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Systematic Review

Treatment for asymptomatic vaginal candidiasis to reduce preterm birth: a systematic review

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ABSTRACT

Vaginal candidiasis, a prevalent fungal infection in women caused by the overgrowth of *Candida* species, primarily *Candida albicans*, often triggers a hyperimmune response. While it is rarely life-threatening, it can be uncomfortable, posing risks to both pregnant mothers and their unborn children, thus affecting quality of life. This systematic review aimed to determine whether treating asymptomatic vaginal candidiasis during pregnancy reduces the incidence of preterm birth. Literature search was conducted across four electronic databases finds randomised controlled trials (RCTs) comparing the treatment of vaginal candidiasis (clotrimazole) with usual care (no-treatment). The search was updated in August 2024, with no language restrictions. Participants were pregnant women between 12 and 20 weeks of gestation. The primary outcome measured was the rate of preterm birth, while secondary outcomes included adverse pregnancy events such as premature rupture of membranes, perinatal death, low birth weight, and stillbirth. Data analysis utilized review manager (RevMan) software. Three RCTs involving 3,868 pregnant women were included, with 1,942 in the clotrimazole group and 1,926 in the usual care group. The primary outcome revealed spontaneous preterm birth rates of 2% in the treatment group compared to 6.3% in the usual care group. Meta-analysis indicated a statistically significant effect favouring treatment, with a pooled effect size of -0.05 (95% CI -0.09, -0.01). Treating asymptomatic candidiasis in early pregnancy appears to reduce preterm birth risk. However, results should be interpreted cautiously due to the limited number of studies. Further well-designed trials are needed to optimise treatment strategies and assess their impact on neonatal outcomes.

Keywords: Asymptomatic vaginal candidiasis, Preterm birth, Treatment, Pregnancy complications, Antifungal therapy, Maternal health, Review

INTRODUCTION

Vaginal candidiasis, commonly known as yeast infection, is a fungal infection affecting women's vagina and vulva worldwide. The infection is caused by an overgrowth of *Candida* species, primarily *Candida albicans*, a type of yeast naturally found in the vaginal area and gastrointestinal tract, with symptoms associated with a hyperimmune response.[1] An imbalance of the naturally occurring yeast, due to weak immunity, causes *Candida* to proliferate, causing an infection termed *candidiasis*. Although vaginal candidiasis seldom poses a life-threatening risk, it can nonetheless be extremely uncomfortable, posing a risk to both mother and unborn child and negatively impacting the quality of life.[2]

Recent studies have demonstrated a link between vaginal candidiasis and adverse pregnancy outcomes, including preterm birth. This has led to an increase in interest in the management of pregnancy-related candidiasis.[3] Evidence suggests that the prevalence of vaginal candidiasis varies significantly depending on the population of interest and the diagnostic standards applied.[4] In a recent systematic review and meta-analysis of 45 studies including more than 10,000 pregnant women, the overall prevalence of vaginal candidiasis was found to be 20.3%.[5] This

demonstrates the requirement for efficient prevention and treatment methods to lower the risk of adverse pregnancy outcomes linked to this illness.[6]

Antifungal drugs are among the most common treatments for vaginal candidiasis, with topical antifungal creams, namely topical azole creams, being the most recommended treatment.[7] Fluconazole and other azole antifungals, which have broad-spectrum activity against pathogenic yeast, are frequently used to treat vaginal candidiasis.[8] Recent research has prompted questions about fluconazole's safety during pregnancy due to concerns that it may be associated with stillbirth.[9] One study associated a higher incidence of spontaneous abortion with the use of fluconazole during the first trimester of pregnancy.[10] The results have led to a reconsideration of fluconazole's use during pregnancy, with current recommendations discouraging its use, particularly in the first trimester of pregnancy.[11]

Topical antifungal medications for vaginal candidiasis like clotrimazole (Lotrimin AF) and miconazole (Monistat 3) are usually prescribed for seven days to optimise the effectiveness and are alternatives to oral antifungals, as they are applied directly to the afflicted area with a lower risk of systemic side effects.[7,12] There is, however, little research on the safety and effectiveness of these medications during pregnancy. Clotrimazole was found to be successful in treating vaginal candidiasis during pregnancy.[13] Nevertheless, further investigation is required to ascertain the ideal treatment plan and assess the safety of medications in pregnancy.

On the other hand, antifungal vaginal suppositories, placed directly into the vagina, deliver localised treatment, can be prescribed as treatment in pregnancy.[3,7] These suppositories (miconazole, clotrimazole, and terconazole) are over-the-counter options and have proven safe and effective for foetuses and pregnant women.[3] The first line of antifungals include clotrimazole, miconazole and nystatin, and second-line antifungal agents are butenafine, ciclopirox, naftifine, and oxiconazole. Econazole should be avoided during the first trimester and used sparingly during the second and third trimesters. Ketoconazole and selenium sulphide are likely safe but should be limited to small periods.[14]

Numerous studies have explored the relationship between vaginal candidiasis and adverse pregnancy outcomes, particularly preterm birth.[15] Estimates suggest that 15 million preterm births occur globally each year, and vaginal candidiasis is considered a potential risk factor, highlighting its public health importance.[15,16] However, the literature presents contrasting evidence on this relationship. Some studies indicate that pregnant women with symptomatic candidiasis have a higher likelihood of preterm birth and lower birth weight compared to those without the condition, emphasising the importance of early diagnosis and treatment of vaginal candidiasis during pregnancy to reduce adverse outcomes.[17] Other studies showed that asymptomatic vaginal *Candida* colonisation is not linked to preterm birth or other adverse pregnancy outcomes.[18]

This systematic review and meta-analysis aimed to determine whether treating asymptomatic vaginal candidiasis during pregnancy reduces the risk of preterm birth based on evidence from randomised controlled trials.

METHODS

Study design

This systematic review was performed per the Cochrane handbook of systematic reviews of interventions guidelines and preferred reporting items for systematic review and meta-analysis statement.[19] Objective was to evaluate treatment of vulvovaginal candidiasis and its relation to adverse pregnancy outcomes.

Study eligibility

Any study that included pregnant women with both symptomatic and asymptomatic vaginal candidiasis, with laboratory confirmation and pregnancy outcomes reported. All included studies compared therapeutic treatments for vaginal candidiasis with placebo or no treatment. The primary outcome measured preterm birth (babies born alive before 37 weeks of gestation). The secondary outcomes included adverse pregnancy outcomes: premature rupture of membranes, defined as the rupture of gestational membranes before the onset of labour and before 37 weeks of gestation), perinatal death (death of a baby between 20 to 22 weeks of gestation, low birth weight (babies weighing less than 8 ounces at birth) and stillbirth (loss of a baby at or after 20 weeks of gestation).

Excluded studies were those with no comparison groups, prophylactic administration of treatment, no reported pregnancy outcomes, or immunocompromised women such as those with human immunodeficiency virus. Table 1 illustrates the eligibility criteria.

Table 1: Details of the inclusion and exclusion criteria using the participants, intervention, comparisons and outcomes (PICO) framework.[24]

Variables	Inclusion Criteria	Exclusion Criteria
Study design	Randomised control trials (RCTs) and Quasi-RCTs	Letters, commentaries, editorials and reviews. Cohort studies, case-control studies, animal studies

Continued.

Variables	Inclusion Criteria	Exclusion Criteria
Participants	Pregnant women with diagnosed vaginal candidiasis	Any immunocompromised pregnant women including HIV infected women presenting with preterm labour
Intervention	Any proven therapeutic agent (fluconazole, clotrimazole, miconazole and itraconazole)	No treatment
Comparisons	No treatment or placebo	No comparison group or treatment given prophylactically
Outcomes	Preterm birth and other adverse pregnancy outcomes including still birth, PROM, low birth weight and late miscarriage	No reported pregnancy outcomes

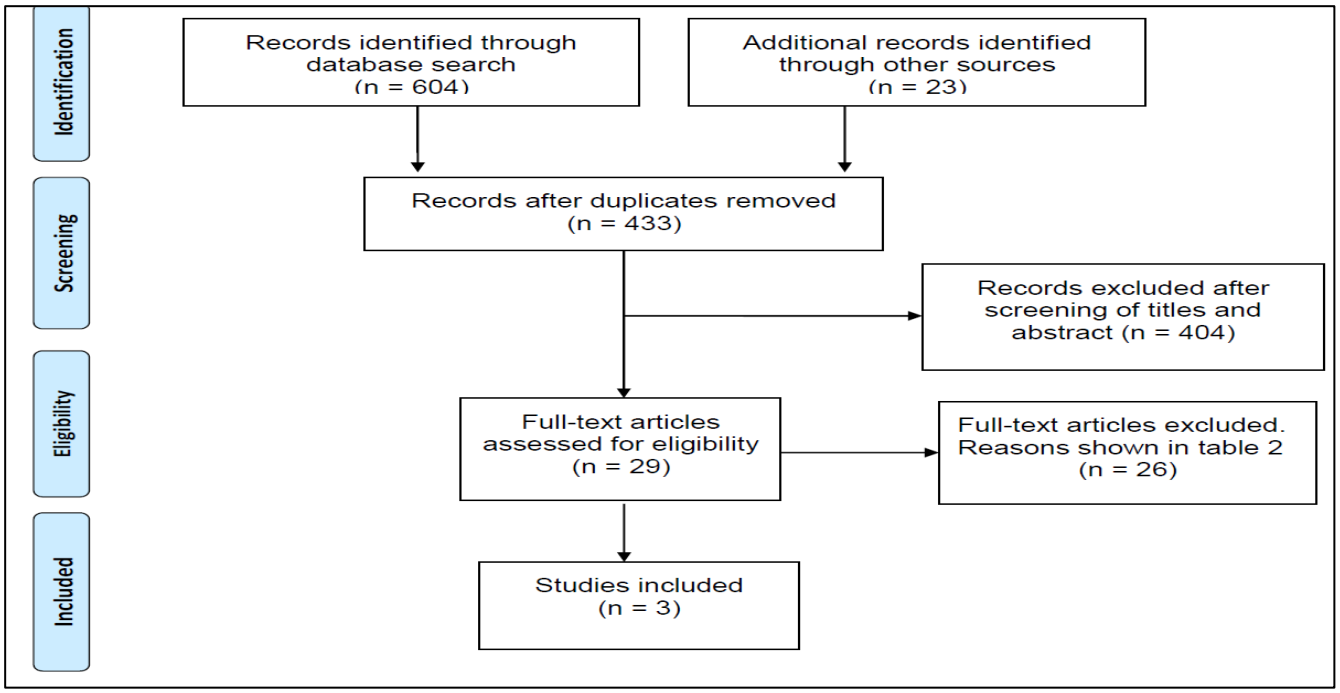

Figure 1: Outlines PRISMA flow diagram following Cochrane handbook for systematic reviews of interventions.[24]

Study identification

The literature search was conducted on publications from 1947 to 20 June 2023 and last updated on 17 August 2024 using EMBASE, MEDLINE, PubMed, and Google Scholar. Two independent researchers (HA and SA) performed the literature search. Search strategy included MeSH and text search terms, agreed upon by research team, combined with Boolean operators "and" and "or". Only randomised control trials and quasi-randomised control trials were included. Search criteria were limited to adult humans (over 18 years old). Citation lists of included studies were manually reviewed for additional relevant studies. A manual search of international conference abstract databases, including the congress of perinatal society of Australia and New Zealand, was performed. No restrictions on language or publication types were applied.

Study selection

Two researchers (HA and SA) independently screened and assessed all titles and abstracts retrieved for eligibility. Using Microsoft excel, duplicates were removed, and irrelevant articles were excluded. Two researchers (HA and SA) independently assessed the full text of identified studies for eligibility. Studies meeting the eligibility criteria were included following the Cochrane handbook for systematic reviews of interventions.

Data extraction

Data was extracted and inputted into a Microsoft excel spreadsheet, and non-English articles were translated completely. All corresponding authors of included studies with any missing data were contacted.

Data synthesis

Quantitative analysis was performed using RevMan™ (Web version 5.6.0, The Cochrane collaboration).[20]

A meta-analysis was performed for the primary outcome, with results expressed as mean difference and 95% confidence interval (CI) and secondary outcome results

expressed as risk ratio (RR) and 95% CI. A p<0.05 (95% CI) was considered statistically significant. Heterogeneity between studies was assessed by the I^2 score, using the random-effects meta-analysis model to account for data heterogeneity.[20]

Assessment of risk of bias and study quality

The risk of bias across studies was assessed following the Cochrane handbook for systematic reviews and analysed using RevMan™ software. The quality of the included studies was evaluated with GRADES software.

Identification of studies and study selection

Six hundred and twenty-seven records were identified by electronic database searching, manual searching, and reference list screening. After removing duplicates, four hundred and thirty-three records were selected for full-text review. Three randomised control trials met the inclusion criteria and were included in systematic review (Figure 1).[21-23]***Study characteristics***

Table 2 shows the characteristics of included studies. The three included studies were published between 2001 and 2017; two studies were conducted in Australia, and one in Austria.[21-23] All studies compared the treatment of asymptomatic vaginal candidiasis in pregnancy.[21-23] A total of 3,868 pregnant women were included: 1,942 women allocated to the treatment of vaginal candidiasis with clotrimazole group versus 1,926 women allocated to the no-treatment group. The aim of the three studies was to evaluate if the treatment of asymptomatic vaginal candidiasis in pregnancy reduces preterm birth.[21-23]

The three studies had approval from their respective governmental sector: the Northern Sydney central Coast health service ethics committee, the ethics committee of the university of Vienna medical school, Austria, The human research ethics committee and the New South Wales centre for health record linkage.[21-23]

The included studies varied between a multicentre, prospective, randomised study conducted at nine maternity hospitals in New South Wales (NSW), an open-label, blinded endpoint study in a single centre and a multicentre, prospective, randomised controlled trial at non-hospital based antenatal clinics.[21-23]

Pregnant women enrolled in all studies were between 12 to 20 weeks of gestation. Vaginal smears were taken and transferred to a microscopic slide where the different infections were identified; *Candida* was diagnosed through the presence of yeast cells and hyphae in one study.[23] While another used a screening strategy in pregnant women with vaginal infections, including bacterial vaginosis, candidiasis and trichomoniasis.[21] However, the final study used a swab culture which was self-collected by the asymptomatic pregnant women; at least one colony formed on agar plating was required to diagnose vaginal *Candida.*[22]

The patients with positive smears or cultures were randomised to either six days of clotrimazole vaginal pessaries[22 23] (or treatment with local clotrimazole cream 0.1 gm for six days).[21] Table supplement 1 presents the excluded studies along with the reasons for their exclusion.

Patient characteristics

In one of the included studies, screening for asymptomatic *Candida* was undertaken by contacting 779 women, of which 500 participated, with one lost in the initial swab stage.[23] Of the 499 women, 99 were randomised with asymptomatic and positive cultures of vaginal *Candida* (50 had clotrimazole treatment, and 49 had usual care). One woman was lost to follow-up in the usual care group due to travelling abroad, leaving 98 participants. The species that colonised the most 72 pregnant women was *Candida albicans*, followed by *Candida glabrata*, colonising 14 pregnant women.

In Kiss's study 4,429 pregnant women were approached for enrolment, of which 274 were excluded or lost to follow-up.[21] The study population included 4,155 pregnant women who completed the screening programme in a subgroup analysis by type of infection. In the intervention group (treatment with clotrimazole) for asymptomatic candidiasis, the number of participants was 270/2058 (13.1%) pregnant women in comparison to 259/2058 (12.4%) in the control group.

In the Vastsyan et al study 13,851 pregnant women were enrolled, of which 3,240 had positive cultures for *Candida* and were randomised (n=1622 received clotrimazole treatment versus n=1,618 received standard care).[22]

There was a range of 35 to 50% of asymptomatic *Candida*-positive pregnant, primiparous women in two of the studies.[21,23] The history of preterm delivery in Kiss et al was 2.1% in the intervention group and 2.2% in the control groups compared to 73% in the intervention group and 74% in the control groups in Roberts et al.[21,23]

Primary outcomes

The reported primary outcomes available for 2 studies showed that spontaneous preterm birth was 2/50 (2%) and 7/258 (3%) in treatment group compared to 3/49 (6.3%) and 20/238 (8%) in standard care group.[21,23] Meta-analysis showed statistically significant effect favouring treatment group compared to the standard care group, with a pooled effect size of -0.05 (95% CI -0.09, -0.01) (Figure 2). The quality of studies is very low (Supplement Table 2).

Table 2: The characteristics of included studies.

Authors names	Study period	Study design	Study location	Patient characteristics	Intervention	Comparison	Primary outcomes	Secondary outcomes	Microbiological testing	Timing of testing
Kiss et al[21]	January 2001-October 2002	Multi centre, prospective RCT	25 non-hospital-based obstetricians in the Vienna	Singleton pregnancy gestation of 15-19 weeks, without symptoms of vaginal infection or bleeding.	Candidiasis (spores and hyphae) was treated with local clotrimazole 0.1 gm for six days.	Usual care (No treatment)	The rate of spontaneous pre-term delivery (delivery at less than 37 weeks).	Rate of late miscarriage	Screened by Gram stain for asymptomatic vaginal infection	15-19 weeks
Roberts et al[23]	May 2008 - December 2009	A prospective, open-label, blinded-endpoint RCT	A single Australian tertiary obstetric hospital	Singleton pregnancy, gestation of 12-19 weeks, >18 years, no sensitivity to clotrimazole, no symptoms vaginal infection	6-days of clotrimazole vaginal pessaries (100 mg)	Usual care (No treatment)	The rate of spontaneous pre-term delivery (delivery at less than 37 weeks).	Pregnancy complications, elective preterm delivery, mode of delivery and infant outcomes	Culture positive for *Candida* using self-collection of a vaginal swab	12-19 weeks
Vatsayan et al [22]	December 2010-August 2017	A multicentre, prospective, open-label, blinded-endpoint RCT	Nine maternity hospitals in New South Wales, Australia	Singleton pregnancy, gestation of <20 weeks. No symptoms vaginal infection	6-days course of vaginal clotrimazole pessaries	Usual care (No treatment)	Spontaneous preterm birth (including birth following preterm prelabour rupture of membranes)	Rate of miscarriages, fetal growth restriction, perinatal mortality-includes births ≥200 weeks gestation that resulted in either stillbirth or neonatal death, admission to NICU, morbidity, Maternal length of stay for delivery admission.	Vaginal swab is self-collected, swab culture is positive for *Candida* species, at least one colony formed on agar plating	<20 weeks

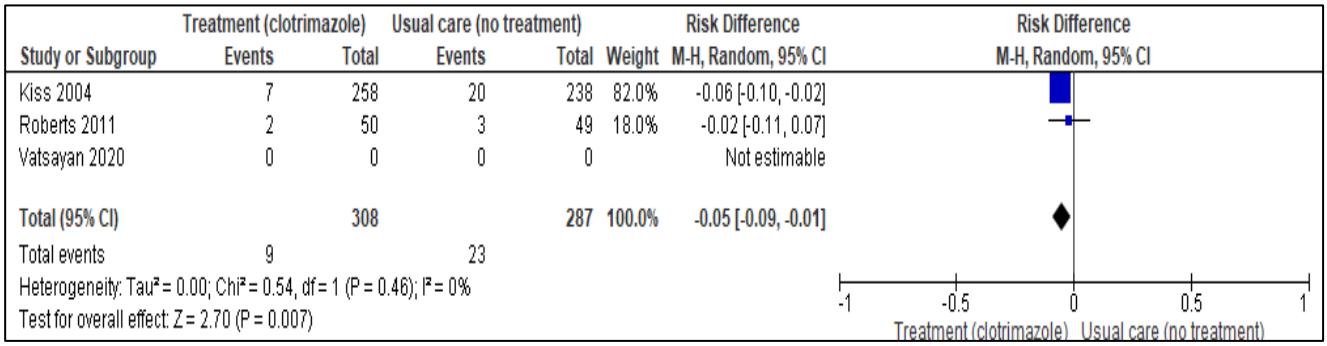

Figure 2: Primary outcomes: rate of preterm birth.

One study did not report any primary outcome results; however, the number of women in the treated group was 1594/1622 (98.3%), and for the standard care group, it was 1590/1618 (98.3%).[22] The authors were contacted for missing data, but there was no reply.

Secondary outcomes

Secondary outcomes reported in one study are pregnancy complications, including gestational diabetes, in the clotrimazole group 6/50 (12%) vs the usual care group 5/49 (10%), and antepartum haemorrhage/abruption in the clotrimazole group 2/50 (4%) vs the usual care group 4/49 (8%).[23] Women with labour induction in the clotrimazole group 16/50 (32%) and the usual care group 11/49 (22%).

Secondary outcomes reported in another study were the number of miscarriages in the intervention group 8/2058 (0.4%) vs the control group 15/2097 (0.7%).[21] The number of women with pre-eclampsia in the intervention group was 9/2058 (0.4%), vs the control group, 8/2097 (0.4%).[21]

The number of pregnant women with placental abnormalities (placenta praevia and abruption) in the intervention group was 4/2058 (0.2%) vs. the control group, 3/2097 (0.1%).[21]

Intrauterine deaths were reported in one study: the intervention group had 10/2058 (0.5%), and the control group had 9/2097 (0.4%), with no intrauterine deaths reported.[21]

Further secondary outcomes were reported in one study, including spontaneous pregnancy loss, foetal growth restriction, perinatal mortality, low birth weight, APGAR score, severe neonatal morbidity, and maternal length of stay; however, the results of these outcomes were requested from the author, and no reply received.[22]

Risk of bias

The risk of bias was assessed using a risk-of-bias graph (Figure 3 A and B). The three included randomised controlled trials had good sequence generation and allocation concealment, followed the 1:1 randomisation schedule, and utilised a computer-generated randomisation list stratified by recruiting hospitals.[21-23]

Reporting of blinding methods was different; women randomised to clotrimazole treatment were notified by phone or email, and central pharmacy or personnel dispensed the study medication, which was mailed to women in the treatment arm within 5 days of the swab collection.[22,23]

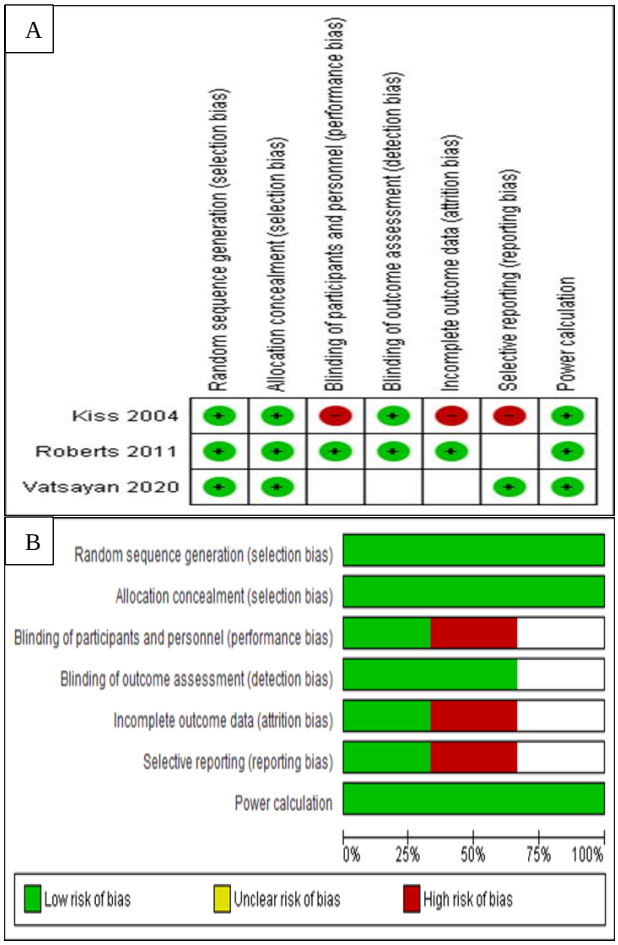

Figure 3 (A and B): Risk of bias graphs.

However, in another study, women in the intervention group received their smear results and were not blinded to

their treatment allocation.[21] In the three randomised control trials the clinicians remained blinded to the test results.[21-23]

The rates of incomplete outcome data in most randomised controlled trials were unclear; in one study, the data was for subgroup analysis with no specific data for the candidiasis group separately.[21] While another study did not report these results.[22] However, one study lost one participant to follow-up due to travelling abroad; the follow-up rate was 99%.[23]

In two studies, the sample size and power calculation were used to detect a reduction in spontaneous preterm births among women with asymptomatic candidiasis.[22.23] However, a further study had this outcome as a subgroup analysis, and the sample size was not calculated based on this outcome.[21] Thus, the assessed risk of bias was low to moderate.

DISCUSSION

This systematic review included the highest level of evidence to establish causal associations in clinical research by only including randomised controlled trials. The results of this review found that the treatment of asymptomatic candidiasis significantly reduces the risk of preterm birth. Preterm birth is a significant public health issue due to its association with adverse neonatal outcomes and long-term effects. Nonetheless, the results of this review should be interpreted with caution as one study assessed the treatment of asymptomatic candidiasis as a subgroup analysis, which was not powered by this assessment.[21] Additionally, the complete results of the third randomised controlled trial were unavailable despite contacting the authors.[22]

Interestingly, previous evidence suggests that the incidence of vaginal colonisation with *Candida* species in pregnant women is estimated to be between 10% and 50%.[24] Evidence from a subgroup analysis showed that women with recurrent *Candida* colonisation had a higher prevalence of spontaneous preterm birth and low birth weight than women without *Candida*.[25] The highest prevalence of *Candida albicans* was reported among pregnant women of the age group 26 to 35 years.[26] Whereas, *Candida glabrata*, resistant to clotrimazole, more frequently causes recurrent candidiasis.[26]

Our results can be compared to recent systematic reviews and meta-analyses, which found that asymptomatic vaginal *Candida* colonisation is not associated with preterm birth and other adverse pregnancy outcomes.[18,27] These systematic reviews included cohort studies, case-control, cross-sectional studies and randomised controlled trials that reported the incidence of adverse pregnancy outcomes among pregnant women that tested for vaginal *Candida* yeast, highlighting the complexity of the interplay between vaginal candidiasis and adverse pregnancy outcomes.

Several studies reported different colonisation rates for symptomatic candidiasis at 22-30 weeks of gestation, which varied from 13-37%, but did not describe rates for asymptomatic candidiasis.[28-30] Included studies reported a colonised rate of 14% and 19.5%, reflecting difference in range of gestational ages.[21,23] Nevertheless, it is important to mention other risk factors for preterm birth and candidiasis, such as smoking, African American ethnicity, low socioeconomic level and maternal health problems.[17]

Pregnancy is a risk factor for candidiasis, with early pregnancy posing the greatest risk for the development of inflammatory responses, increasing the risk of preterm birth. The included studies argue that early treatment of vaginal infections is necessary for effective prevention of infection-related preterm birth.[31] These results agree with a systematic review, including only two trials and recommending more power-calculated trials to ascertain the relationship between early treatment of asymptotic candidiasis and preterm birth.[17] Over the last decade, only one new randomised controlled trial addressed this issue; it was included in this review, furthering our understanding of the association between vaginal candidiasis and adverse pregnancy outcomes.[23]

Future research should aim to elucidate the optimal timing, duration and mode of treatment for asymptomatic vaginal candidiasis in pregnant women. To improve the robustness of studies, further randomised controlled trials with larger sample sizes are needed to clarify the causal relationships between treatment and the reduction of preterm birth rates.

The precise mechanisms underlying the association between vaginal candidiasis and preterm birth are yet to be fully apprehended.[32] Nonetheless, several potential mechanisms have been suggested, including vaginal microbiological dysbiosis, defined as an imbalance in the vaginal microbiota, as well as abnormal placental developments and inflammatory responses.[32] Vaginal candidiasis disrupts the normal vaginal microecology, leading to dysbiosis.[33] The presence of *Candida albicans* initiates the release of pro-inflammatory cytokines and chemokines, which results in a cascade of inflammatory responses in the vaginal mucosa, disrupting cervical integrity and triggering uterine contractions, all of which contribute to preterm labour.[34,35] A study by Dong et al concluded that exposure to *Candida albicans* in the vagina during the first trimester resulted in adverse pregnancy outcomes, including inhibition of the placental development, leading to reduced foetal nutritional and oxygen supplies and increasing the risk of preterm birth.[3]

Strengths and limitations

The quality of a systematic review depends on the quality of the randomised controlled trials and the completion of the data sets. Most of the included studies had good sequence generation and allocation concealment. A further strength of this review is the inclusion of all randomised controlled trials in this field, which is considered the gold

standard for evaluating the effectiveness of interventions. We included all types of publications as articles or abstracts, emphasising the clinically relevant results. Another strength of this systematic review is that we conducted a comprehensive search strategy, including four databases and manual searches within relevant conferences. We had no language restrictions that allowed for the inclusion of all publications spanning different countries. Furthermore, all authors of the included studies were contacted for any missing data.

We acknowledge several limitations. First, the lack of blinding in some trials can be a source of bias. Second, incomplete outcome data can also be a source of bias (attrition bias), as one of three studies had complete outcome data and/or reported the reasons for the loss of follow-up. Third, the limited number of included studies, small sample size, and 1 study reporting subgroup analysis increases the likelihood of type II error. Fourth, variability in patient demographics and diagnostic criteria for asymptomatic vaginal candidiasis may have contributed to the discrepancy in reported outcomes. This diversity underscores importance of standardised methodologies to facilitate meaningful comparisons across trials.

CONCLUSION

This systematic review found that the treatment of asymptomatic candidiasis in early pregnancy reduces spontaneous preterm birth rates. Although this systematic review included only high-quality evidence as randomised control trials, the results should be interpreted cautiously due to the small number of included studies. As the findings suggest a promising avenue for intervention, further well-designed and adequately powered studies are warranted to delineate optimal strategies and assess the effectiveness of treatment of asymptomatic candidiasis in early pregnancy on preterm birth and improve neonatal outcomes.

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Appendix

Table 1: Excluded studies and reason for exclusion.

Author	Reason for exclusion	Author	Reason for exclusion
Disha et al	Review	Honest et al	Review
Fu et al	Different intervention	Ahmad et al	Comparative study
Hellwig et al	Comparative study	Huerta et al	Different intervention
Ajiji et al	Review	Jindal et al	Letter
Goodfellow et al	Evidence summary	Goswami et al	Different outcomes
Djohan et al	Cross sectional	Czeizel et al	Case control
Zeng et al	Cross sectional	Patel et al	Prospective cohort
Bitew et al	Cross sectional	Eckert et al	Cross sectional
Sangare et al	Cross-sectional	Mc Gregor et al	Prospective
Maki et al	Review	Faro et al	Different outcomes
Rasti et al	Letter	Hay et al	Comparative study
Gupta et al	Not vaginal candidiasis	Sobel et al	Different population
Abdelmonem et al	Comparative study	Gerwen et al	Review

Table 2: Grades assessment of the quality of the included studies.

Certainty assessment							No. of patients		Effect			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Primary outcome**	**Placebo**	**Relative (95% CI)**	**Absolute (95% CI)**	**Certainty**	**Importance**
Reduction spontaneous preterm birth												
3	Randomised trials	Serious	Serious	Not serious	Serious	None	8/308 (2.6%)	23/287 (8.0%)	RR 0.32 (0.15 to 0.71)	54 fewer per 1,000 (from 68 fewer to 23 fewer)	⨁◯◯◯ very low	