.20)	Risk factors
Rours *et al*. (2011)[30]	Cohort Netherlands Hospital-based	* 4,055	*C. trachomatis*	Premature birth	1.17 (0.60–2.40)	Maternal age, ethnicity, education, gravidity, and smoking with multiple imputation
Tellapragada *et al*. (2016)[31]	Cohort India Hospital-based	27.10 790	*T. vaginalis* and Bacterial vaginosis	Premature birth	3.20 (1.02–10.41)	*
Thorsen *et al*. (2006)[32]	Cohort Denmark Hospital-based	28 2,221	Bacterial vaginosis	Premature birth	0.80 (0.50–1.50)	*
Vogel *et al*. (2006)[33]	Cohort Denmark Population-based	28 2,662	*M. urealyticum* and Bacterial vaginosis	Premature birth	1.30 (0.80–2)	Smoking, previous low birth weight, previous preterm delivery, and *Escherichia coli*
Watson-Jones *et al*. (2002)[34]	Cohort Tanzania Hospital-based	24.50 380	Syphilis	Premature birth, stillbirth	6.10 (2.50–15.30)	Gravidity and delivery site
Bylykbashi *et al*. (2013)[35]	Cohort Iran Population-based	NR* 1,223	*T. vaginalis* and Bacterial vaginosis	Premature birth	5.99 (3.79–9.49)	*

*Not Reported

Table 2: The main characteristics of case-control and copulation case-control studies

Authors (Year) (Reference number)	Country (Age)	Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
Carlini *et al*. (2002)[36]	Italy (*)	Case (709) Control (3,368) T (4,077)	Bacterial vaginosis	Premature birth	2.00 (1.30–3.10)	*
Discacciati *et al*. (2011)[37]	Brazil (24.80)	Case (37) Control (45) T (82)	Bacterial vaginosis	Premature birth	4.06 (0.30–55.09)	Age <19 years, schooling, smoking, previous urinary tract infection, pH >4.5, ethnic group, bacterial vaginosis, and vaginal infection
Isik *et al*. (2016)[38]	Turkey (30.55)	Case (61) Control (139) **(200)	Bacterial vaginosis	Abortion	*	*
Lim *et al*. (2010)[39]	New Zealand (*)	Case (44) Control (69) ** (113)	Bacterial vaginosis	Premature birth	*	*
Marakoglu *et al*. (2008)[40]	Turkey (*)	Case (20) Control (28) T (48)	Bacterial vaginosis	Premature birth	11.57 (1.26–105.70)	*
Agger *et al*. (2014)[41]	USA (27.70)	Case (54) Control (762) ** (816)	*C. trachomatis*	Premature birth	1.72 (0.91–3.28)	*
Agholor *et al*. (2013)[42]	Nigeria (28.40)	Case (98) Control (98) ** (186)	*C. trachomatis*	Ectopic pregnancy	4.70 (2.33–-8.83)	*
Ahmadi *et al*. (2016)[43]	Iran (*)	Case (109) Control (109) ** (218)	*C. trachomatis*	Abortion	2.19 (1.05–-4.56)	*
Andrews *et al*. (2000)[44]	America (*)	Case (190) Control (190) ** (380)	*C. trachomatis*	Premature birth	2.30 (1.01–5.03)	*
Bakken *et al*. (2007)[45]	Norway (*)	*	*C. trachomatis*	Ectopic pregnancy	1.40 (1.01–1.95)	*
Baud *et al*. (2011)[46]	Switzerland (33.30)	*	*C. trachomatis*	Abortion	2.30 (1.10–5.10)	Age, origin, education, and number of sex partners
Baud *et al*. (2015)[47]	Switzerland (32.40)	Case (146) Control (261) ** (407)	*C. trachomatis*	Premature birth		*
Benjamin *et al*. (2013)[48]	Brunei (*)	Case (118) Control (100) ** (218)	*C. trachomatis*	Ectopic pregnancy		*
Karaer *et al*. (2013)[49]	Turkey (30.40)	*	*C. trachomatis*	Ectopic pregnancy	2.42 (1.1–5.34)	*
Karinen *et al*. (2005)[50]	Finland (27.20)	Case (104) Control (402) **(506)	*C. trachomatis*	Premature birth	1.00 (0.5–2)	*
Mpiima *et al*. (2018)[51]	Uganda (27.50)	Case (25) Control (76) ** (101)	*C. trachomatis*	Ectopic pregnancy	4.90 (1.15–21.29)	*
Abele-Horn *et al*. (2000)[52]	Germany (29)	Case (172) Control (132) T (304)	*M. genitalium*	Premature birth	2.80 (1.80–6.20)	Maternal risk factors
Hitti *et al*. (2010)[53]	USA (*)	Case (661) Control (667) ** (1328)	*M. genitalium*	Premature birth	2.50 (1.20–5)	Maternal age and all other covariates

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Table 2: Contd...

Authors (Year) (Reference number)	Country (Age)	Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
Jurstrand *et al*. (2007)[54]	Sweden (*)	*	*M. genitalium*	Ectopic pregnancy	2.30 (1.40–4)	Age, LAMP, and CT were included in the mode
Ahmadi *et al*. (2014)[55]	Iran (30.50)	Case (109) Control (109) ** (218)	*M. urealyticum*	Abortion	*	*
Harada *et al*. (2008)[56]	Japan (30.80)	Case (45) Control (100) T (145)	*M. urealyticum*	Premature birth	3.30 (1.20–8.80)	*
Kafetzis *et al*. (2004)[57]	Greece (30)	Case (126) Control (125) **(251)	*M. urealyticum*	Premature birth	*	*
Farhadifar *et al*. (2016)[58]	Iran (29.60)	Case (109) Control (109) ** (218)	*M. hominis*	Abortion	0.49 (0.08–2.73)	*
Arnesen *et al*. (2015)[59]	America (*)	Case (1,461) Control (366,690) Total (368,151)	Syphilis	Stillbirth	1.88 (1.25–2.83)	Maternal risk factors
Dou *et al*. (2013)[60]	China (*)	*	Syphilis	Premature birth	3.70 (2.36–5.8)	Maternal age, residence location, education, and job
Geelhoed *et al*. (2015)[61]	Belgium (24.70)	Case (150) Control (300) Total (450)	Syphilis	Stillbirth	*	*
Ahmadi *et al*. (2018)[62]	Iran (*)	Case (109) Control (109) Total (218)	*T. Vaginalis*	Abortion	*	*
Buchmayer *et al*. (2003)[63]	Sweden (*)	*	*T. Vaginalis*	Premature birth	1.10 (0.70–1.70)	Maternal age and parity
Kamal *et al*. (2018)[64]	Egypt (*)		*T. Vaginalis*	Premature birth	*	*
Eleje *et al*. (2015)[65]	Nigeria (30.70)	Case (105) Control (105) Total (210)	*G. vaginalis*	Premature birth	12.17 (1.54–96.07)	*
Heumann *et al*. (2017)[66]	USA (*)	*	*N. Gonorrhoeae*	Premature birth	1.50 (1.20–1.90)	Marital status and smoking status
Nejad *et al*. (2008)[67]	Iran (*)	Case (80) Control (80) Total (160)	Bacterial vaginosis	Premature birth	2.63 (1.03–6.85)	Job, history of abortion, and educational level
Pereira *et al*. (2016)[68]	Brazil (*)	Case (109) Control (218) Total (327)	Bacterial vaginosis	Premature birth	1.44 (0.51–3.77)	*
Subtil *et al*. (2002)[69]	France (*)	Case (102) Control (102) Total (204)	Bacterial vaginosis	Premature birth	13.80 (7.70–22)	*
Svare *et al*. (2007)[70]	Denmark (NR)	Case (170) Control (3,092) Total (3,262)	Bacterial vaginosis	Premature birth	1.50 (1–2.10)	*
Ashshi *et al*. (2015)[71]	Saudi Arabia (*)	*	*C. trachomatis* and *M. genitalium*	Ectopic pregnancy	3.07 (1.30–12.30)	*
Burton *et al*. (2018)[72]	Australia (25.80)	Case (361) Control (372) Total (433)	*C. trachomatis*, *T. vaginalis*, and *N. Gonorrhoeae*	Premature birth	2.92 (1.07–7.97)	Previous preterm birth, smoking, frequency of antenatal care hypertensive

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Table 2: Contd...

Authors (Year) (Reference number)	Country (Age)	Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
						disease and antepartum hemorrhage, and remoteness and method of pregnancy dating
Donders *et al*. (2009)[73]	Belgium (29)	*	Bacterial vaginosis and *M. hominis*	Premature birth	2.43 (1.10–4.70)	*
Edwards *et al*. (2006)[74]	USA (25)	*	Bacterial vaginosis, *G. vaginalis*, *M. genitalium*, *M. urealyticum*, and *M. hominis*	Premature birth	0.90 (0.18–4.59)	*
Kataoka *et al*. (2006)[75]	Japan (29.60)	Case (21) Control (856) Total (877)	*M. genitalium*, *M. urealyticum*, and *M. hominis*	Premature birth	*	*
Kilpatrick *et al*. (2006)[76]	USA (26.30)	Case (102) Control (316) Total (418)	Bacterial vaginosis, *C. trachomatis*, and *N. Gonorrhoeae*	Premature birth	1.60 (0.70–3.60)	*
Nakubulwa *et al*. (2015)[77]	Uganda (*)	Case (87) Control (87) Total (174)	*T. Vaginalis*	Premature birth	1.15 (0.63–2.09)	*
Nyári *et al*. (2001)[78]	Hungary (*)	Case (148) Control (6,008) Total (6,156)	*C. trachomatis*	Stillbirth	1.80 (1.10–3.30)	*
Pientong *et al*. (2009)[79]	Thailand (*)	Case (32) Control (57) Total (89)	*C. trachomatis*	Ectopic pregnancy	5.04 (1.12–-21.13)	*
Rantsi *et al*. (2016)[80]	Finland (*)	Case (243) Control (1,347) Total (1,590)	*C. trachomatis*	Premature birth, abortion, and ectopic pregnancy	1.00 (0.82–1.21)	*
Zhu *et al*. (2014)[81]	China (*)	Case (72) Control (146) Total (218)	*C. trachomatis*	Ectopic pregnancy	1.60 (0.67–3.83)	*
Povlsen *et al*. (2001)[82]	Denmark (*)	Case (84) Control (400) Total (484)	Bacterial vaginosis and *M. genitalium*	Premature birth	0.77 (0.33–1.60)	*
Schwab *et al*. (2016)[83]	Switzerland (26.70)	Case (23) Control (39) Total (62)	*M. urealyticum* and *M. hominis*	Premature birth	0.52 (0.15–1.57)	*
Silveira *et al*. (2009)[84]	USA (*)	*	Bacterial vaginosis, *C. trachomatis*, Syphilis, *T. vaginalis*, and *N. Gonorrhoeae*	Premature birth	1.00 (0.4–2.60)	Maternal age, maternal race, marital status, previous delivery, previous preterm birth, maternal alcohol use, maternal smoking, maternal drug use, hypertension, diabetes, thyroid dysfunction, and aniemia
Ramazanzadeh *et al*. (2016)[85]	Iran (29.60)	Case (109) Control (109) Total (218)	*M. genitalium*	Abortion	*	*

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Table 2: Contd...

Authors (Year) (Reference number)	Country (Age)	Sample size	Type of infection	Type of outcomes	Measurement of association	Controlled variables
Romero *et al*. (2014)[86]	USA (21)	Case (18) Control (72) Total (90)	*G. vaginalis*	Premature birth	*	*

*Not Reported, **Treatment. Abbreviations: LAMP=Loop-mediated isothermal amplification, CT=Computed tomography

Table 3: Relationship between vaginal infections and preterm delivery, abortion, and ectopic pregnancy in pregnant women (in case-control studies) based on the type of colonization

Outcomes	Subgroups		Odds ratio (95% CI)	Between studies			Between subgroups	
				I square	Q	$p_{heterogeneity}$	Q	$p_{heterogeneity}$
Preterm Birth	Colonization	Blood	1.17 (0.98–1.40)	81.02%	15.81	0.001	36.50	0.001
		Vaginal	1.98 (1.76–2.24)	95.07%	121.63	0.001		
		Cervix	1.23 (1.07–1.42)	55.04%	6.67	0.081		
		Uteri	1.65 (1.24–2.19)	90.34%	20.7	0.001		
	Type of vaginal infection	Bacterial vaginosis	1.54 (1.39–1.70)	86.81%	53.05	0.001	98.16	0.001
		Chlamydia trachomatis	1.03 (0.84–1.27)	75.02%	12.01	0.010		
		Mycoplasma genitalium	1.53 (1.25–1.88)	0.00%	0.06	0.810		
		Ureaplasma urealyticum	7.96 (5.50–11.51)	91.98%	12.47	0.001		
		Trichomonas vaginalis	1.18 (0.98–1.42)	96.09%	25.58	0.001		
	Diagnosis method	Culture	1.58 (1.46–1.71)	93.15%	175.24	0.001	14.36	0.001
		Serology	0.92 (0.70–1.21)	55.35%	10.72	0.090		
		Molecular	1.40 (1.11–1.76)	0.00%	5.00	0.610		
Abortion	Colonization	Blood	1.09 (0.96–1.24)	67.13%	3.04	0.082	3.43	0.060
		Cervix	1.37 (1.12–1.69)	43.84%	7.12	0.132		
	Diagnosis method	Culture	2.44 (1.16–5.11)	0.00%	0.34	0.555	5.95	0.050
		Serology	1.09 (0.96–1.24)	67.13%	3.04	0.089		
		Molecular	1.31 (1.05–1.62)	34.85%	4.60	0.200		
Ectopic pregnancy	Colonization	Blood	1.10 (1.03–1.19)	84.81%	32.92	0.001	0.37	0.54
		Cervix	1.16 (1.01–1.34)	0.00%	0.09	0.760		
	Type of vaginal infection	*Chlamydia trachomatis*	1.09 (1.02–1.17)	78.78%	0.001	28.28	5.10	-0.02
		Mycoplasma genitalium	1.44 (1.03–1.88)	-	-	-		
	Diagnosis method	Serology	1.11 (1.03–1.19)	81.85%	0.001	33.06	0.31	0.58
		Molecular	1.16 (1.00–1.34)	-	-	-		

studies were included in the meta-analysis. The results of merging case-control studies showed that pregnant women with bacterial infections (regardless of the type of infection) were 1.16 times more likely to have an abortion than pregnant women without infection (OR: 1.16; 95% CI, 1.04–1.29). The heterogeneity in this meta-analysis was low (55.36%), with a significance level of 0.030. The highest and lowest ORs in these six case-control studies corresponded to the studies of Ahmadi and Farhadifar, respectively [Figure 2].[43,55,58,62] The results of publication bias are shown in Figure 3. In addition, the findings of Egger's test showed no publication bias in the effect of bacterial infections in abortion in pregnant women (coefficient, 1.10; SE, 0.552; $p = 0.341$).

In this study, the subgroup analysis was performed in case-control studies based on the type of colonization, the type of bacterial infection, and the type of bacterial infection detection method. For example, for the type of colonization, the results suggest that based on blood and cervical samples, bacterial infections increase the odds of abortion in pregnant women by 1.09 (OR: 1.09; 95% CI, 0.96–1.24) and 1.37 (OR: 1.37; 95% CI, 1.12–1.69), respectively [Table 3]. The odds of abortion varies based on the diagnostic method, but according to the molecular method, it is estimated at 1.31 (OR: 1.31; 95% CI, 1.05–1.62; Table 3).

3) Ectopic pregnancy outcomes

Regarding bacterial infections and ectopic pregnancy in pregnant women, eight case-control studies were included in the meta-analysis. The results of merging case-control studies indicated that pregnant women with bacterial infections (regardless of the type of infection) were 1.12 times more likely to have an ectopic pregnancy than pregnant women without infections (OR: 1.12; 95% CI, 1.05–1.19). The degree of heterogeneity in this meta-analysis was low (79.03%) with a significance level

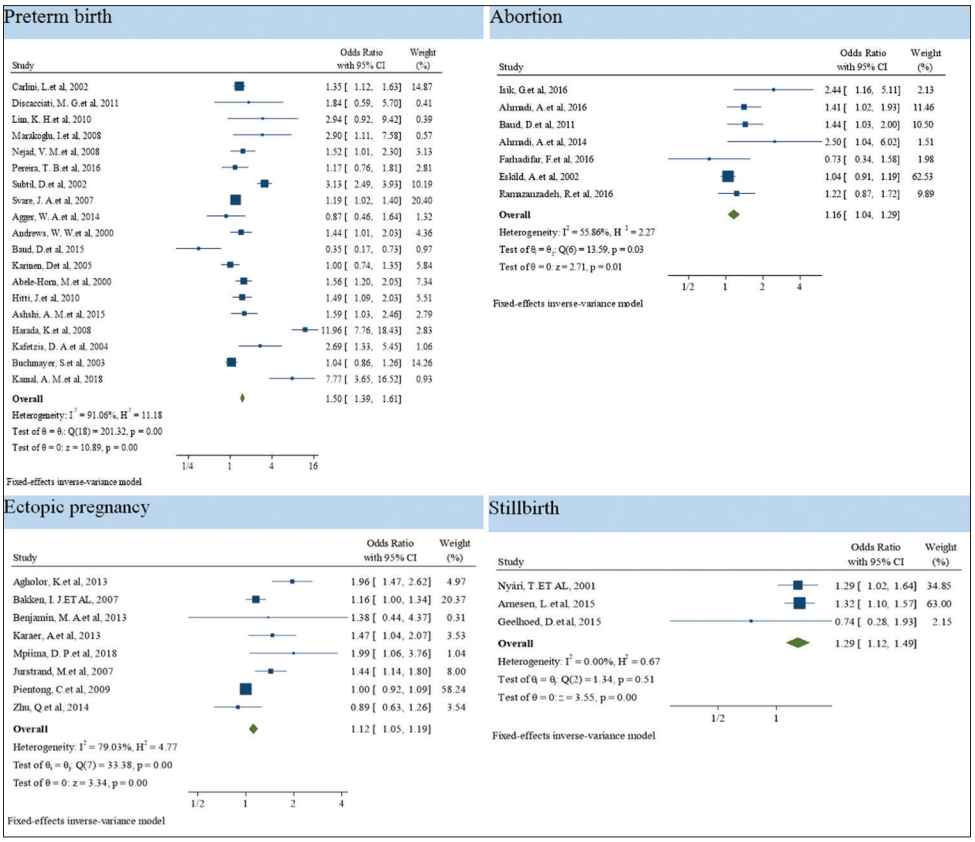

Figure 2: Cumulative as ratio of the effect of vaginal infections on preterm delivery and abortion in pregnant women based on case-control studies

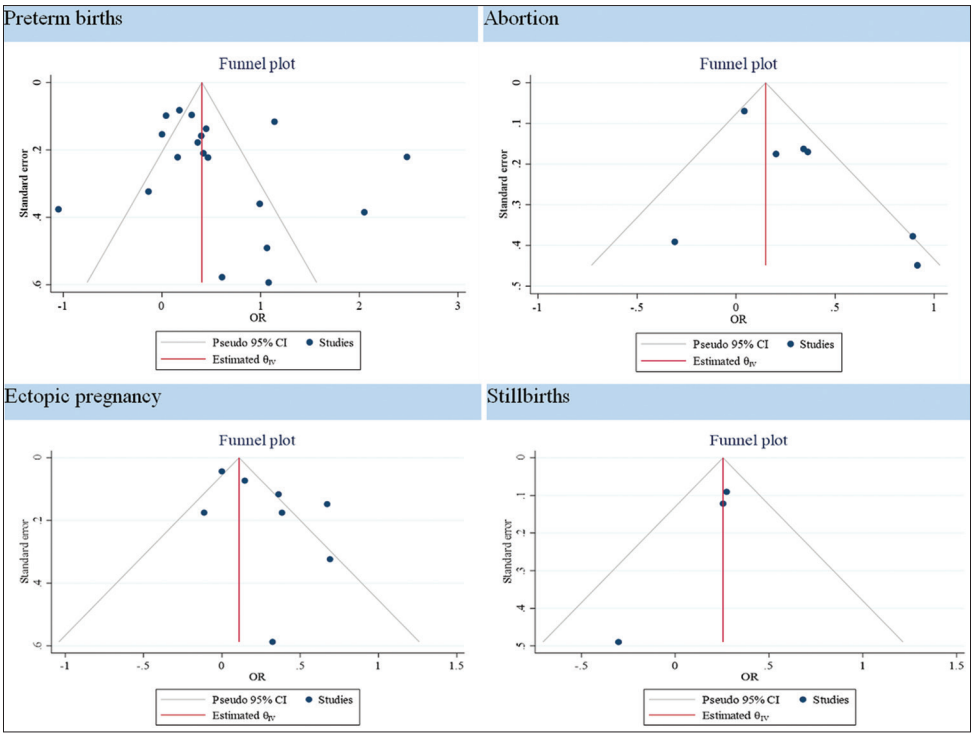

Figure 3: Publication bias of the cumulative effect of vaginal infections on preterm delivery and abortion in pregnant women based on case-control studies

of 0.001. The highest and lowest ORs in these eight case-control studies resembled those reported by Mpiima and Zhu, respectively [Figure 2].[51,81] Publication bias was also examined, and the results are presented in Figure 3. In addition, the results of Egger's test showed no publication bias in the effect of bacterial infections in abortion in

pregnant women (coefficient, 1.00; SE, 0.341; p = 0.098). In this study, the subgroup analysis was performed in case-control studies based on the type of colonization, the type of bacterial infection, and the type of bacterial infection detection method. Based on blood and cervical samples, the type of colonization showed that bacterial infections increased the odds of ectopic pregnancy in pregnant women by 1.10 (OR, 1.10; 95% CI, 1.03–1.19) and 1.16 (OR, 1.16; 95% CI, 1.01–1.34), respectively. Based on the diagnostic method, the odds of ectopic pregnancy differed, but according to the molecular method, it was estimated at 1.16 (OR, 1.16; 95% CI, 1.00–1.34; Table 3).

4) Stillbirths outcomes

Regarding bacterial infections and stillbirth in pregnant mothers, three case studies were included in the meta-analysis. The lowest OR was reported by Geelhoed *et al*. (OR, 0.74; 95% CI, 0.28–1.93) and the highest by Arnesen *et al*. (OR, 1.32; 95% CI, 1.10–1.57).[59,61] After merging control case studies, the overall OR was 1.29 (OR, 1.29; 95% CI, 1.12–1.49). The degree of heterogeneity was estimated at 0%, which was not statistically significant [Figure 2]. Due to the small number of studies, subgroup analysis was not performed to investigate this relationship. In addition, the results of Egger's test showed no publication bias in the effect of bacterial infections in stillbirth in pregnant women (coefficient, 1.10; SE, 0.221; p = 0.260; Figure 3).

Analysis of cohort studies

Screening articles for two outcomes of preterm delivery and abortion in pregnant women revealed the adequacy of data for meta-analysis. Accordingly, 14 cohort studies on preterm delivery and three cohort studies on abortion were included in the final analysis. After merging the results of these studies, the RR of preterm delivery in pregnant women with vaginal infections was calculated to be 1.57 (RR, 1.57; 95% CI, 1.46–1.67), whereas the RR of abortion was 2.02 (RR, 2.02; 95% CI, 1.72–2.38; Figures 4 and 5).

Table 3 shows the subgroup analysis based on colonization, infection type, diagnostic method, and study type to determine the effect of bacterial infections on preterm labor and its outcomes. According to the results, RR was 1.70 (RR, 1.70; 95% CI, 1.56–1.85) in population-based studies and 1.70 (RR, 1.70; 95% CI, 1.56–1.85) in hospital-based studies [Table 4].

Discussion

This systematic review and meta-analysis investigated and analyzed studies on vaginal bacterial infections and pregnancy outcomes. In the subgroup analysis, the results of the present meta-analysis showed that regarding the relationship between vaginal infections and preterm birth, the main source of heterogeneity in general estimation was OR because heterogeneity in the diagnosis groups decreased compared to the general likelihood based on culture, serology, and molecular analysis. Furthermore, different diagnostic techniques and types of colonization are the primary sources of heterogeneity in studying the relationship between vaginal infections and abortion in pregnant women because the degree of heterogeneity declined in these groups. In analyzing and combining the results of cohort studies, the current meta-analysis was the only one with sufficient studies to estimate the association of vaginal infections with preterm birth. The subgroup results based on colonization showed that infections of the normal cervical floor had a greater effect than infections of the normal pelvic floor on inducing preterm birth in pregnant women. As for the agents of vaginal infections, the effect of *C. trachomatis* is greater than that of bacterial vaginosis on causing preterm birth in pregnant women. Since the degree of heterogeneity in these subgroups of analysis was not changed significantly, it could be concluded that the type of infection and colonization cannot be a source of heterogeneity in the overall estimation of the impact of bacterial infections on preterm birth after merging cohort studies. The results of combining population-based cohort studies revealed that the heterogeneity of RR was lower than the RR obtained from merging hospital-based cohort studies. In the study by Ahmadi *et al*.[87] (2018), the prevalence of *C. trachomatis* infections was estimated based on preterm delivery using cross-sectional (OR, 0.16; 95% CI, 0.11–0.21) and case-control (OR, 0.13; 95% CI,

Table 4: Evaluation of the relationship between vaginal infections and preterm delivery in pregnant women (in cohort studies) based on the type of infection, type of colonization and type of infection diagnostic technique

Outcomes	Subgroups		RR (95% CI)	Between studies			Between subgroups	
				I square	Q	$p_{heterogeneity}$	Q	$p_{heterogeneity}$
Preterm birth	Colonization	Vaginal	1.47 (1.37–1.58)	92.13%	117.08	0.001	29.40	0.001
		Cervix	2.67 (2.18–3.28)	6.95%	3.22	0.362		
	Type of vaginal infection	Bacterial vaginosis	1.54 (1.41–1.69)	94.97%	115.20	0.001	0.03	0.865
		Chlamydia trachomatis	1.57 (1.39–1.77)	66.44%	18.94	0.062		
	Methods of detection	Culture	1.55 (1.42–1.69)	93.12%	116.22	0.001	0.44	0.510
		Molecular	1.66 (1.38–1.99)	92.02%	25.07	0.001		
	Study population	Hospital-based	1.70 (1.56–1.85)	91.73%	120.98	0.001	1.66	0.200
		Population-based	1.54 (1.35–1.75)	66.50%	8.70	0.776		

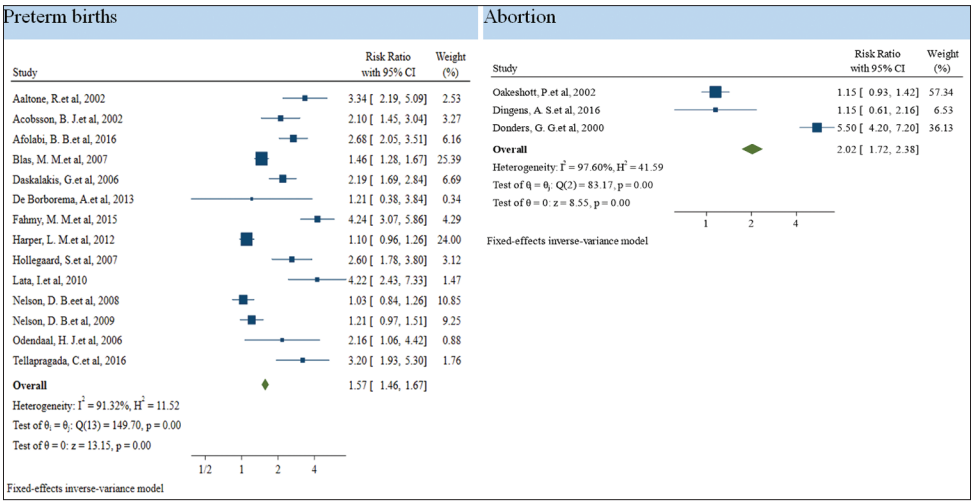

Figure 4: Cumulative RR of the effect of vaginal infections on preterm delivery and abortion in pregnant women based on cohort studies

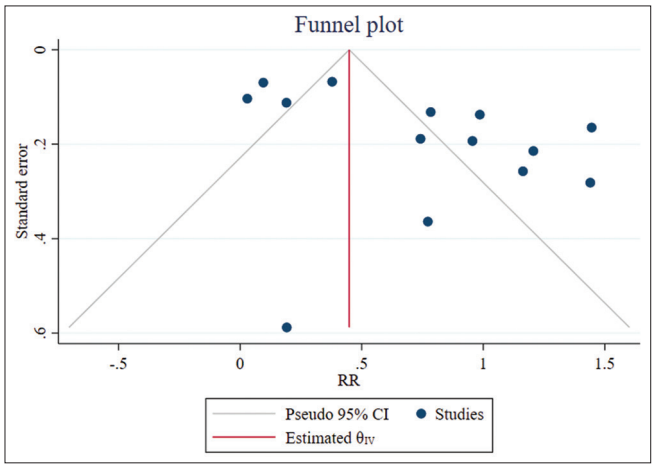

Figure 5: Publication bias of the cumulative effect of vaginal infections on preterm delivery in pregnant women based on cohort studies

0.08–-0.17) methods. The prevalence of *C. trachomatis* infections in women was estimated based on preterm delivery using polymerase chain reaction (PCR; OR, 0.06; 95% CI, 0.04–0.09), serology (OR, 0.23; 95% CI, 0.10–0.35), and culture (OR, 0.17; 95% CI, 0.10–0.24) techniques. The overall prevalence of *C. trachomatis* infections in women based on preterm delivery was calculated to be 0.13% (95% CI, 0.11–0.16). In this study, an OR of 2.16 (95% CI, 1.3–3.57) was obtained. It can be concluded that women with *C. trachomatis* infection are 2.16 times more likely to give birth prematurely than healthy women. Harald *et al*.[88] (2003) explored the relationship between bacterial vaginosis and preterm delivery in a meta-analysis. They reviewed 18 articles, finding that bacterial fibrosis increased the risk of preterm delivery (OR, 2.19; 95% CI, 1.54–3.12) and even spontaneous abortion (OR, 9.91; 95% CI, 1.99–49.34). These results are in line with those of case-control articles reviewed in the current paper. Weihua *et al*.[89] investigated the association of *C. trachomatis* infection with pregnancy outcomes in a meta-analysis. In their review of 50 articles, they reported that *C. trachomatis* infection increased the risk of preterm delivery in 30 articles (OR, 1.731; 95% CI, 1.343–2.230); also, the review of 18 studies showed a significant relationship between *C. trachomatis* and rupture of membranes (OR, 2.574; 95% CI, 1.213–5.464; p = 0.014). Also, in four studies, no relationship was found between chlamydia infection and neonatal stillbirth (OR, 0.993; 95% CI, 0.489–2.015; p = 0.984). In this paper, similar to our study, there were few studies on stillbirth outcomes. In general, the results of the present meta-analysis suggest that the ORs obtained from different subgroups after merging the case-control studies have a narrower CI, which is due to the larger number of studies compared to cohort studies examining the relationship between vaginal infection and pregnancy outcomes; however, the built-in bias should also be taken into account. The main strength of our study lies in the review of ample articles as case-control and cohort studies, as well as the comparison of the results obtained from these two types of studies in different subgroups. Another strength of our study is the analysis of literature based on sample type, infection type, and testing. This helps identify the sources of heterogeneity in the overall meta-analysis estimate. One of the limitations of the present meta-analysis is the small number of studies in some subgroups by the type of study. Also, to estimate all pregnancy outcomes, the number of studies was limited.

Conclusion

Based on the results of this meta-analysis, the presence of bacterial infections in pregnant women can lead increase the risk of pregnancy outcomes, especially infant birth, preterm delivery, abortion, stillbirth, and ectopic pregnancy. So, it is necessary that the health policy makers develop new healthcare programs with an emphasis on the implementation of support programs to early detect bacterial infections in pregnant women. As well as it is recommended to conduct appropriate intervention studies

in order to evaluate the intervention programs formulated in different societies and to select the best intervention with the greatest effect to reduce these infections in the pregnant women.

Acknowledgements

This work was supported by the Deputy of Research of Kurdistan University of Medical Sciences.

Financial support and sponsorship

Deputy of Research of Kurdistan University of Medical Sciences

Conflicts of interest

Nothing to declare.

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