Treating vaginal candidiasis for the prevention of preterm birth: protocol for a systematic review and meta-analysis

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Abstract

**Background:** Although the connection between ascending infection and preterm birth is undisputed, research focused on finding effective treatments has been disappointing. However evidence that eradication of Candida in pregnancy may reduce the risk of preterm birth is emerging. The objective of this systematic review and meta-analysis is to assess the effect of treating pregnant women with vulvovaginal candidiasis on preterm birth rates and other adverse birth outcomes.

**Methods and design:** A systematic search of Cochrane Central Register of Controlled Trials, Medline and Embase will be undertaken. Article titles and abstracts will be evaluated by two reviewers for potential relevance. Published randomised controlled trial in which pregnant women were treated for vulvovaginal candidias (in isolation or in combination with treatment of other vaginal infections) and where preterm birth is reported as an outcome will be reviewed for potential inclusion. Primary outcome of interest is preterm birth (<37 completed weeks of gestation) following spontaneous onset of labour or following preterm prelabour rupture of membranes. Secondary infant and maternal outcomes will be assessed. No language restrictions will be applied. Methodological quality and heterogeneity of studies will be assessed. Data extraction from identified articles will be undertaken by two independent reviewers using a uniform template. Meta-analyses will be performed to ascertain the risk of preterm birth and, where sufficient numbers, by symptomatic versus asymptomatic candidiasis, candida species, and type and timing of treatment.

**Discussion:** If it can be demonstrated that treatment of candidiasis reduces the risk of preterm birth, this will change the management of pregnancy worldwide.

**Keywords:** pregnancy, preterm birth, premature infant, candida, candidiasis, candidosis, yeasts
Background
Prevention of spontaneous preterm birth remains one of the most important challenges in modern maternity care. Whilst an association between ascending infection and preterm birth is undisputed, research focussed on finding effective preventive treatments has been disappointing. To date, most treatment trials (e.g. for bacterial vaginosis, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, trichomoniasis) have found little effect on the rate of preterm birth. In contrast, in a randomized controlled trial of early antenatal screening (15-19 weeks) and treatment for asymptomatic bacterial vaginosis, candidiasis and/or trichomoniasis in early pregnancy, Kiss and colleagues reported a 46% reduction in the spontaneous preterm birth rate. Post-hoc subgroup analyses of this trial suggest the benefit was primarily among those women who were treated for asymptomatic candidiasis.

The results of observational studies of the association between candidiasis and preterm birth are mixed. Two cohort studies conducted in high-risk obstetric populations in the United States in the 1980s found no significant association between preterm birth and moderate to heavy growth of *Candida albicans* or other *Candida* species at 22-30 weeks gestation. In contrast, retrospective analyses of the prevalence of preterm birth in population-based data from Hungary found that vaginal clotrimazole treatment of candidiasis during pregnancy was associated with a significantly higher mean gestational age, resulting in a 34-64% reduction in the prevalence of preterm birth. A similar reduction in preterm birth (49%) was observed in retrospective study of Latina women in New York who were treated with intravaginal azoles for *Candida* vaginitis.

Pregnant women have a two-fold increase in the prevalence of vaginal colonization by *Candida* species compared with non-pregnant women. This association is influenced by increased levels of circulating oestrogens and deposition of glycogen and other substrates in the vagina during pregnancy. Trials of treatment of candidiasis in pregnancy have been limited to women with symptomatic candidiasis (thrush) and the outcomes limited to successful eradication of *Candida* colonization OR amelioration of symptoms, not pregnancy outcomes.

Our aim was to undertake a systematic review and meta-analysis to assess the effect of treating pregnant women with vulvovaginal candidiasis on preterm birth rates and other adverse birth outcomes.

Methods

Criteria for considering studies for this review

Types of studies
All published RCTs in which pregnant women were treated for vulvovaginal candidiasis (in isolation or in combination with treatment of other vaginal infections) and where preterm birth is reported as an outcome. We will not include abstracts.

Types of participants
Studies which reported outcomes for pregnant women with vulvovaginal candidiasis (symptomatic or asymptomatic) will be included. The diagnosis of vulvovaginal candidiasis must be confirmed mycologically (ie a positive culture and/or microscopy for yeast). Studies involving only or primarily women who are HIV positive, immunocompromised, diabetic or not pregnant will be excluded.
Types of interventions
• Intervention: imidazoles or other proven therapeutic agent
• Comparisons: placebo or no intervention

Primary outcomes
Preterm birth (<37 completed weeks of gestation) following spontaneous onset of labour or following preterm prelabour rupture of membranes

Secondary outcomes
Infant
1. Any birth before 37 weeks
2. Medically indicated birth (by labour induction or prelabour Caesarean section) before <37 weeks
3. Birth before 32 weeks
4. Birthweight less than the tenth percentile for gestational age
5. Birthweight <2500 grams
6. Apgar score of less than seven at five minutes
7. Respiratory distress syndrome
8. Use of mechanical ventilation
9. Duration of mechanical ventilation
10. Intraventricular haemorrhage
11. Retinopathy of prematurity
12. Chronic lung disease
13. Necrotising enterocolitis
14. Perinatal mortality (stillbirth or neonatal death)
15. Admission to neonatal intensive care unit
16. Neonatal length of hospital stay
17. Breastfeeding

Maternal
1. Preterm prelabour rupture of the membranes
2. Spontaneous pregnancy loss <20 weeks gestation,
3. Mode of birth
4. Duration of maternal hospitalisation at the time of birth
5. Maternal views/satisfaction with the therapy
6. Maternal anxiety

Search methods for identification of studies
Electronic searches for the Cochrane Central Register of Controlled Trials, Medline and Embase. There will be no language restrictions. The database searches will be supplemented by hand-searching reference lists of relevant publications. No attempt will be made to identify unpublished studies. Search terms (all exploded) will include “candida” or “candidiasis” or “candidosis” or “yeasts” and “pregnancy” or “preterm/premature birth” or “preterm/premature infant”.

Data collection and analysis
We will assess all potential studies identified for inclusion as a result of the search strategy.

Selection of studies
Two review authors will independently assess for inclusion all the potential studies we identify as a result of the search strategy. Abstracts will not be included. We will resolve any disagreement through discussion or, if required, we will consult the third review author.

Data extraction and management
We will design a form and we will extract data from the clinical trials. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult the third review author. We will enter data into an Excel spreadsheet, and check for accuracy.

Assessment of risk of bias in included studies
Two review authors will independently assess risk of bias for each study using the criteria outlined below. We will resolve any disagreement by discussion or by involving the third review author.

1. Random sequence generation (checking for possible selection bias)
We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:
- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

2. Allocation concealment (checking for possible selection bias)
We will describe for each included study the method used to conceal allocation to interventions prior to assignment and will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We will assess the methods as:
- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

3.1. Blinding of participants and personnel (checking for possible performance bias)
We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for different outcomes or classes of outcomes. We will assess the methods as:
- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

3.2. Blinding of outcome assessment (checking for possible detection bias)
We will describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes. We will assess methods used to blind outcome assessment as low, high or unclear risk of bias.
4. Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake. We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; ’as treated’ analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

5. Other bias (checking for bias due to problems not covered by 1 to 4 above)

We will describe for each included study any important concerns we have about other possible sources of bias. We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

7. Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias. With reference to (1) to (5) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analysis (see Sensitivity analysis).

Measures of treatment effect

We will explore the impact of the level of bias through undertaking sensitivity analysis. For **dichotomous data**, we will present results as summary risk ratios (RRs) with 95% confidence intervals (CIs).

For **continuous data**, we will use the mean difference (MD) if outcomes are measured in the same way between trials. We will use the standardised mean difference (SMD) to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

**Multi-arm trials**

If we identify any multi-arm trials, we will include these if any pair-wise comparisons of the intervention groups are relevant to the review and meet our inclusion criteria. We will report all the intervention groups involved in the study in the ’Characteristics of included studies’ section, but we will include only those intervention groups relevant to the review in the analysis. We will address pair-wise comparisons in multi-arm trials in relevant metaanalyses if they are eligible for the analysis, and we will ensure that data from any individual are included only once when pooling data. If there are multiple intervention groups in a particular metaanalysis, we will combine all relevant experimental intervention groups of the study into
a single intervention group and combine all relevant control intervention groups into a single control group.\(^\text{12}\)

**Dealing with missing data**

For included studies, we will note levels of attrition. We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis. For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial will be the number randomised minus any participants whose outcomes are known to be missing.

**Assessment of heterogeneity**

We will assess statistical heterogeneity in each meta-analysis using the \(I^2\) and \(\chi^2\) statistics. We will regard heterogeneity as substantial if \(I^2\) is greater than 30% or there is a low P value (less than 0.10) in the \(\chi^2\) test for heterogeneity.

**Assessment of reporting biases**

If there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually, and use formal tests for funnel plot asymmetry. For continuous outcomes we will use the test proposed by Egger 1997, and for dichotomous outcomes we will use the test proposed by Harbord 2006.\(^\text{13,14}\) If asymmetry is detected in any of these tests or is suggested by a visual assessment, we will perform exploratory analysis to investigate it.

**Data synthesis**

We will carry out statistical analysis using the ‘metan’ command in STATA. We will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect: i.e. where trials are examining the same intervention, and the trials’ populations and methods are judged sufficiently similar. If there is clinical heterogeneity sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, we will use random-effects meta-analysis to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. The random-effects summary will be treated as the average range of possible treatment effects and we will discuss the clinical implications of treatment effects differing between trials. If the average treatment effect is not clinically meaningful we will not combine trials. If we use the random-effects model, the results will be presented as the average treatment effect with 95% confidence intervals, and the estimates of \(I^2\).

**Subgroup analysis and investigation of heterogeneity**

If we identify substantial heterogeneity, we will investigate it using subgroup analysis and sensitivity analysis. We will consider whether an overall summary is meaningful, and if it is, use random-effects analysis to produce it.

**Planned subgroup analyses** include:

- Symptomatic and asymptomatic candidiasis
- Commencing treatment (before 20 weeks’ gestation versus after 20 weeks’ gestation)
- Type of treatment (imidazoles versus nystatin or other therapies)
- **Candida** species (*Candida albicans* versus other *Candida* species). We will use only the primary outcome in subgroup analysis and will report the treatment effect (RR, 95% CI) by subgroup. We will also report the χ² statistic and p-value, for tests of the null hypothesis that there is no difference in effect between subgroups.

**Sensitivity analysis**

We will carry out sensitivity analysis to explore the effects of trial quality assessed by allocation concealment and other risk of bias components, by omitting studies rated as ’high risk of bias’ for these components. We will restrict this to the primary outcomes.

**References**