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

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Abstract

Background: Recognition that ascending infection leads to preterm birth has led to a number of studies that have evaluated the treatment of vaginal infections in pregnancy to reduce preterm birth rates. However, the role of candidiasis is relatively unexplored. Our aim was to undertake a systematic review and meta-analysis to assess whether treatment of pregnant women with vulvovaginal candidiasis reduces preterm birth rates and other adverse birth outcomes.

Methods: We undertook a systematic review and meta-analysis of randomised controlled trials (RCTs) in which pregnant women were treated for vulvovaginal candidias (compared to placebo or no treatment) and where preterm birth was reported as an outcome. Trials were identified by searching the Cochrane Central Register of Controlled Trials, Medline and Embase databases to January 2014. Trial eligibility and outcomes were pre-specified. Two reviewers independently assessed the studies against the agreed criteria and extracted relevant data using a standard data extraction form. Meta-analysis was used to calculate pooled rate ratios (RR) and 95% confidence intervals (CI) using a fixed-effects model.

Results: There were 2 eligible RCTs both among women with *asymptomatic* candidiasis, with a total of 685 women randomised. Both trials compared treatment with usual care (no screening for, or treatment of, asymptomatic candidiasis). Data from one trial involved a post-hoc analysis of a larger trial of treatment of asymptomatic infections in pregnancy (n=586) and the other was a pilot study (n=99). There was a significant reduction in spontaneous preterm births in treated compared with untreated women (meta-analysis RR=0.36, 95%CI 0.17-0.75). No other outcomes were assessed by both trials.

Conclusions: This systematic review found two trials comparing treatment of vaginal candidiasis in pregnancy for the outcome of preterm birth. Although the effect estimate provides support for the hypothesis that treatment of asymptomatic candidiasis may reduce

the risk of preterm birth, the result needs to be interpreted with caution as the primary driver for the pooled estimate comes from a post-hoc analysis. A prospective trial with sufficient power to answer the clinical question ‘does treatment of asymptomatic candidiasis in early pregnancy prevent preterm birth’ is warranted.

Systematic review registration: PROSPERO CRD42014009241

Keywords: pregnancy, preterm birth, premature infant, candida, candidiasis, yeasts, randomized controlled trial, met-analysis

Background

Preterm birth is a major pregnancy complication affecting 5-18% of births worldwide.[1, 2] Infants born preterm are at increased risk of death, significant neonatal complications, long-term adverse health outcomes and developmental impairment.[3-5]

Preterm birth (birth before 37 completed weeks' of gestation) results from either spontaneous onset of labour (including preterm prelabour rupture of the membranes) or a clinical decision that planned birth should occur because of pregnancy complications. The cause of spontaneous preterm birth is often unknown, but intrauterine infection is implicated in up to 40%.[4, 6, 7] The likely pathway to intrauterine infection is ascending genital tract infection.[6-9] Genital tract infection is more frequent among women with spontaneous preterm births at lower gestational ages.[7, 10] Importantly infection may occur before or early in pregnancy, may be asymptomatic and may remain undetected.[7, 11]

The role of infection in preterm birth is thought to be a chronic process, with early pregnancy a period of vulnerability to establishment of inflammatory responses that may be the trigger for preterm parturition.[6, 9, 11] Organisms detected in the uterus before membrane rupture are typically of low virulence, probably accounting for both the chronicity of intrauterine infections and the frequent absence of overt clinical signs of infection.[6, 8]

Pregnancy increases the frequency of vaginal *Candida* colonization.[12] This is thought to be the consequence of increased levels of circulating oestrogens and deposition of glycogen and other substrates in the vagina during pregnancy.[12] *Candida* colonisation may disrupt normal vaginal flora so that there is a decrease in lactobacilli and an increase in proinflammatory organisms.[9, 13] However few studies have assessed associations between

candidiasis and preterm birth. Studies utilising population-based data from Hungary found that vaginal clotrimazole treatment of candidiasis during pregnancy was associated with a 34-64% reduction in the prevalence of preterm birth.[14-16] In contrast, two cohort studies found no significant association between preterm birth and moderate to heavy growth of *Candida* species among women at 22-30 weeks gestation.[17, 18] Therefore, our aim was to undertake a systematic review and meta-analysis to assess whether treatment of pregnant women with vulvovaginal candidiasis reduces preterm birth rates and other adverse birth outcomes.

Methods

The study procedure and outcomes were pre-specified.[19] We identified relevant studies by searching the Cochrane Central Register of Controlled Trials, Medline and Embase from data base inception through 31 January 2014. There were no language restrictions. The database searches were supplemented by hand-searching reference lists of relevant publications. Search terms (all exploded) included ("candida" or "candidiasis" or "candidosis" or "yeasts") and ("pregnancy" or "preterm/premature birth") and "antifungal agents". Abstracts were not included and no attempt was made to identify unpublished studies.

Randomised controlled trials (RCT) in which pregnant women were treated for vulvovaginal candidiasis and where preterm birth was reported as an outcome were the prespecified eligibility criteria.[19] Only RCTs that compared treatment (imidazoles or other proven therapeutic agents) with placebo or no intervention could answer the research question. Quasi-randomised designs, such as alternate allocation or use of medical record numbers, were not eligible. Studies of pregnant women with vulvovaginal candidiasis (symptomatic or

asymptomatic) were eligible for inclusion. Mycologically confirmed diagnoses of vulvovaginal candidiasis (ie a positive culture and/or microscopy for yeast) were required.

The titles and abstracts of all potential studies identified for inclusion as a result of the search strategy were independently assessed for inclusion by two reviewers. Two reviewers also assessed the full papers of potentially eligible studies or where eligibility was unclear. Discrepancies were resolved through discussion.

Two review authors also independently assessed the risk of bias (as low, high or unclear) for each study using the following pre-specified criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and completeness of outcome data.[19]

Preterm birth (<37 completed weeks of gestation) following spontaneous onset of labour and/or preterm prelabour rupture of membranes was the primary outcome. Secondary infant outcomes included: any birth before 37 weeks, medically indicated birth (by labour induction or prelabour caesarean section) before <37 weeks, birth before 32 weeks, birthweight less than the tenth percentile for gestational age, birthweight <2500 grams, Apgar score of less than seven at five minutes, respiratory distress syndrome, use of mechanical ventilation, duration of mechanical ventilation, intraventricular haemorrhage, retinopathy of prematurity, chronic lung disease, necrotising enterocolitis, neonatal sepsis, perinatal mortality (stillbirth or neonatal death), admission to neonatal intensive care unit, neonatal length of hospital stay and breastfeeding. Secondary maternal outcomes included: preterm prelabour rupture of the membranes, spontaneous pregnancy loss <20 weeks gestation, mode of birth, duration of maternal hospitalisation at the time of birth, treatment side effects, maternal views/satisfaction with the therapy and maternal anxiety.

We also prespecified two subgroup analyses for the primary outcome: symptomatic and asymptomatic candidiasis, and commencing treatment before 20 weeks' gestation versus after 20 weeks' gestation.

Data were independently extracted from each paper by two reviewers onto a standard data extraction form. Statistical analyses were performed using the 'metan' command in STATA. (STATA statistical software version 11.0, STATA, College Station, USA). Where data were missing (incomplete follow up on all women), the results reported in the studies as the numerator and denominator were used. For each dichotomous outcome of interest within individual studies, relative risks (RR) and 95% confidence intervals (CIs) were calculated according to the intention to treat. For continuous variables, the weighted mean differences and 95% CIs were calculated (with a log transformation for mean length of stay). The assumption of homogeneity of treatment effect between studies would use Cochran's Q test statistic and the I^2 test, if more than two trials were identified. Overall estimates of effect utilised a fixed effect model (Mantel–Haenszel), unless the assumption of homogeneity was rejected ($P < 0.1$) when a random effects model would be used.

Results

A total of 1014 unique articles were identified (Figure 1). Of these 17 underwent full review as potentially eligible or where the eligibility was unclear from the title and abstract.[20-36] There were no potentially eligible studies that utilised quasi-randomised designs. Only 3 papers compared treatment versus placebo or no intervention for pregnancy women with candidiasis.[28, 34, 36] One of these trials compared treatment with placebo for women with confirmed (clinically and mycologically) vaginal candidiasis at 32-36 weeks gestation.[36] However, the only outcomes reported in this trial were maternal and infant *Candida*

colonisation at the time of birth, no birth outcomes. Furthermore, the gestation at enrolment was not consistent with preventing preterm birth. The remaining two studies included asymptomatic women with vaginal candidiasis and both compared treatment with clotrimazole to no treatment (Table 1).[28, 34] Preterm birth was the primary outcome for both studies.

The aim of the study by Kiss and colleagues was to assess whether general screening for, and treatment of, asymptomatic vaginal infections (bacterial vaginosis, candidiasis and/or trichomoniasis) was effective in reducing the rate of preterm birth and late miscarriage.[28] Women who were culture positive for any of the 3 conditions (N=4429) were randomised to treatment (appropriate to the organism: clindamycin, clotrimazole and/or metronidazole respectively) or to usual care (culture result not revealed and no treatment). The information on treatment of asymptomatic candidiasis from this trial was obtained post-hoc from the published paper. Overall, the preterm birth rate in this trial was reduced from 5.3% to 3.0% ($P<0.001$).

Drawing on the post-hoc findings by Kiss et al, Roberts and colleagues undertook a pilot study with the specific aim of assessing treatment of asymptomatic candidiasis to prevent preterm birth.[34] The study design was essentially the same although the eligibility criteria were limited to women with asymptomatic candidiasis.

Both studies utilised computer random number generation and central randomisation procedures. In the Kiss et al study, women who were randomised to treatment (and their obstetricians) were not blinded to the treatment allocation. However the untreated group (93% of women screened) included both women without infections, and those with

asymptomatic infections who were randomised to usual care. Clinicians and women were blinded to the colonisation-status within this group. Roberts et al used a similar method but women allocated to treatment were notified and treated by the study personnel. So although the treated women were not blinded, clinicians were blinded to treatment allocation unless it was revealed during the subsequent pregnancy management. Like the Kiss et al study, the untreated group (90% of participants) included women with and without asymptomatic candidiasis and the clinicians and women were blinded to this information. This partial blinding of participants and personnel was considered unlikely to affect results. Furthermore the assessment of outcomes from medical records was blinded. Because the analysis of candidiasis in the Kiss et al study was post-hoc, loss to follow-up by treatment group for women with candidiasis cannot be assessed. However overall 3.2% women were lost to follow-up and there were 3.0% post-randomisation exclusions (1.5% multiple pregnancies; 1.5% did not fulfil the inclusion criteria). The follow-up rate was 99% in the Roberts et al study with no post-randomisation exclusions.

For both studies, the risk of bias was considered low for all aspects assessed: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and completeness of outcome data.

The asymptomatic *Candida* colonisation rate was 14.1% (15-19 weeks gestation) in the Kiss et al study and 19.6% (12-19 weeks gestation) in the Roberts et al study. Kiss et al reports women were to be retested, and if necessary retreated, at 24 to 27 weeks. However overall only 22% of women in the entire treatment arm had a follow-up gram stain and of these 27% still had a vaginal infection present, including 78 (27%) with candidiasis, all of whom were

retreated. Roberts et al report a post-treatment colonisation rate of 48% on average 10 weeks after recruitment but women were not offered further treatment.

The only outcome available from both studies was spontaneous preterm birth. Among the 586 women with candidiasis in the Kiss study, treatment was associated with a reduction in spontaneous preterm births from 22 (7.5%) in the usual care group to 8 (2.7%) in the clotrimazole. Roberts et al reported comparable preterm birth rates (3 (6%) and 1 (2%) respectively, but with very small numbers. Meta-analysis showed an overall reduction in preterm birth (RR 0.36, 95% CI 0.17, 0.75) with similar point estimates from both studies but little contribution (and very wide confidence intervals) around the estimate from the pilot study by Roberts et al. (Figure 1).

Roberts et al also reported no differences between the treated and untreated groups of women for any preterm birth, pregnancy complications, mode of delivery and birth weight but interpretation is again limited by the small numbers.

Discussion

This systematic review found two trials comparing treatment of asymptomatic vaginal candidiasis in pregnancy with usual care (no screening and no treatment of asymptomatic vaginal candidiasis) for the outcome of preterm birth. The similarity of the individual trial effect estimates provides support for the hypothesis that treatment of asymptomatic candidiasis may reduce the risk of preterm birth in most maternal populations. However, although the two studies had similar methods, treatment regimens and findings among different populations, the result needs to be interpreted with caution as the primary driver for the pooled estimate is a post-hoc analysis of the Kiss trial. We believe the meta-analysis

result supports the need for a larger trial that specifically addresses the question of whether treatment of asymptomatic candidiasis early in pregnancy can reduce the risk of spontaneous preterm birth.

The two trials reported different colonisation rates of asymptomatic candidiasis (14.1% and 19.6%).[28, 34] This reflects different population baseline characteristics and slightly varying gestational age ranges for recruitment. Other studies report colonisation rates that range from 14% to 38% for symptomatic candidiasis at 22-30 weeks gestation but do not report asymptomatic rates.[17, 18, 37] Some of the population risk factors for candidiasis are also risk factors for preterm birth including African-American women, low socio-economic status, smoking, maternal medical conditions, and bacterial vaginosis.[15, 17, 28]

Both trials included in the meta-analysis used a similar design, described by Roberts et al as a Prospective, Randomised, Open-label, Blinded-Endpoint (PROBE) design. PROBE designs have been used in cardiovascular disease trials,[38-45] and the two trials in this review may be the first obstetric trials to use this design. Features include strict randomisation and allocation concealment procedures, and blinding of those assessing the trial endpoints.[40] The drug interventions are typically commercially available as indicated in the Roberts trial.[34] Consequently, as the treatment protocol adheres closely to routine clinical practice, the results from a PROBE design may be more generalisable to the pragmatic management of patients than double-blind, placebo-controlled trials.[40, 44] Roberts et al suggest two other potential disadvantages of a placebo-controlled trial for answering this preterm birth prevention question: 1) knowledge of vaginal colonisation with *Candida* may change participants' behaviour such that they seek active therapy (clotrimazole is available over the

counter); 2) a vaginally administered placebo may be biologically active as it would have to contain an alcohol preservative that could have an independent affect on vaginal flora.[34]

This review is limited by the lack of trials, and that one of the included trials is a small pilot study. Previous research has mostly focussed on the question of best treatment for eradicating *Candida* colonisation in pregnant women with symptomatic candidiasis. The availability of only two trials precludes the opportunity to explore issues like heterogeneity and any impact of reporting biases in sensitivity and subgroup analyses. Only one outcome (spontaneous preterm birth) was available from both studies, and future trials should consider other potential pregnancy outcomes and treatment side effects.[46] Although we identified 11 treatment trials of symptomatic candidiasis in pregnancy, all were published before 1985, only one compared treatment to placebo and none reported pregnancy outcomes, only the rate of *Candida* eradication.[24, 35, 36, 47-54] Furthermore, the seven studies that reported gestational age at recruitment all included women who were too advanced in pregnancy to have an impact on preterm birth.[24, 35, 36, 48, 50, 52, 54]

In contrast, the rationale of the two included trials is that early treatment of vaginal infections is necessary for effective prevention of infection-related preterm birth, as early pregnancy is the period of greatest risk for the establishment of inflammatory responses to low virulence organisms that increase the risk of preterm birth.[6-9] Treatment later in pregnancy may have limited effect in preventing preterm parturition if the inflammatory responses are not fully reversible.[4] Importantly, treatment does not necessarily eradicate *Candida* in all women nor prevent recolonisation. Post-treatment '*Candida* eradication rates' (assessed at 3-6 weeks) for *symptomatic* candidiasis in pregnancy range from 69% to 100% (5 trials, median 88%)[55] and for *asymptomatic* candidiasis was 73% (assessed at 4-5 weeks) in the Kiss

trial[28] and 52% (assessed at 10 weeks) in the Roberts trial.[34] However it is not clear whether post-treatment colonisation represents persistent colonisation or recolonisation.

It is somewhat surprising that only two trials could contribute to this review, given the interest in infection as a risk factor for preterm birth. Perhaps as *Candida* is considered a vaginal commensal organism,[13] the role of candidiasis in preterm birth has not been pursued with the same attention as bacterial vaginosis and other vaginal organisms.[11, 56-59]

Conclusion

The findings of this review support the hypothesis that screening for and treating asymptomatic candidiasis in early pregnancy may reduce spontaneous preterm birth rates. If a simple, inexpensive intervention is demonstrated to reduce spontaneous preterm birth, this would change current maternity care internationally. A significant reduction in preterm birth would not only reduce perinatal mortality and morbidity but have major resource implications, such as reduced need for neonatal intensive care and childhood hospitalisations. This systematic review suggests that a trial with sufficient power to answer the clinical question ‘does treatment of asymptomatic candidiasis in early pregnancy prevent preterm birth’ is warranted.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CLR, CSA and JMM conceived the study and drafted the study protocol. CLR performed the literature searches. CLR and KR assessed the literature and extracted data. CSA undertook statistical analyses and provided statistical expertise. All authors participated in the interpretation of the results, critically reviewed drafts of the manuscript, and read and approved the final manuscript.

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Table 1: Characteristics of randomised controlled trials assessing treatment of vaginal candidiasis to prevent preterm birth

Study	Study period & location	Study population	Study size (Candidiasis)	Intervention	Comparison	Available outcomes among women with candidiasis
Kiss et al	2001-2002 25 non-hospital based obstetricians Vienna, Austria	Pregnant women 15^0-19^6 weeks gestation No symptoms of vaginal infection, bleeding or contractions	586 294 randomised to treatment 292 randomised to usual care	Vaginal clotrimazole 0.1g for six days	Usual care (vaginal culture result not revealed, no treatment)	Spontaneous preterm birth
Roberts et al	2008-2009 Single tertiary obstetric hospital, Sydney, Australia	Pregnant women 12^0-19^6 weeks gestation No symptoms vaginal infection	99 50 randomised to treatment 49 randomised to usual care	Vaginal clotrimazole 0.1g for six days	Usual care (vaginal culture result not revealed, no treatment)	Spontaneous preterm birth; any preterm birth; pregnancy complications; mode of delivery, birthweight.

Figure legends

Figure 1: Summary of evidence search and selection

Figure 2: Meta-analysis: relative risk of spontaneous preterm birth among women with asymptomatic candidiasis: clotrimazole versus usual care (no screening and no treatment for asymptomatic candidiasis)