BMC Women's Health

RESEARCH

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Vulvovaginal yeast infections during pregnancy and perinatal outcomes: systematic review and meta-analysis

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Abstract

Background Vulvovaginal yeast infections in pregnancy are common and can cause extensive inflammation, which could contribute to adverse pregnancy outcomes. Symptomatic yeast infections are likely to cause more inflammation than asymptomatic. The objective of this study was to investigate associations between symptomatic and asymptomatic vulvovaginal yeast infections in pregnancy and perinatal outcomes.

Methods We did a systematic review and searched eight databases until 01 July 2022. We included studies reporting on pregnant women with and without laboratory confirmed vulvovaginal yeast infection and preterm birth or eight other perinatal outcomes. We used random effects meta-analysis to calculate summary odds ratios (OR), 95% confidence intervals (CI) and prediction intervals for the association between yeast infection and outcomes. We described findings from studies with multivariable analyses. We assessed the risk of bias using published tools.

Results We screened 3909 references and included 57 studies. Only 22/57 studies reported information about participant vulvovaginal symptoms. Preterm birth was an outcome in 35/57 studies (49,161 women). In 32/35 studies with available data, the summary OR from univariable analyses was 1.01 (95% CI 0.84–1.21, I^2 60%, prediction interval 0.45–2.23). In analyses stratified by symptom status, we found ORs of 1.44 (95% CI 0.92–2.26) in two studies with ≥ 50% symptomatic participants, 0.84 (95% CI 0.45–1.58) in seven studies with < 50% symptomatic participants, and 1.12 (95% CI 0.94–1.35) in four studies with asymptomatic participants. In three studies with multivariable analysis, adjusted ORs were greater than one but CIs were compatible with there being no association. We did not find associations between vulvovaginal yeast infection and any secondary outcome. Most studies were at high risk of bias in at least one domain and only three studies controlled for confounding.

Conclusions We did not find strong statistical evidence of an increased risk for preterm birth or eight other adverse perinatal outcomes, in pregnant women with either symptomatic or asymptomatic vulvovaginal yeast infection. The available evidence is insufficient to make recommendations about testing and treatment of vulvovaginal yeast infection in pregnancy. Future studies should assess vulvovaginal symptoms, yeast organism loads, concomitant vaginal or cervical infections, and microbiota using state-of-the-art diagnostics.

Systematic review registration PROSPERO CRD42020197564

Keywords Vaginal candida, Vaginal yeast, Pregnancy, Preterm birth, Adverse perinatal outcomes, Systematic review

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Background

Vulvovaginal yeast infections in pregnancy are common and can cause extensive inflammation, which could contribute to adverse perinatal outcomes [1]. Preterm birth is the most common cause of neonatal death worldwide [2]. The causes of preterm birth include socio-economic factors, underlying maternal conditions, foetal conditions, and infectious causes [3]. Infectious causes include upper, and possibly lower, genital tract infections [4], with some evidence that early preterm birth is more commonly infection-related than late preterm birth [5]. Vulvovaginal yeast infections caused by *Candida* species, are more common in pregnant women than non-pregnant women [1, 6, 7], potentially because of hormonal and immunological changes that occur during pregnancy [8]. It is not known whether yeast organism loads are higher in pregnant than non-pregnant women or whether they are associated with levels of inflammation or adverse perinatal outcomes [9].

Microorganisms in the female genital tract may have direct pathogenic effects in pregnancy through infection of the amniotic cavity and/or through stimulating inflammatory cascades [4]. Besides prostaglandins, chemokines and pro-inflammatory cytokines can ripen the cervix and induce contractions [10]. These pathways may be activated by infections during pregnancy and lead to preterm birth [10]. Yeast infections in the female genital tract cause inflammation and therefore increase proinflammatory mediators in the vaginal fluid, such as interleukin-8, which have been associated with preterm birth [11, 12]. A systematic review reporting on studies of asymptomatic *Candida* colonization published up to May 2020 did not find an association with adverse pregnancy outcomes [13]. Symptomatic yeast infections are likely to cause more inflammation than asymptomatic infection, however. The objective of this study was to investigate associations between both symptomatic and asymptomatic vulvovaginal yeast infections in pregnancy and preterm birth and other perinatal outcomes.

Methods

We did a systematic review and registered the protocol in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42020197564). We followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines for reporting the review [14].

Search strategy

We searched Medline (Ovid), PubMed, Embase (Ovid), the Cochrane Library, CINAHL, African Index Medicus, LILACS and ClinicalTrials.gov (Supplementary search strategy, Additional File 1) from inception until 01 July 2022 without language restrictions. Additional studies were retrieved by checking reference lists of relevant articles. For articles in languages not spoken by our team, we used DeepL to translate [15].

Eligibility criteria

We included cross-sectional, case-control, cohort studies and clinical trials. Eligible studies were those that included pregnant women who had a laboratory test for vulvovaginal yeast infection before the outcome occurred and reported on pre-defined outcomes. We excluded studies in which all included pregnant women had confirmed vulvovaginal yeast infection without a control group for comparison.

Study selection

One reviewer (RG) screened all titles and abstracts, and a second reviewer (DB) cross-checked a random sample of 10%. Discrepancies were resolved by discussion. The full texts of potentially eligible manuscripts were assessed by one reviewer (RG) and all were verified by another (DB, KT, CD, NL). Final decisions were made by consensus or adjudication by a third reviewer (NL).

Outcome definitions

Preterm birth, defined as birth before 37 completed weeks of pregnancy, was our primary outcome [16]. Secondary outcomes included spontaneous abortion (delivery of a dead foetus before 22 completed weeks of pregnancy), stillbirth (delivery of a dead foetus after 22 completed weeks of pregnancy), preterm premature rupture of membranes (spontaneous tearing of the membranes surrounding the foetus before 37 weeks of gestation), premature rupture of membranes (spontaneous tearing of the membranes surrounding the foetus any time before the onset of obstetric labour), low birth weight (less than 2500 g), small for gestational age (birth weight below the 10th centile for gestational age), inflammation of the placenta or uterus (endometritis, chorioamnionitis, villitis, or funisitis), and neonatal death (death of a live-born infant during the first 28 completed days of life) [3, 16, 17].

Data extraction

We designed online forms in the Research Electronic Data Capture software (REDCap) [18] to extract data about study design, basic study population characteristics, symptom status, risk factors, laboratory characteristics, and study outcomes (Supplementary REDCap data extraction forms, Additional File 2). Symptom status was defined as the presence or absence of vulvovaginitis, curdy white discharge, vulval or vaginal itch or vaginal discharge, either self-reported or clinician-observed.

One reviewer (RG, DB, KT, CD, or NL) extracted data into the forms and a second reviewer (RG, DB, KT, CD, or NL) verified all the extracted data, with discrepancies resolved by discussion. We contacted the authors for data that were not reported in the article. If we did not receive a reply by 01 November 2022, we excluded the study from the review. If vulvovaginal specimens were taken at multiple timepoints during pregnancy, we extracted the data from the first timepoint as this included the largest number of participants and was most consistent with the timepoint of other included studies. If more than one article reported on the same study population, we considered these as a single study, but extracted relevant information from any linked publication.

Risk of bias assessment

Two reviewers (RG, DB, KT, CD, or NL) assessed the risk of bias independently using published tools [19, 20], developed by the Clarity group of evidence-based healthcare experts (https://www.clarityresearch.ca). For clinical trials and cross-sectional studies, we assessed the risk of bias with the tool designed for cohort studies, which included the relevant questions. We added two relevant questions: (1) was the study designed specifically to assess the association between vulvovaginal yeast infection and pregnancy outcomes, and (2) did the authors control for confounding in their analysis. Where there were ten or more studies, we generated funnel plots to assess evidence for publication bias and other small study biases [21].

Data synthesis

We assessed heterogeneity between studies visually with forest plots and used the I^2 statistic to describe the proportion of variability other than that due to chance [22]. Where appropriate, we conducted random effects meta-analysis to calculate summary odds ratios (OR) and 95% confidence intervals (CI), which shows the average size of the association between yeast infection and each outcome in included studies. Where there were three or more studies, we also calculated the 95% prediction interval, which gives a range for the strength of association in a future study [22]. Meta-analyses and forest plots were produced using R 4.1.2 [23]. The completeness and comprehensiveness of symptom reporting varied between studies, therefore we stratified studies reporting on preterm birth into five groups. Few studies reported the proportion of women with symptoms and one enrolled only symptomatic participants [24]. We split these studies at the halfway mark. The categories were: (1) no symptoms (observed or self-reported), (2) $<50\%$ participants with symptoms, (3) $\geq 50\%$ participants with symptoms, (4) participants with symptoms included but proportion unknown, and (5) symptom status not reported. We also stratified studies reporting about preterm birth by study design, income setting (according to The World Bank classification) [25], and human immunodeficiency virus (HIV) infection status. Post-hoc, we stratified studies by trimester of testing and diagnostic methods used. For studies in which authors conducted a multivariable analysis, we plotted the unadjusted and adjusted OR (and 95% CI) and recorded the variables that were adjusted for in each study.

Results

We screened 3909 references and included 57 different studies. The main reasons for exclusion were due to studies not reporting any of our outcomes of interest, or having insufficient numerical data (Fig. 1). Table 1 summarises characteristics of the included studies, from 27 different countries, published between 1969 and 2022 with a median sample size of 347 participants (interquartile range, IQR 200–1000). Five were cross-sectional studies [24, 26–29], 15 were case–control studies [30–44], 35 were cohort studies [45–81], and two were randomised clinical trials [82, 83] (Table 1).

We included 58 records that reported on 57 different studies (Table 1). Among the 57 included studies, 22 (38.6%) described whether participants had reported symptoms and assessed symptom status. Of these 22 studies, 17 included participants with symptoms (14 reported the percentage of participants with symptoms) [24, 29, 39, 42, 43, 45–47, 58, 59, 65, 67, 69, 77–79, 84] and five studies included only participants without symptoms [55–57, 70, 82, 83]. Reporting about symptom in terms of self-reported or clinician-observed symptoms and the level of detail varied between studies. Of the 22 studies, eight studies reported symptoms observed by the clinician [42, 45, 46, 54, 59, 67, 69, 77], two only self-reported [43, 78], five studies both [29, 58, 65, 79, 82] and seven did not reported if the symptoms were self-reported or clinician-observed [24, 39, 47, 55–57, 70, 83]. Of the 17 studies which included participants with symptoms, six studies report proportions of different types of vaginal discharge and other symptoms which are associated with genital tract infections [29, 43, 47, 54, 65, 67], ten reported if symptoms from a defined group of symptoms were present or absent [24, 39, 42, 45, 58, 59, 69, 77–79], one did not report the type or definition of symptoms [46]. Where symptom status was reported, the information was captured at baseline. The main laboratory methods used were culture and microscopy (Table 1). Thirty-one studies reported on the yeast species detected, and *Candida albicans* was most frequently reported. Of the 57 studies, 39 provided information about the timing of testing during pregnancy (Table 1).

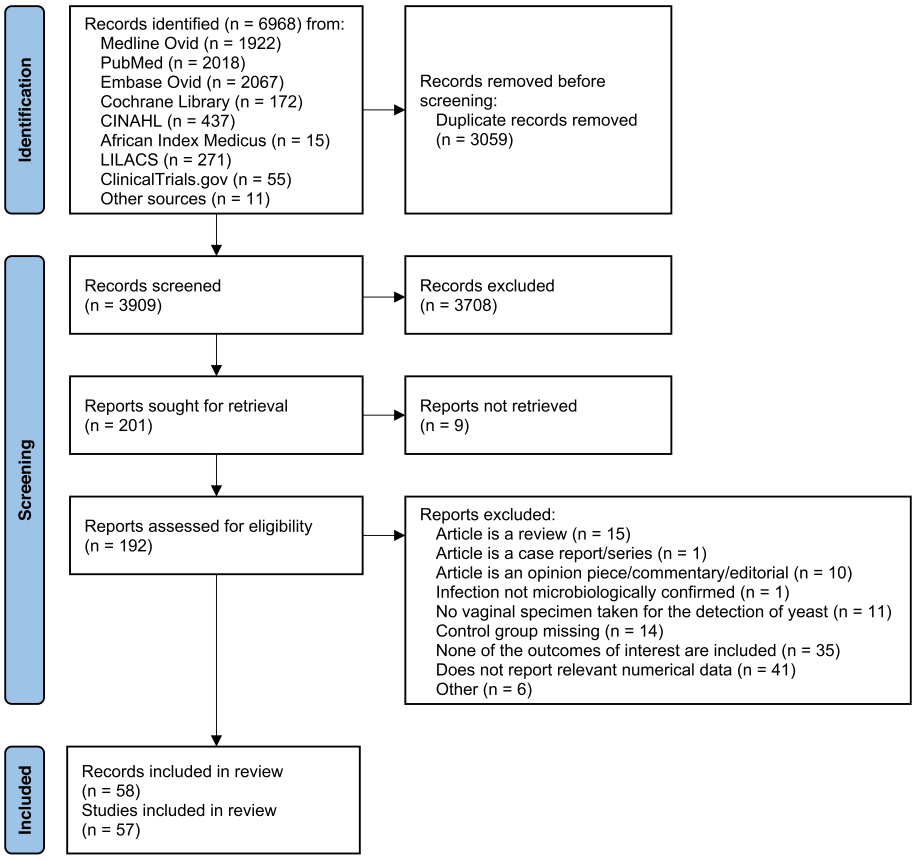

Fig. 1 Flowchart of the selection process of articles

Only five studies tested at multiple timepoints during pregnancy for all or a subset of participants [55, 56, 58, 60, 63, 83]. Other infections are reported in 46 studies but only nine report outcome data on co-infections of vulvovaginal yeast infections [29, 37, 39, 55, 56, 59, 70, 74, 78, 82].

The primary outcome, preterm birth, was reported in 35 studies with data on 49,161 women. Univariable data were available for 32 studies and data from a multivariable model for three studies [61, 74, 81]. Figure 2 shows the studies reporting univariable data according to reported symptom status and Fig. 3 studies with multivariable data. For all included studies reporting on preterm birth, we found a summary OR of 1.01 (95% CI 0.84–1.21, I^2 60%, prediction interval 0.45–2.23, 32 studies). Within groups according to symptom status, heterogeneity was mostly low (Table 2). The OR for preterm birth was 1.44 (95% CI 0.92–2.26, I^2 0%) in two studies with ≥ 50% participants with symptoms [24, 29], 0.84 (95% CI 0.45–1.58, I^2 88%, prediction interval 0.10–6.81) in seven studies with < 50% participants with symptoms [43, 45–47, 65, 78, 79], 1.12 (95% CI 0.94–1.35, I^2 0%, prediction interval 0.75–1.68) in four studies only with participants without self-reported or observed symptoms [55, 56, 70, 82, 83], and 1.05 (95% CI 0.87–1.26, I^2 2%, prediction interval 0.70–1.57) in 17 studies in which symptom status was not reported [27, 28, 32, 37, 40, 44, 50, 53, 61, 63, 64, 66, 68, 72, 74–76]. The prediction intervals for all groups with sufficient data included the null value. Of the three studies not included in the meta-analysis, one reported 90% confidence intervals (OR 0.88, 90% 0.61–1.27) [49], one assessed three testing timepoints and analysed the data in five groups, concluding from univariate logistic regression that different 'trends' of vulvovaginal candidiasis were not associated with preterm birth [60], and one only reported adjusted estimates [81].

Heterogeneity assessed by the I^2 test was very low. One study by Goel et al. was an outliner in which vulvovaginal yeast infections were associated with lower odds of preterm birth [47]. Goel et al. (2018) enrolled 500 pregnant women at any gestational age from a medical institute in India. Preterm risk factors were not part of the enrolment criteria. This study reported that 67.8% of women had a preterm delivery, but there was no definition of preterm delivery nor any discussion about the high number of preterm deliveries [47].

Table 1 Summary of characteristics of studies included in the systematic review

Participant characteristics	Total	No symptoms	Asymptomatic and symptomatic	Only symptomatic	Not reported
Number of studies, n	57	5	16	1	35
Study design, n					
Cohort	35	3	12	0	20
Case-control	15	0	3	0	12
Cross-sectional	5	0	1	1	3
Clinical trial	2	2	0	0	0
Publication, year median (IQR)	2012 (1995–2018)	2014 (2011–2015)	2016 (1997–2019)	2020	2008 (1995–2016)
Number of women, total (median, IQR)	71,500 (374, 200–1000)	13,923 (500, 347–4429)	22,574 (331, 202–1220)	258	34,745 (300, 156–912)
Outcomes, reported, n					
Preterm birth	35	4	10	1	20
Spontaneous abortion	5	1	2	0	2
Stillbirth	4	1	3	0	0
PPROM	11	0	3	0	8
PROM	15	1	5	0	9
Low birth weight	11	1	5	0	5
Small for gestational age	1	0	0	0	1
Inflammation of the placenta or uterus	3	0	1	0	2
Neonatal death	1	0	1	0	0
Time of testing, n					
1st trimester	12	2	2	0	8
2nd trimester	24	3	4	0	17
3rd trimester	27	2	5	1	19
not reported	18	1	8	0	9
Specimen type, n					
Vaginal swab	41	4	11	1	25
Endocervical swab	14	0	2	0	12
Other[a]	5	1	3	0	1
not reported	4	0	1	0	3
Diagnostic method, n					
Microscopy	30	2	12	0	16
Culture	34	3	10	1	20
PCR	3	1	1	0	1
not reported	7	0	0	0	7

IQR Interquartile range, *PCR* Polymerase chain reaction, *PPROM* Preterm premature rupture of membranes, *PROM* Premature rupture of membranes

[a] Vaginal smears, endocervical smears, vaginal wash, cervicovaginal fluid

The total number of studies included is 57. The totals for each item can sum to more than 57 because a study might have reported on more than one item

There was no strong statistical evidence of an association in meta-analyses about vulvovaginal yeast infections and preterm birth in pre-specified subgroups stratified by study design and income setting or in post-specified subgroups stratified by diagnostic methods used and time of testing (Supplementary forest plots of stratified meta-analyses, Additional File 3). Only four studies reported on the inclusion or exclusion of women living with HIV and results for the association between yeast infection and preterm birth were not stratified according to HIV infection status (three excluded HIV positive women [67, 72, 76], one included HIV positive women but did not stratify results by HIV status [78]).

There were three studies reporting adjusted estimates from multivariable analysis (Fig. 3) [61, 74, 81]. McDonald et al. and Rittenschober-Bohm et al. adjusted for known preterm risk factors and infections and Sule-Odu et al. (who reported only the adjusted OR) adjusted for

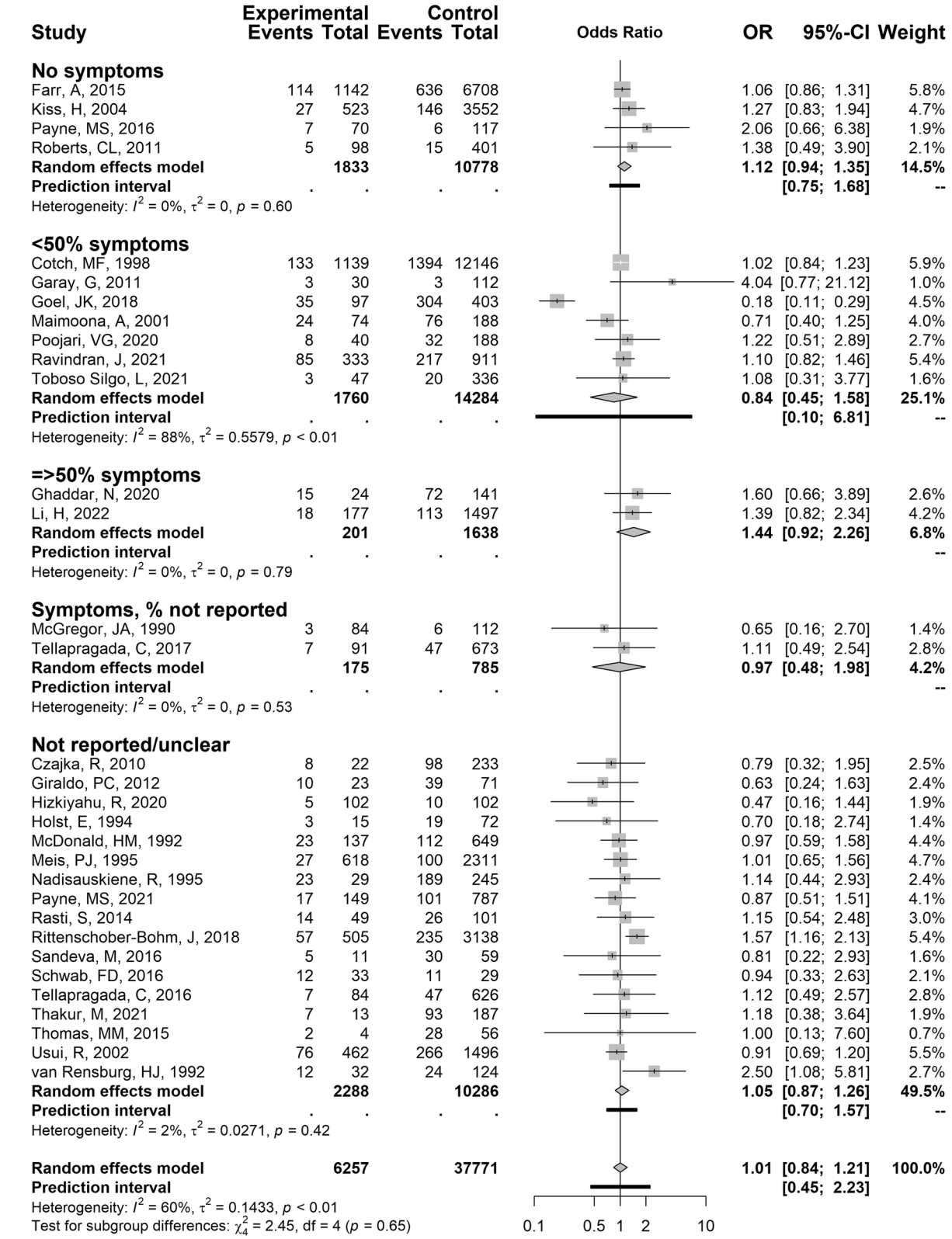

Fig. 2 Forest plot of meta-analysis vulvovaginal yeast infections and preterm birth stratified by symptom status. Legend: vertical line, line of no association (odds ratio 1.0); horizontal line, 95% confidence interval; vertical line inside the box, point estimate of odds ratio; grey box, study size; diamond, summary estimate with 95% confidence interval; black bar, 95% prediction interval. To the left of the line of no association, preterm birth was less likely in women with vulvovaginal yeast infection; to the right of the line of no association, preterm birth was more likely

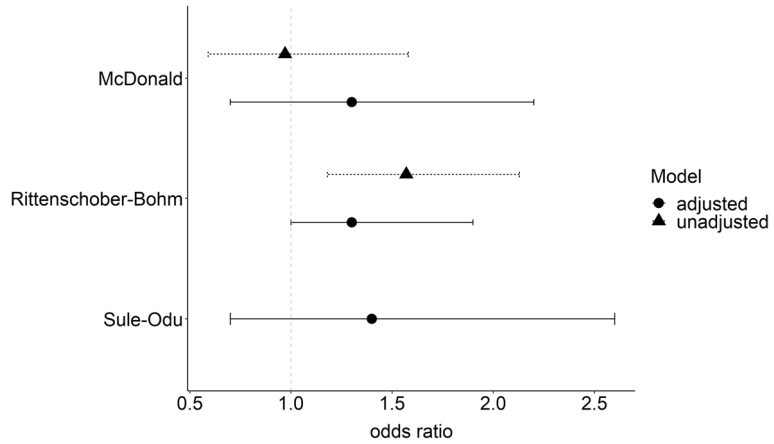

Fig. 3 Forest plot of unadjusted and adjusted estimates on vaginal yeast infections and preterm birth. Legend: horizontal lines, 95% confidence intervals; dot/triangle, odds ratio. Unadjusted estimates were calculated from raw numbers (not provided for Sule-Odu [81]); adjusted estimates are those reported by the authors. McDonald [61] adjusted for previous preterm delivery (> 20 weeks), previous midtrimester miscarriage, multiple pregnancy, cervical incompetence, polyhydramnios, uterine malformation, pyelonephritis during pregnancy, *Gardnerella vaginalis*, *Ureaplasma urealyticum*, *Mycoplasma hominis*, *Bacteroides* spp, *Peptostreptococcus* spp, Group B streptococci, *Escherichia coli*, *Klebsiella* spp, *Staphylococcus aureus*, *Haemophilus* spp, yeast. Rittenschober-Bohm [74] adjusted for bacterial vaginosis, vaginal candidiasis, history of preterm birth, smoking, age, *Ureaplasma urealyticum* positive, *U. parvum* positive, *U. urealyticum* and *U. parvum* positive. Sule-Odu [81] adjusted for age, parity, educational level, socioeconomic status, birth weight, gestational age at delivery

Table 2 Association between vulvovaginal yeast infection and secondary outcomes, from univariate analysis

Outcome	Number of studies included in meta-analysis	OR	95% CI	I^2 value
Spontaneous abortion [26, 55, 56, 58, 62]	4	1.01	0.60–1.72	44%
Stillbirth [45, 55, 56, 69]	3	1.09	0.66–1.78	0%
Preterm premature rupture of membranes [28, 30, 34, 35, 41, 42, 45, 48, 61, 65]	10	0.82	0.51–1.31	70%
Premature rupture of membranes [29, 31, 33, 36, 38, 39, 41, 45, 46, 51, 57, 66, 71, 79, 80]	15	1.02	0.74–1.41	64%
Low birth weight [29, 45, 52, 54–56, 59, 66, 72, 79]	9	1.02	0.78–1.34	41%
Small for gestational age [49]	1	1.80	90% CI 1.17–2.77	N/A
Inflammation of the placenta or uterus [41, 44]	2	1.20	0.59–2.41	0%
Neonatal death [45]	1	1.08	0.46–2.53	N/A

OR Odds ratio, *CI* Confidence interval, *N/A* Not applicable for strata with a single study

socioeconomic factors but not for infections. CIs for all adjusted ORs included the null value. The CIs of the adjusted ORs overlapped with those of the unadjusted estimates in the studies by McDonald et al. and Rittenschober-Bohm et al. and the direction of the OR after adjustment for potential confounders was not consistent.

We did not find strong statistical evidence of associations between vulvovaginal yeast infection and any secondary outcome, reported in 1–15 studies (Table 2 and Supplementary forest plots of secondary outcomes, Additional File 4). For one study that reported on the outcome small for gestational age, authors reported a 90% CI (OR 1.80, 90% CI 1.17–2.77) [49].

Risk of bias

We judged most studies to have a high risk of bias in at least one domain (Supplementary summary of risk of bias assessment, Additional File 5). There were concerns about the participant selection, diagnostic tools used to detect vulvovaginal yeast infections, frequency of testing during pregnancy and incomplete reporting. As described, only three studies included a multivariable analysis to control for confounding. For the three outcomes (preterm birth, preterm premature rupture of membranes, premature rupture of membranes) with more than ten included studies, funnel plots were symmetrical, indicating low risk of small study biases (Fig. 4

and supplementary funnel plots of secondary outcomes, Additional File 6) [21].

Discussion

Summary of findings

In this systematic review of 57 studies, for the association between vulvovaginal yeast infection and preterm birth the summary OR was 1.01 (95% CI 0.84–1.21, I^2 60%, prediction interval 0.45–2.23, 32 studies). For studies including ≥ 50% participants with symptoms the summary OR was 1.44 (95% CI 0.92–2.26, I^2 0%, two studies), studies with < 50% participants with symptoms 0.84 (95% CI 0.45–1.58, I^2 88%, seven studies) and studies including women without symptoms 1.12 (95% CI 0.94–1.35, I^2 0%, four studies). Most studies had a high risk of bias in at least one domain.

Strengths and limitations

This review has several strengths. We had a broad search strategy with no language exclusion. By contacting authors, we obtained data that were not reported in the original publication and which added to this review (2 studies) [45, 79]. We pre-specified the analysis according to symptom status and described reporting and its association with preterm birth in detail. The main limitations of the review result from the high risk of bias and incomplete reporting of symptoms, which affect the certainty with which the findings can be interpreted. A methodological limitation is that only about 10% of the screened title and abstracts were verified by a second reviewer. Since this resulted in less than 3% additional studies for full-text screening, we decided that it is unlikely that the missed articles would have changed the results. Another methodological limitation is that, instead of two people extracting data independently, a second person verified the extracted data, which sped up the process but makes errors in the extracted data more likely.

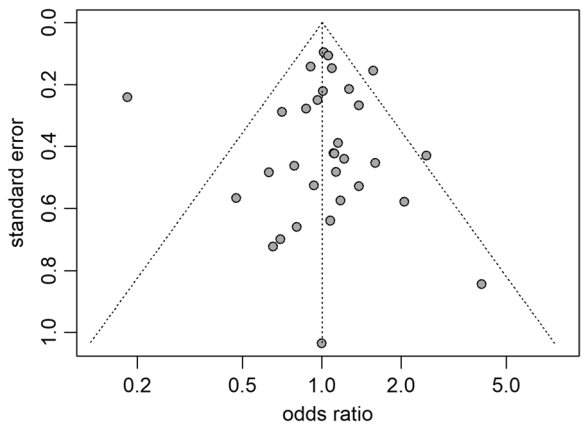

Fig. 4 Funnel plot of published studies reporting on preterm birth. Legend: circle, represents one study; triangle, region where 95% of the data points would lie in absence of small study biases; vertical dashed line, odds ratio from meta-analysis

Comparison with other studies and interpretation

We found two relevant systematic reviews. Our findings are consistent with those of Schuster et al., who combined 15 studies and found no association between pregnant women with asymptomatic *Candida* colonisation and preterm birth (OR 1.10, 95% CI 0.99–1.22) [13]. In our review, we found that 11 studies in the meta-analysis by Schuster et al. included some women with symptoms of yeast infection, or in which the presence or absence of symptoms was not reported [45, 46, 49, 50, 60, 61, 63, 67, 85–87]. The second systematic review examined the effect of screening and treating women for asymptomatic vulvovaginal candidiasis during pregnancy [88]. In their meta-analysis of two randomised control trials [82, 83], women who received clotrimazole for diagnosed vaginal *Candida* were less likely to have a spontaneous preterm birth than women who received usual care (risk ratio 0.36, 95% CI 0.17–0.75). It is not clear why treatment of asymptomatic *Candida* in pregnancy was associated with a reduction in preterm birth in these two randomised control trials when no association was found in observational studies in which potential confounders were controlled for. The authors of the intervention review called for caution in the interpretation of their findings because data from the largest trial, which dominated the meta-analysis, were from an unplanned subgroup analysis [82].

We expected to observe a stronger association between symptomatic vulvovaginal yeast infections and preterm birth than for asymptomatic colonisation because we assumed increased inflammation in women with symptomatic infections [11]. The OR and the CI of the group with 50% or more symptomatic women are in the expected direction (OR 1.44, 95% CI 0.92–2.26) but the confidence intervals of the < 50% symptomatic and the group with no symptoms overlap and include one (OR 1.12, 95% CI 0.94–1.35). However, the quality of reporting in these studies varies and most studies were judged to have a high risk of bias in at least one domain. Despite this, the statistical heterogeneity between studies was mostly low. The three studies which provided an adjusted estimate also found ORs above one, in expected direction, but CIs were compatible with no association.

There are several possible reasons for the absence of an observed association in our meta-analyses of observational studies. First, the timepoint of testing during pregnancy varied in the assessed literature and most studies included only one timepoint; if women who had vulvovaginal yeast infections late in pregnancy, the onset of preterm labour would not be expected to be influenced

[11]. Second, diagnostic factors might have played a role if testing was only done from the lower genital tract. If upper genital tract infection is a necessary precursor of preterm labour [4], test results from the upper genital tract would be needed. Third, different laboratory methods were used in the studies included in the review. Most included studies used culture which remains the gold standard, fewer used microscopy which is not as accurate as culture or polymerase chain reaction [89]. Even though we do not see a difference in the results when stratified by laboratory method used (Supplementary forest plots of stratified meta-analyses, Additional File 3), misclassification of the presence or absence of vulvovaginal yeast infection might have reduced the strength of association when studies were combined in meta-analysis. Fourth, treatment given differed between studies. Therefore, the effect of clearing of the infection versus persistent infection cannot be assessed.

Conclusion

We systematically reviewed the literature about vulvovaginal yeast infections in pregnancy and adverse perinatal outcomes. We did not find strong statistical evidence of an increased risk for preterm birth or eight other adverse perinatal outcomes, in pregnant women with either symptomatic or asymptomatic vulvovaginal yeast infection. Further well-designed studies to collect detailed information about vulvovaginal yeast infections, symptom status and adverse pregnancy outcomes are warranted [89]. Use of molecular diagnostic methods would allow accurate detection and quantification of organism load to determine whether the presence of symptoms is associated with higher organism load, and whether higher organism loads are associated with a higher risk of preterm birth [9]. Finally, yeast infections cannot be seen in isolation and comprehensive evaluation of the role of concomitant vaginal or cervical infections, or certain microbiota should also be investigated in holistic studies [90–92]. Given the methodological limitations of observational studies and inconsistency with the findings of randomised controlled trials, there is insufficient evidence to make recommendations about testing and treatment of yeast infections in pregnancy to prevent preterm birth.

Abbreviations

CI	Confidence interval
HIV	Human immunodeficiency virus
PROSPERO	International prospective register of systematic reviews
IQR	Interquartile range
OR	Odds ratio
PCR	Polymerase chain reaction
PPROM	Preterm premature rupture of membranes
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PROM	Premature rupture of membranes
REDCap	Research electronic data capture software

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12905-023-02258-7.

Additional file 1. Search strategy. Search terms used for the literature search in eight databases.

Additional file 2. REDCap data extraction forms. Data extraction forms on REDCap which were designed and used to extract data from published articles for our systematic review.

Additional file 3. Forest plots of stratified meta-analyses. Forest plots of meta-analyses about vulvovaginal yeast infection and preterm birth stratified by study design, diagnostic method used, income setting, and time of testing.

Additional file 4. Forest plots of secondary outcomes. Forest plots of meta-analyses about vulvovaginal yeast infection and spontaneous abortion, stillbirth, preterm premature rupture of membranes, premature rupture of membranes, low birth weight, inflammation of the placenta or uterus.

Additional file 5. Summary of risk of bias assessment for cohort studies, cross-sectional studies, clinical trials, and case–control studies.

Additional file 6. Funnel plots of secondary outcomes preterm premature rupture of membranes and premature rupture of membranes.

Acknowledgements

We thank Beatrice Minder and Doris Kopp from the Institute of Social and Preventive Medicine at the University of Bern for assisting with the development of the search strategy and with deduplication of the results of the literature searches, Dianne Egli-Gany from the Institute of Social and Preventive Medicine at the University of Bern for assisting with piloting the extraction forms, and Radek Panczak from the Institute of Social and Preventive Medicine at the University of Bern for assisting with data extraction of Polish articles. Preliminary results of this manuscript have been presented in an oral presentation at the 23rd International Union against Sexually Transmitted Infections World Congress, Zimbabwe, 4-7 September 2022.

Authors' contributions

Conception and design of the review: NL, RG, JW. Abstract and articles screening, reviewing, extraction: RG, DB, KT, CD, NL. Data analysis and interpretation: RG, NL, JW, RP. Drafting the article: RG. Critical revision and approval of manuscript: all authors. All authors read and approved the final manuscript.

Funding

This project was funded by an MD-PhD scholarship from the Swiss National Science Foundation (grant number 191225), a Swiss National Science Foundation project (number 197831), and a Swiss government excellence scholarship (grant number 2019.0774), and the SSPH + Global PhD Fellowship Programme in Public Health Sciences of the Swiss School of Public Health.

Availability of data and materials

All data generated or analysed during this study are included in this published article, its supplementary information files or can be obtained via request to the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable because only already published articles were reviewed.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 20 January 2023 Accepted: 6 March 2023
Published online: 21 March 2023

References

1. Chatzivasileiou P, Vyzantiadis TA. Vaginal yeast colonisation: From a potential harmless condition to clinical implications and management approaches-A literature review. Mycoses. 2019. https://doi.org/10.1111/myc.12920.
2. UN Inter-agency group for child mortality estimation. Levels & trends in child mortality: report 2019. New York: United Nations Children's Fund; 2019.
3. March of Dimes, PMNCH, Save the children, World Health Organization. Born Too Soon: The Global Action Report on Preterm Birth. Geneva: World Health Organization; 2012.
4. Romero R, Espinoza J, Kusanovic JP, Gotsch F, Hassan S, Erez O, et al. The preterm parturition syndrome. BJOG. 2006. https://doi.org/10.1111/j.1471-0528.2006.01120.x.
5. Andrews WW, Hauth JC, Goldenberg RL, Gomez R, Romero R, Cassell GH. Amniotic fluid interleukin-6: correlation with upper genital tract microbial colonization and gestational age in women delivered after spontaneous labor versus indicated delivery. Am J Obstet Gynecol. 1995. https://doi.org/10.1016/0002-9378(95)90290-2.
6. Romero R, Hassan SS, Gajer P, Tarca AL, Fadrosh DW, Nikita L, et al. The composition and stability of the vaginal microbiota of normal pregnant women is different from that of non-pregnant women. Microbiome. 2014. https://doi.org/10.1186/2049-2618-2-4.
7. Sabour S, Arzanlou M, Vaez H, Rahimi G, Sahebkar A, Khademi F. Prevalence of bacterial vaginosis in pregnant and non-pregnant Iranian women: a systematic review and meta-analysis. Arch Gynecol Obstet. 2018. https://doi.org/10.1007/s00404-018-4722-8.
8. Aguin TJ, Sobel JD. Vulvovaginal candidiasis in pregnancy. Curr Infect Dis Rep. 2015. https://doi.org/10.1007/s11908-015-0462-0.
9. Goodfellow L, Verwijs MC, Care A, Sharp A, Ivandic J, Poljak B, et al. Vaginal bacterial load in the second trimester is associated with early preterm birth recurrence: a nested case-control study. BJOG. 2021. https://doi.org/10.1111/1471-0528.16816.
10. MacIntyre DA, Sykes L, Teoh TG, Bennett PR. Prevention of preterm labour via the modulation of inflammatory pathways. J Matern Fetal Neonatal Med. 2012. https://doi.org/10.3109/14767058.2012.666114.
11. Cauci S, Culhane JF. Modulation of vaginal immune response among pregnant women with bacterial vaginosis by *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and yeast. Am J Obstet Gynecol. 2007;196:133.e1–7.
12. Discacciati MG, Simoes JA, Silva MG, Marconi C, Brolazo E, Costa ML, et al. Microbiological characteristics and inflammatory cytokines associated with preterm labor. Arch Gynecol Obstet. 2011. https://doi.org/10.1007/s00404-010-1427-z.
13. Schuster HJ, de Jonghe BA, Limpens J, Budding AE, Painter RC. Asymptomatic vaginal *Candida* colonization and adverse pregnancy outcomes including preterm birth: a systematic review and meta-analysis. Am J Obstet Gynecol MFM. 2020. https://doi.org/10.1016/j.ajogmf.2020.100163.
14. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. Int J Surg. 2021. https://doi.org/10.1016/j.ijsu.2021.105906.
15. DeepL SE. DeepL Translator, Cologne. 2022. https://www.deepl.com. Accessed 30 Oct 2022.
16. World Health Organization. ICD-10 International statistical classification of diseases and related health problems. 5th ed. Geneva: World Health Organization; 2016.
17. Lawn JE, Blencowe H, Pattinson R, Cousens S, Kumar R, Ibiebele I, et al. Stillbirths: Where? When? Why? How to make the data count? Lancet. 2011. 10.1016/s0140-6736(10)62187-3.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009. 10.1016/j.jbi.2008.08.010.
19. Systematic Review & Literature Review Software. Tool to Assess Risk of Bias in Case Control Studies. DistillerSR Inc. 2022. www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-case-control-studies-distillersr. Accessed 27 May 2022.
20. Systematic Review & Literature Review Software. Tool to Assess Risk of Bias in Cohort Studies. DistillerSR Inc. 2022. www.evidencepartners.com/resources/methodological-resources/tool-to-assess-risk-of-bias-in-cohort-studies-distillersr. Accessed 27 May 2022.
21. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997. https://doi.org/10.1136/bmj.315.7109.629.
22. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ. 2011. https://doi.org/10.1136/bmj.d549.
23. RStudio Team. RStudio: Integrated Development for R. Boston: RStudio; 2022.
24. Ghaddar N, Anastasiadis E, Halimeh R, Ghaddar A, Dhar R, AlFouzan W, et al. Prevalence and antifungal susceptibility of Candida albicans causing vaginal discharge among pregnant women in Lebanon. BMC Infect Dis. 2020. https://doi.org/10.1186/s12879-019-4736-2.
25. The World Bank Group. World Bank Country and Lending Groups Country Classification. The World Bank Group. 2022. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups. Accessed 12 Nov 2022.
26. Liu XL, Xiao Y, Zhang H, Wu LJ. Comparison of vaginal flora in patients with spontaneous abortion and women with normal first-trimester. Reprod Dev Med. 2018. https://doi.org/10.4103/2096-2924.248490.
27. Giraldo PC, Araujo ED, Junior JE, do Amaral RL, Passos MR, Goncalves AK. The prevalence of urogenital infections in pregnant women experiencing preterm and full-term labor. Infect Dis Obstet Gynecol. 2012. https://doi.org/10.1155/2012/878241.
28. Hizkiyahu R, Baumfeld Y, Paz Levy D, Lanxner Battat T, Imterat M, Weintraub AY. Antepartum vaginal *Candida* colonization and the risk for obstetrical tears. J Matern Fetal Neonatal Med. 2020. https://doi.org/10.1080/14767058.2020.1712701.
29. Li H, Dong M, Xie W, Qi W, Teng F, Li H, et al. Mixed Vaginitis in the Third Trimester of Pregnancy Is Associated With Adverse Pregnancy Outcomes: A Cross-Sectional Study. Front Cell Infect Microbiol. 2022. https://doi.org/10.3389/fcimb.2022.798738.
30. Karat C, Madhivanan P, Krupp K, Poornima S, Jayanthi NV, Suguna JS, et al. The clinical and microbiological correlates of premature rupture of membranes. Indian J Med Microbiol. 2006. https://doi.org/10.4103/0255-0857.29388.
31. Machalski T, Der J, Sikora J. Vaginal candidiasis in pregnant women. Mikologia Lekarska. 2006;13:185–6.
32. Thomas MM, Sulek K, McKenzie EJ, Jones B, Han TL, Villas-Boas SG, et al. Metabolite profile of cervicovaginal fluids from early pregnancy is not predictive of spontaneous preterm birth. Int J Mol Sci. 2015. https://doi.org/10.3390/ijms161126052.
33. Aboyeji AP, Abdul IF, Ijaiya MA, Nwabuisi C, Ologe MO. The bacteriology of pre-labour rupture of membranes in a Nigerian teaching hospital. J Obstet Gynaecol. 2005. https://doi.org/10.1080/01443610500314876.
34. Eleje GU, Adinma JI, Ugwuanyi DC, Ikechebelu JI, Okafor CI, Ezeama CO, et al. Genital tract microbial isolate in women with preterm pre-labour rupture of membranes in resource-constrained community setting. J Obstet Gynaecol. 2015. https://doi.org/10.3109/01443615.2014.970145.
35. Evaldson G, Carlstrom G, Lagrelius A, Malmborg AS, Nord CE. Microbiological findings in pregnant women with premature rupture of the

membranes. Med Microbiol Immunol. 1980. https://doi.org/10.1007/BF02121812.
36. Gejdel E. Role of vaginitis and cervicitis in the etiology of premature rupture of fetal membranes. Wiad Lek. 1983;36:1255–9.
37. Holst E, Goffeng AR, Andersch B. Bacterial vaginosis and vaginal microorganisms in idiopathic premature labor and association with pregnancy outcome. J Clin Microbiol. 1994. https://doi.org/10.1128/jcm.32.1.176-186.1994.
38. Kovavisarach E, Sermsak P, Kanjanahareutai S. Aerobic microbiological study in term pregnant women with premature rupture of the membranes: a case-control study. J Med Assoc Thai. 2001;84:19–23.
39. 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. https://doi.org/10.1186/s13104-015-1545-6.
40. Sandeva M, Parahuleva N, Uchikova E. Frequency of Preterm Birth in Women with Cervical Vaginal Infections. Akush Ginekol. 2016;55(Suppl 2):14–8.
41. Veleminsky M, Tosner J. Relationship of vaginal microflora to PROM, pPROM and the risk of early-onset neonatal sepsis. Neuro Endocrinol Lett. 2008;29:205–21.
42. Zhang LX, Sun Y, Zhao H, Zhu N, Sun XD, Jin X, et al. A Bayesian Stepwise Discriminant Model for Predicting Risk Factors of Preterm Premature Rupture of Membranes: A Case-control Study. Chin Med J. 2017. https://doi.org/10.4103/0366-6999.216396.
43. Maimoona A, Rizwan I, Iffat S. Colonization of candida albicans in pregnant women. Pak J Med Res. 2001;40:24–6.
44. Thakur M, Lata S, Pal A, Sharma H, Dhiman B. Relationship between histologic chorioamnionitis and genital tract cultures in pre term labour. J Obstet Gynaecol. 2021. https://doi.org/10.1080/01443615.2020.1789955.
45. Cotch MF, Hillier SL, Gibbs RS, Eschenbach DA, Yaffe SJ, Catz CS, et al. Epidemiology and outcomes associated with moderate to heavy *Candida* colonization during pregnancy. Am J Obstet Gynecol. 1998. https://doi.org/10.1016/s0002-9378(98)80028-8.
46. Garay G, Fraca M, Martinez I, da Silva A, Lopez-Valverde M, Esteban V, et al. Utility of vaginal pH determination in the diagnosis of vulvovaginitis and its association with obstetric pathology. Progresos de Obstetricia y Ginecologia. 2011. https://doi.org/10.1016/j.pog.2011.07.001.
47. Goel JK, Mani A, Goyal R, Jaiswal M, Sah S. Cervical cytology and its correlation with cervicovaginal infection in antenatal patients: A study in a tertiary care hospital. Journal of SAFOG. 2018. https://doi.org/10.5005/jp-journals-10006-1611.
48. Grice AC. Vaginal infection causing spontaneous rupture of the membranes and premature delivery. Aust N Z J Obstet Gynaecol. 1974. https://doi.org/10.1111/j.1479-828X.1974.tb00833.x.
49. Polk F, Berlin L, Kanchanaraksa S, Munoz A, Kramer F, Spence M, et al. Association of *Chlamydia trachomatis* and *Mycoplasma hominis* with intrauterine growth retardation and preterm delivery. Am J Epidemiol. 1989. https://doi.org/10.1093/oxfordjournals.aje.a115244.
50. Schwab FD, Zettler EK, Moh A, Schotzau A, Gross U, Gunthert AR. Predictive factors for preterm delivery under rural conditions in post-tsunami Banda Aceh. J Perinat Med. 2016. https://doi.org/10.1515/jpm-2015-0004.
51. Blok R, Klejewski A, Szumala-Kakol A. The role of lower genital tract infection in PROM. Ginekol Pol. 1997;68:449–58.
52. Chiang Mai Low Birth Weight Study Group, Mangklabruks A, Rerkasem A, Wongthanee A, Rerkasem K, Chiowanich P, et al. The risk factors of low birth weight infants in the Northern part of Thailand. J Med Assoc Thai. 2012;95:358–65.
53. Czajka R, Rzepka R, Kwiatkowski S, Torbe A, Swiszczowska A, Mikolajek-Bedner W, et al. Vaginal and cervical bacterial colonization in patients with threatening preterm labor. Ginekol Pol. 2010;81:840–3.
54. Donders GG, van Straeten D, Hooft P, De Wet GH. Detection of *Candida* cell forms in Pap smears during pregnancy. Eur J Obstet Gynecol Reprod Biol. 1992. https://doi.org/10.1016/0028-2243(92)90237-s.
55. Farr A, Kiss H, Hagmann M, Marschalek J, Husslein P, Petricevic L. Routine Use of an Antenatal Infection Screen-and-Treat Program to Prevent Preterm Birth: Long-Term Experience at a Tertiary Referral Center. Birth. 2015. https://doi.org/10.1111/birt.12154.
56. Farr A, Kiss H, Holzer I, Husslein P, Hagmann M, Petricevic L. Effect of asymptomatic vaginal colonization with *Candida albicans* on pregnancy outcome. Acta Obstet Gynecol Scand. 2015. https://doi.org/10.1111/aogs.12697.
57. Filippidi A, Galanakis E, Maraki S, Galani I, Drogari-Apiranthitou M, Kalmanti M, et al. The effect of maternal flora on *Candida* colonisation in the neonate. Mycoses. 2014. https://doi.org/10.1111/myc.12100.
58. Frerich W, Gad A. The frequency of Candida infections in pregnancy and their treatment with clotrimazole. Curr Med Res Opin. 1977;4:640–4.
59. Hardy PH, Hardy JB, Nell EE, Graham DA, Spence MR, Rosenbaum RC. Prevalence of six sexually transmitted disease agents among pregnant inner-city adolescents and pregnancy outcome. Lancet. 1984. https://doi.org/10.1016/s0140-6736(84)92698-9.
60. Hu CY, Li FL, Hua XG, Jiang W, Zhang XJ. Longitudinal trajectory of vulvovaginal candidiasis, trichomoniasis, and bacterial vaginosis during pregnancy as well as the impact on pregnancy outcomes: a preliminary study. J Matern Fetal Neonatal Med. 2019. https://doi.org/10.1080/14767058.2018.1469125.
61. McDonald HM, O'Loughlin JA, Jolley P, Vigneswaran R, McDonald PJ. Prenatal microbiological risk factors associated with preterm birth. Br J Obstet Gynaecol. 1992. https://doi.org/10.1111/j.1471-0528.1992.tb13888.x.
62. McLennan MT, McLennan CE. Failure of vaginal wall cytologic smears to predict abortion. Am J Obstet Gynecol. 1969. https://doi.org/10.1016/s0002-9378(16)34393-9.
63. Meis PJ, Goldenberg RL, Mercer B, Moawad A, Das A, McNellis D, et al. The preterm prediction study: Significance of vaginal infections. Am J Obstet Gynecol. 1995. https://doi.org/10.1016/0002-9378(95)91360-2.
64. Nadisauskiene R, Bergstrom S, Stankeviciene I, Spukaite T. Endocervical pathogens in women with preterm and term labour. Gynecol Obstet Invest. 1995. https://doi.org/10.1159/000292331.
65. Poojari VG, Dawson S, Vasudeva A, Hegde N, Kaipa G, Eshwara V, et al. Multimodality Screening for Lower Genital Tract Infections Between 18 and 24 Weeks of Pregnancy and its Efficacy in Predicting Spontaneous Preterm Delivery. J Obstet Gynaecol India. 2020. https://doi.org/10.1007/s13224-019-01287-3.
66. Rasti S, Asadi MA, Taghriri A, Behrashi M, Mousavie G. Vaginal candidiasis complications on pregnant women. Jundishapur J Microbiol. 2014. https://doi.org/10.5812/jjm.10078.
67. Tellapragada C, Eshwara VK, Bhat P, Kamath A, Aletty S, Mukhopadhyay C. Screening of vulvovaginal infections during pregnancy in resource constrained settings: Implications on preterm delivery. J Infect Public Health. 2017. https://doi.org/10.1016/j.jiph.2016.06.003.
68. van Rensburg HJ, Odendaal HJ. The prevalence of potential pathogenic micro-organisms in the endocervix of pregnant women at Tygerberg Hospital. SAMJ. 1992;81:156–7.
69. Warr AJ, Pintye J, Kinuthia J, Drake AL, Unger JA, McClelland RS, et al. Sexually transmitted infections during pregnancy and subsequent risk of stillbirth and infant mortality in Kenya: a prospective study. Sex Transm Infect. 2018. https://doi.org/10.1136/sextrans-2018-053597.
70. Payne MS, Ireland DJ, Watts R, Nathan EA, Furfaro LL, Kemp MW, et al. *Ureaplasma parvum* genotype, combined vaginal colonisation with *Candida albicans*, and spontaneous preterm birth in an Australian cohort of pregnant women. BMC Pregnancy Childbirth. 2016. https://doi.org/10.1186/s12884-016-1110-x.
71. Minkoff H, Grunebaum AN, Schwarz RH, Feldman J, Cummings M, Crombleholme W, et al. Risk factors for prematurity and premature rupture of membranes: a prospective study of the vaginal flora in pregnancy. Am J Obstet Gynecol. 1984. https://doi.org/10.1016/0002-9378(84)90392-2.
72. Tellapragada C, Eshwara VK, Bhat P, Acharya S, Kamath A, Bhat S, et al. Risk Factors for Preterm Birth and Low Birth Weight Among Pregnant Indian Women: A Hospital-based Prospective Study. J Prev Med Public Health. 2016. https://doi.org/10.3961/jpmph.16.022.
73. Braga VL, Rocha LPS, Bernardo DD, Cruz CO, Riera R. What do cochrane systematic reviews say about probiotics as preventive interventions? Sao Paulo Med J. 2017. https://doi.org/10.1590/1516-3180.2017.0310241017.
74. Rittenschober-Bohm J, Waldhoer T, Schulz SM, Stihsen B, Pimpel B, Goeral K, et al. First Trimester Vaginal *Ureaplasma* Biovar Colonization and Preterm Birth: Results of a Prospective Multicenter Study. Neonatology. 2018. https://doi.org/10.1159/000480065.
75. Usui R, Ohkuchi A, Matsubara S, Izumi A, Watanabe T, Suzuki M, et al. Vaginal lactobacilli and preterm birth. J Perinat Med. 2002. https://doi.org/10.1515/JPM.2002.072.

76. Payne MS, Newnham JP, Doherty DA, Furfaro LL, Pendal NL, Loh DE, et al. A specific bacterial DNA signature in the vagina of Australian women in midpregnancy predicts high risk of spontaneous preterm birth (the Predict1000 study). Am J Obstet Gynecol. 2021. https://doi.org/10.1016/j.ajog.2020.08.034.
77. McGregor JA, French JI, Richter R, Franco-Buff A, Johnson A, Hillier S, et al. Antenatal microbiologic and maternal risk factors associated with prematurity. Am J Obstet Gynecol. 1990. https://doi.org/10.1016/0002-9378(90)90607-9.
78. Ravindran J, Richardson B, Kinuthia J, Unger JA, Drake AL, Osborn L, et al. Chlamydia, Gonorrhea, and Incident HIV Infection During Pregnancy Predict Preterm Birth Despite Treatment. J Infect Dis. 2021. https://doi.org/10.1093/infdis/jiab277.
79. Toboso Silgo L, Cruz-Melguizo S, de la Cruz Conty ML, Encinas Pardilla MB, Munoz Algarra M, Nieto Jimenez Y, et al. Screening for Vaginal and Endocervical Infections in the First Trimester of Pregnancy? A Study That Ignites an Old Debate. Pathogens. 2021. https://doi.org/10.3390/pathogens10121610.
80. Wang W, Hao J, An R. Abnormal vaginal flora correlates with pregnancy outcomes: A retrospective study from 737 pregnant women. Eur J Obstet Gynecol Reprod Biol. 2022. https://doi.org/10.1016/j.ejogrb.2022.03.013.
81. Sule-Odu AO, Akadri AA, Oluwole AA, Osinupebi OA, Andu BA, Akiseku AK, et al. Vaginal *Candida* infection in pregnancy and its implications for fetal well-being. Afr J Reprod Health. 2020. https://doi.org/10.29063/ajrh2020/v24i3.4.
82. Kiss H, Petricevic L, Husslein P. Prospective randomised controlled trial of an infection screening programme to reduce the rate of preterm delivery. BMJ. 2004. https://doi.org/10.1136/bmj.38169.519653.EB.
83. Roberts CL, Rickard K, Kotsiou G, Morris JM. Treatment of asymptomatic vaginal candidiasis in pregnancy to prevent preterm birth: an open-label pilot randomized controlled trial. BMC Pregnancy Childbirth. 2011. https://doi.org/10.1186/1471-2393-11-18.
84. Donders GG, Van Calsteren C, Bellen G, Reybrouck R, Van den Bosch T, Riphagen I, et al. Association between abnormal vaginal flora and cervical length as risk factors for preterm birth. Ultrasound Obstet Gynecol. 2010. https://doi.org/10.1002/uog.7568.
85. Poojari VG, Vasudeva A, Dawson S, Kaipa G, Eshwara V, Tellapragada C, et al. Diagnosis of lower genital tract infection in pregnancy: Routine mid-trimester high vaginal swab followed by gram staining, seems to be the best strategy. Curr Women's Health Rev. 2019. https://doi.org/10.2174/1573404815666190603113717.
86. McGregor JA, French JI, Jones W, Milligan K, McKinney PJ, Patterson E, et al. Bacterial vaginosis is associated with prematurity and vaginal fluid mucinase and sialidase: results of a controlled trial of topical clindamycin cream. Am J Obstet Gynecol. 1994;170:1048–59.
87. Beltrán Montoya J, Avila-Vergara MA, Vadillo-Ortega F, Hernández-Guerrero C, Peraza-Garay F, Olivares-Morales S. Cervicovaginal infection as a risk factor for premature labor. Ginecol Obstet Mex. 2002;70:203–9.
88. Roberts CL, Algert CS, Rickard KL, Morris JM. Treatment of vaginal candidiasis for the prevention of preterm birth: a systematic review and meta-analysis. Syst Rev. 2015. https://doi.org/10.1186/s13643-015-0018-2.
89. Nyirjesy P, Brookhart C, Lazenby G, Schwebke J, Sobel JD. Vulvovaginal Candidiasis: A Review of the Evidence for the 2021 Centers for Disease Control and Prevention of Sexually Transmitted Infections Treatment Guidelines. Clin Infect Dis. 2022. https://doi.org/10.1093/cid/ciab1057.
90. Cunnington M, Kortsalioudaki C, Heath P. Genitourinary pathogens and preterm birth. Curr Opin Infect Dis. 2013. https://doi.org/10.1097/QCO.0b013e328360dc31.
91. Goldenberg RL, Culhane JF. Infection as a cause of preterm birth. Clin Perinatol. 2003. https://doi.org/10.1016/s0095-5108(03)00110-6.
92. Payne MS, Bayatibojakhi S. Exploring preterm birth as a polymicrobial disease: an overview of the uterine microbiome. Front Immunol. 2014. https://doi.org/10.3389/fimmu.2014.00595.

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