OBSTETRICS

Treatment of abnormal vaginal flora in early pregnancy with clindamycin for the prevention of spontaneous preterm birth: a systematic review and metaanalysis

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The purpose of this study was to determine whether the administration of clindamycin to women with abnormal vaginal flora at <22 weeks of gestation reduces the risk of preterm birth and late miscarriage. We conducted a systematic review and metaanalysis of randomized controlled trials of the early administration of clindamycin to women with abnormal vaginal flora at <22 weeks of gestation. Five trials that comprised 2346 women were included. Clindamycin that was administered at <22 weeks of gestation was associated with a significantly reduced risk of preterm birth at <37 weeks of gestation and late miscarriage. There were no overall differences in the risk of preterm birth at <33 weeks of gestation, low birthweight, very low birthweight, admission to neonatal intensive care unit, stillbirth, peripartum infection, and adverse effects. Clindamycin in early pregnancy in women with abnormal vaginal flora reduces the risk of spontaneous preterm birth at <37 weeks of gestation and late miscarriage. There is evidence to justify further randomized controlled trials of clindamycin for the prevention of preterm birth. However, a deeper understanding of the vaginal microbiome, mucosal immunity, and the biology of bacterial vaginosis will be needed to inform the design of such trials.

Key words: antibiotic, bacterial vaginosis, clindamycin, late miscarriage, preterm birth

Spontaneous preterm labor and delivery is a syndrome caused by multiple pathologic processes that activate the common pathway of parturition.[1,2] Mechanisms of disease involved in the "preterm labor syndrome" include infection/inflammation,[3-14] vascular disease,[15-17] uterine overdistension,[18-21] abnormal allograft reaction (eg, rejection),[22-24] an allergic-like phenomenon,[25-28] a progesterone deficiency,[29-32] and cervical disorders.[33-36] The first mechanism of disease responsible for preterm labor and delivery for which a causal link was well-established is infection.[3,8,11,13,37-39] Moreover, the mechanisms responsible for this process have been identified and involve pattern recognition receptors,[40-44] chemokines,[45-49] or inflammatory cytokines.[50-53]

A conventional view is that most cases of intrauterine infection responsible for preterm labor and delivery result from ascending infection;[3,8] therefore, multiple investigators have attempted to identify the patient at risk for preterm labor and delivery by assessing the microbiologic state of the lower genital tract.[54-61] Several cohort studies have attempted to establish a relationship between a change in the lower genital tract flora and the risk of preterm delivery.[62-72] Moreover, randomized clinical trials have been undertaken to test the effect of antibiotics in patients with bacterial vaginosis (BV),[73-87] *Trichomonas vaginalis*,[88] group B streptococci (GBS),[89,90] *Ureaplasma urealyticum*,[91,92] and Chlamydia trachomatis.[93]

The initial expectation that assessing the lower genital tract for the presence of certain microorganisms or changes in the microbial flora (ie, BV) followed by treatment has not met initial hopes. We believe that the disappointing results are not due to any question about the importance of infection in the etiology of preterm labor and delivery (with intact or ruptured membranes), but rather the limitations of the experimental design of the randomized clinical trials implemented to test the effects of antimicrobial agents.

A fundamental principle of randomized clinical trials is that all patients included in a particular trial must potentially benefit from the intervention under study (in this case, antibiotics). Therefore, if the goal of antibiotic administration is to reduce preterm labor and delivery, this can only be accomplished by preventing infection-induced preterm labor and delivery.[94,95] Consequently, randomized clinical trials designed to test hypotheses must identify patients at risk for infection, and such risks must be substantial in order for the trial to have a reasonable expectation of success.

Intraamniotic infection/inflammation can be readily identified by analysis of amniotic fluid.[96] However, it would be

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convenient to identify these patients by examining changes in the microbial flora of the lower genital tract, because this would be relatively easy and non-invasive. BV is characterized by a change in the microbial ecosystem of the vagina.[97,98] Its presence is associated with an increased risk for spontaneous preterm delivery[71,97-108] and intraamniotic infection.[109-112] Therefore, investigators reason that identification and treatment of BV would result in a decreased rate of preterm delivery. Many randomized clinical trials have been conducted to test this hypothesis, and the results have been largely negative;[73-81] although, some trials have yielded positive results.[82-87]

The contradictory results among trials of BV have been attributed to: (1) the definition of BV; (2) the gestational age at diagnosis and enrollment; (3) the choice of antimicrobial agent used, as well as the dose and route of administration; (4) whether antibiotic administration has been followed by a test of cure; (5) the primary outcome of the study (most have used delivery at <37 weeks rather than early preterm delivery, where most of the infection-related preterm births [PTBs] occur);[113] (6) gene-environment interactions related to the inflammatory response;[114-116] and (7) patient population, etc.

For antibiotics to be effective in reducing the rate of preterm delivery, several criteria must be met:[95] (1) antimicrobials must be effective against the target organism or the clinical condition under study (eg, BV); (2) antimicrobials should be used only in women who can benefit because they are at substantial risk for infection or an infection-related condition; and (3) antimicrobials must be used early enough[117] so that eradication of the microorganisms would be followed by resolution of any inflammatory response[66,118,119] and its unintended consequences (eg, damage of the chorioamniotic membranes, microbial invasion of the amniotic cavity, fetal microbial invasion, and fetal inflammation).[120-122]

The importance of the timing of antibiotic administration has recently become more apparent because there is evidence that exposure to either bacterial products (eg, endotoxin or lipopolysaccharide) or bacteria itself, which is not enough to signal the onset of preterm labor, may predispose to a subsequent viral infection, and this, in turn, leads to both preterm labor and fetal damage.[123]

Several systematic reviews and meta-analyses have been conducted to determine the effect of antimicrobial agents for the prevention of PTB in women with BV.[124-133] Such efforts need to be revisited to focus both on clindamycin and early treatment.[86,87,134]

The purpose of this study was to conduct a systematic review and metaanalysis to determine whether treatment of patients with BV with clindamycin before 22 weeks of gestation can reduce the rate of spontaneous PTB. The justification for the study is that several trials have suggested a beneficial effect of this antibiotic in reducing the rate of PTB in patients at risk when administered early during pregnancy. Most studies aimed at reducing the rate of PTB have used metronidazole, and such studies have yielded negative results.

Materials and methods

The systematic review was conducted using a prospectively prepared protocol and reported with the use of the Preferred Reporting Items for Systematic Reviews and Meta-analyses.[135]

Literature search

A computerized search was performed with PubMed, Embase, Cinahl, and Lilacs (all from inception of database to July 31, 2011), ISI Web of science (http://www.isiknowledge.com; 1960 to July 31, 2011), the Cochrane Central Register of Controlled Trials (http://www.mrw.interscience.wiley.com/cochrane/cochrane_clcentral_articles_fs.html; 1960 to July 31, 2011), and Research Registries of ongoing trials (www.clinicaltrials.gov, www.controlled-trials.com, www.centerwatch.com, www.actr.org.au, www.nrr.nhs.uk, and www.umin.ac.jp/ctr) with a combination of key and text words that are related to antibiotics, BV, prevention, or PTB. Proceedings of the Society for Maternal-Fetal Medicine and international meetings on PTB, reference lists of identified studies, textbooks, previously published systematic reviews, and review articles were also explored. No language restrictions were applied. All searches were carried out independently by 2 authors (R.F.L. and C.N.), and the results were merged. For studies that were reported in multiple publications, the data from the publication with the report of the primary outcomes and the largest sample size were used.

Study selection

We included randomized controlled trials that compared early treatment of women at <22 completed weeks of gestation with abnormal vaginal flora and asymptomatic BV that was diagnosed using objective criteria, with either oral clindamycin or clindamycin vaginal cream (CVC) vs placebo or no intervention. Only studies whose primary aim was to prevent PTB (delivery at <37 weeks of gestation) were included in the analysis. Quasirandomized studies were excluded. Other inclusion criteria consisted of pregnant women with a gestational age of <22 weeks of gestation at screening and commencement of treatment who were not in labor, had no vaginal bleeding, and did not report symptoms of lower genital tract infection. The diagnosis of BV was based on first trimester or early second trimester screening programs through the identification of abnormal lower genital tract flora and BV with the use of screening Gram stains scored by the Spiegel et al,[136] Nugent et al,[137] Hay et al,[71] or Ison and Hay[138] criteria. Studies with rescreening and retreatment protocols were included in the final analysis. All studies that were deemed appropriate were retrieved and reviewed independently by the 2 screening authors to determine inclusion. Disagreements were resolved through consensus discussions.

Outcome measures

The primary outcomes of interest were spontaneous PTB at <37 completed weeks of gestation and late miscarriage (LM; birth between 16 and 23 completed weeks of gestation). Spontaneous PTB <37 completed weeks of gestation was chosen because this primary outcome was used in most metaanalyses that evaluated preventative strategies for

PTB. Secondary outcomes included birthweight, low birthweight, very low birthweight, gestational age at delivery, early PTB (<30 completed weeks of gestation), admission to the neonatal intensive care unit (NICU), success of treatment according to degree of abnormal flora, persistent or recurrent BV, peripartum infections, and long-term follow-up evaluation.

Study quality assessment

We developed a quality assessment tool for studies of clindamycin effectiveness using the recommendations of Health Technology Assessment for the identification of systematic reviews.[139] The format for the quality assessment tool previously has been used in a systematic review of the efficacy of nifedipine as a tocolytic.[140,141] The quality of study methods was assessed with a tailored quality checklist that structured items in 2 broad categories: topic-specific or method-specific items. Furthermore, these items were divided into 3 general subcategories: selection bias, performance bias, and measurement bias. All quality determinations were scored as (1) adequate, (2) inadequate, or (3) not stated in the article. Consensus among the authors was reached through discussion and reevaluation.

Data abstraction

Two reviewers (R.F.L. and C.N.) scanned the abstracts and titles. Hard copies for all potentially relevant articles were acquired and evaluated independently by the 2 reviewers; authorship of the articles was not blinded. All outcome data were extracted independently, in duplicate form, by 2 reviewers. Information was extracted on study methods, study group demographics, intervention details (dose, type, placebo, no treatment), the use of rescreening and retreatment in the studies, and the outcomes (number of outcome events). Consensus among the authors was reached through discussion and reevaluation.

Statistical analysis

Data from each of the studies considered in this study were organized in 2 × 2 contingency tables that contained the number of patients who were classified according to pregnancy outcome and the clindamycin treatment (treated, not treated). We calculated the summary relative risk (RR) for dichotomous data and weighted mean difference for continuous data with associated 95% CIs. Two prespecified subgroup analyses were performed to compare clindamycin with placebo/no treatment according to the route of administration (vaginal vs oral) and re-treatment (yes vs no). In addition, we conducted sensitivity analyses to explore the robustness of the findings for the primary outcome according to a statistical model (fixed-effects vs random-effects), use of placebo (yes vs no), and study quality (high vs not high). However, the sensitivity analysis according to study quality was not performed because all trials that were included were considered as high quality.

Heterogeneity of the results among studies was tested with the quantity I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than chance.[142] A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥50% indicate a substantial level of heterogeneity.[142] We planned to pool data across studies using the fixed-effects models if substantial statistical heterogeneity was not present. We used random-effects models to pool data across studies if I^2 values were ≥50%.

We assessed publication and related biases visually by examining the symmetry of funnel plots and statistically by using the test of Egger et al.[143] The larger the deviation of the intercept of the regression line from zero, the greater the asymmetry and the more likely it was that the metaanalysis would yield biased estimates of effect. As suggested by Egger et al,[143] we considered a probability value of < .1 to indicate significant asymmetry.

We also calculated the number that was needed to treat (NNT) for an additional beneficial outcome with its 95% confidence intervals (CIs) for outcomes in which the treatment effect was significant at the 5% level (the 95% CI for the absolute risk difference did not include zero).[144] NNT was computed from the results of metaanalysis of RRs: NNT = 1/control group event rate × (1-RR).

In this review, NNT for an additional beneficial outcome is the number of women with abnormal vaginal flora who need to be treated with clindamycin at <22 weeks of gestation rather than with placebo or no treatment to prevent 1 case of spontaneous PTB at <37 weeks of gestation or 1 LM between 16 and 23 completed weeks of gestation. Analyses were performed with the Review Manager (RevMan; software version 5.0.23; The Nordic Cochrane Centre, Copenhagen, Denmark).

Results

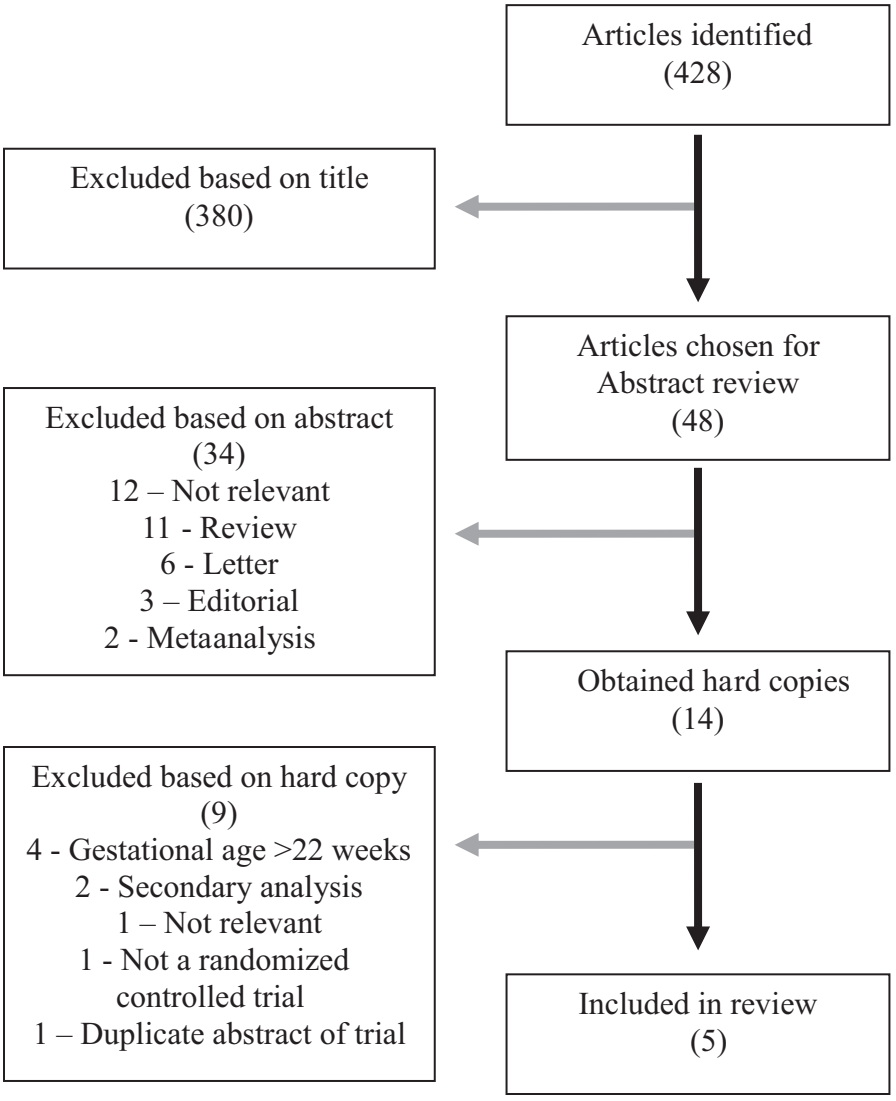
Literature identification

The flow of the electronic literature search is shown in Figure 1. Of the 428 potentially relevant citations that were identified, 414 were excluded based on the title or on review of the abstract. Based on abstract review, hard copies of 14 articles were obtained. After a detailed review, 5 studies fulfilled the inclusion criteria and are included in the analysis.[80,85-87,145] Of the 9 studies that were excluded, 2 were subgroup analyses of larger studies;[75,79] 1 article was not a randomized controlled trial;[84] 4 trials included patients who were screened and treated at >22 weeks of gestation;[74,77,81,105] 1 trial was a conference abstract[146] of 1 of the included studies,[85] and 1 article was an observational study.[102] We contacted the first authors of 3 trials[74,81,105] to request further information. None of these authors were able to provide data for the subgroup of women who were treated at <22 weeks of gestation, so these studies were excluded from the primary analysis. The 5 trials comprised a total of 2346 women.

Study quality assessment

The results of the evaluation of the studies' adherence to the criteria within the 2 domains of quality (method- and topic-specific items) are presented in Table 1. For all the method-specific items of quality, most of the studies were adequate. For 11 of the 16 topic-specific items of quality, most of the studies were considered adequate. In 14 of the 16 topic-spe-

FIGURE 1
Flowchart of literature search



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cific items of quality, none of the studies were considered inadequate, although a number of studies failed to state data on reference items of quality.

Characteristics of included studies

The characteristics of the included studies are shown in Table 2. Two studies were performed in the United Kingdom[85,87] and 1 each in Finland,[80] Austria,[145] and Sweden.[86] In 4 studies, CVC was used;[80,85,86,145] only 1 study used clindamycin orally.[87] No study used a combination of both oral and CVC. Three studies compared clindamycin with placebo,[80,85,87] and 2 studies compared clindamycin with no treatment.[86,145] In 4 studies, women with other genital-tract infections were treated but excluded from the study;[80,85-87] however, in one study, women with *Candidiasis* or *Trichomoniasis* were treated and included in the study.[145] Nevertheless, it was possible to extract the outcome data on those women with BV alone who were allocated to receive clindamycin or no treatment, so these were included in the analysis.[145] Four of the studies rescreened,[80,85,86,145] but at different time intervals; 3 studies re-treated if abnormal flora was still present after rescreening.[85,86,145] Ugwumadu et al[87] did not rescreen or re-treat. Kekki et al[80] rescreened 1 week after treatment and again between 30 and 36 weeks of gestation but did not re-treat. Lamont et al[85] rescreened 20-24 days after the first course of treatment and re-treated with a 7-day course of CVC or placebo according to the original randomization. Kiss et al[145] rescreened between 24 and 27 completed weeks of gestation and, if BV were still present, re-treated with a 7-day course of oral clindamycin, 300 mg twice daily. Larsson et al[86] rescreened the intervention group at 24 and 31 weeks of gestation (±2 weeks). If BV or intermediate flora were present, a repeat 7-day course of CVC was administered.

PTB at <37 weeks of gestation was the primary outcome of all 5 studies,[80,85-87,145] 2 of which[86,87] reported PTB as <33 completed weeks of gestation and LM. Two studies commented on mean or median birthweight and very low birthweight,[85,87] and 3 studies commented on low birthweight.[85-87] Three studies commented on gestational age or prolongation of gestation.[85-87] Three studies commented on admission to the NICU,[85-87] and 1 study carried out a cost-benefit analysis.[86] One of the studies provided data on the success of treatment according to the degree of abnormal flora,[87] and another study provided data on outcome after persistent or recurrent BV and peripartum infections.[80] Only one study provided data on long-term follow-up evaluation.[86]

Primary outcomes

Overall, 44 of 1183 women (3.7%) who received clindamycin delivered at <37 completed weeks of gestation, compared with 72 of 1163 (6.2%) in the control group (pooled RR, 0.60; 95% CI, 0.42–86; $P < .001$; Figure 2). Clindamycin was also associated with a significantly reduced risk of LM (2 studies; RR, 0.20; 95% CI, 0.05–0.76) and a significant increase in gestational age at birth (2 studies; weighted mean difference, 0.64 weeks; 95% CI, 0.28–1.01; Table 3). Forty women with abnormal vaginal flora who were treated at <22 weeks of gestation with clindamycin, rather than

TABLE 1
Assessment of quality items

Variable	Study				
	Kekki et al, 2001[80]	Lamont et al, 2003[85]	Ugwumadu et al, 2003[87]	Kiss et al, 2004[145]	Larsson et al, 2006[86]
Method specific items of quality					
Randomization	Unstated	Adequate	Adequate	Adequate	Adequate
Concealment	Inadequate	Adequate	Adequate	Adequate	Adequate
Blinding	Adequate	Adequate	Adequate	Inadequate	Inadequate
Attrition bias	Adequate	Adequate	Adequate	Adequate	Adequate
A priori sample size calculation	Adequate	Adequate	Adequate	Adequate	Adequate
TOPIC-SPECIFIC ITEMS OF QUALITY					
Selection bias					
Age	Adequate	Adequate	Adequate	Unstated	Adequate
Parity	Adequate	Adequate	Adequate	Adequate	Adequate
Socioeconomic status	Unstated	Unstated	Unstated	Unstated	Unstated
Race	Unstated	Adequate	Adequate	Adequate	Unstated
Smoking	Unstated	Adequate	Unstated	Unstated	Adequate
Substance abuse	Unstated	Adequate	Unstated	Unstated	Unstated
Previous preterm birth	Unstated	Adequate	Adequate	Adequate	Adequate
Previous late miscarriage	Unstated	Unstated	Adequate	Unstated	Unstated
Performance bias					
Frequency	Adequate	Adequate	Adequate	Unstated	Unstated
Dose	Adequate	Adequate	Adequate	Adequate	Unstated
Duration	Adequate	Adequate	Adequate	Adequate	Adequate
Route of administration	Adequate	Adequate	Adequate	Adequate	Adequate
Measurement bias	Adequate	Adequate	Adequate	Adequate	Adequate
Rescreening	Adequate	Adequate	Inadequate	Adequate	Adequate
Re-treating	Inadequate	Adequate	Inadequate	Adequate	Adequate
Long-term follow up	Unstated	Unstated	Unstated	Unstated	Adequate

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with placebo, were needed to prevent 1 case of spontaneous PTB (95% CI, 25–121). The corresponding NNT for LM is 66 (95% CI, 47–228).

Sensitivity analysis

Having obtained no additional data from the trials that included women who were screened and treated at >22 weeks of gestation,[74,81,105] we performed a sensitivity analysis by adding data for 100 women from the trial by Guaschino et al[81] (mean gestational age at enrollment, 19.2 weeks) and 302 women from the trial by Joesoef et al[74] who were enrolled at <21 weeks of gestation. Women from the study by McGregor et al[105] were not included in this sensitivity analysis because the mean gestational age at enrollment was 21.5 weeks. We assumed that frequencies of PTB at <37 weeks of gestation in clindamycin and placebo groups were similar to those of women of all gestational ages who were enrolled in each group. The significantly decreased risk of PTB at <37 weeks of gestation was demonstrated even in this sensitivity analysis (7 studies; 2748 women; RR, 0.72; 95% CI, 0.54–0.96; I^2, 40%).

The random-effects analysis of the primary outcome of spontaneous PTB at <37 weeks of gestation yielded an effect size similar in magnitude and direction to that obtained from the fixed-effects analysis, although it was not significant (RR, 0.64; 95% CI, 0.39–1.05; Table 4). The decrease in the risk of PTB at <37 weeks of gestation was nominally greater in trials that used placebo (RR, 0.55; 95% CI, 0.27–1.11) than in trials that did not use placebo (RR, 0.87; 95% CI, 0.45–1.68).

The significantly decreased risk of PTB at <37 weeks of gestation was demon-

TABLE 2
Characteristics of included studies

Study	Location	Inclusion/exclusion criteria	Diagnosis criteria	Gestational age at screening	Gestational age at treatment	Treatment, n	Control, n	Clindamycin	Rescreening	Re-treatment
Kekki et al, 2001[80]	Finland, 28 centers	Inclusion: women with singleton pregnancy; exclusion: history of previous preterm delivery	Spiegel criteria: Gram stain with semiquantitative scale	Range, 10–17 wk	12-19 wk	187	188 (Placebo)	7-day course of 2% clindamycin vaginal cream	Rescreened 1 wk after treatment and again at 30-36 wk of gestation	No re-treatment
Ugwumadu et al 2003[87]	UK, 2 centers	Inclusion: women with singleton pregnancy; exclusion: multiple pregnancy, previous cerclage or cone biopsy, uterine anomaly, maternal disease, symptomatic vaginosis	Nugent score: 4–6 for abnormal flora and 7-10 for bacterial vaginosis	Range, 12–16 wk for 20 months, then 12–22 wk; mean gestational age at screening, 16 wk	Immediately at the time of randomization: 76% treated by 17 wk	244	241 (Placebo)	5-day course of oral clindamycin 300 mg twice daily	No rescreening	No re-treatment
Lamont et al, 2003[85]	UK, 3 centers	Inclusion: asymptomatic women with single gestation; exclusion: women with sensitivity to clindamycin, and a history of colitis and those with *Trichomonas vaginalis* or *Chlamydia trachomatis*	Nugent score: grade II for abnormal flora or III for bacterial vaginosis	Range, 13–20 wk; mean gestational age at treatment, 16 wk	98% treated at <20 wk; 60% treated at <16 wk	208	201 (Placebo)	3-day course of 2% clindamycin vaginal cream	Rescreened 20-24 days after first course of treatment	Women with abnormal flora on rescreening given a 7-day course of clindamycin vaginal cream or placebo, according to the original randomization
Kiss et al, 2004[145]	Austria, 25 non-hospital–based obstetricians	Inclusion: asymptomatic women with single gestation	Nugent score: grade III	Range, 15–19 6/7 wk; mean gestational age at treatment, 17 wk	Within 7-10 days of diagnosis	149	143 (Not treated for bacterial vaginosis)	6-day course of 2% clindamycin vaginal cream	Rescreened between 24 and 27 completed weeks of gestation	A 7-day course of oral clindamycin 300 mg twice daily, if bacterial vaginosis is still present on rescreening
Larsson et al, 2006[86]	Sweden, southeast Health Care region with unspecified number of centers	Inclusion: asymptomatic women with single gestation without antibiotic treatment in early pregnancy; exclusion: early spontaneous or missed abortion, postinclusion cerclage, or treatment with metronidazole or clindamycin	Nugent score ≥6: Hay/Ison criteria	Range,10–14 wk	Treatment was usually within 1 week of diagnosis; 90% treated at <16 wk; mean gestational age at start of treatment, 14 wk	395	390 (Not treated for bacterial vaginosis)	7-day course of 2% clindamycin vaginal cream	Intervention group rescreened at 24-31 wk of gestation (± 2 wk)	A repeat 7-day course of 2% clindamycin vaginal cream, if bacterial vaginosis or intermediate flora present on rescreening

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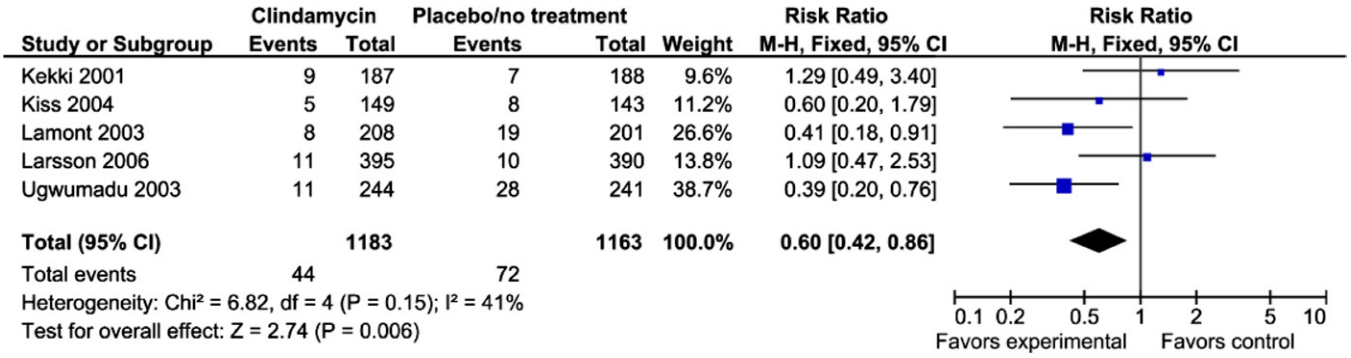
FIGURE 2
Preterm birth at <37 weeks of gestation (5 studies; fixed effects model)



df, degrees of freedom; *M-H*, Mantel-Haenszel test.

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strated in the subgroup of 1 trial (485 women) that used oral clindamycin (RR, 0.39; 95% CI, 0.20–0.76). Nevertheless, no statistically significant differences between groups were seen in the subgroup of trials that used vaginal clindamycin (4 trials; RR, 0.73; 95% CI, 0.47–1.14) or that used (3 trials; RR, 0.63; 95% CI, 0.38–1.04) or did not use (2 trials; RR, 0.67; 95% CI, 0.21–2.18) re-treatment, although this may be due to the weighting of the trial of Ugwumadu et al.[87]

Secondary outcomes

There was no overall difference in the risk of PTB at <33 weeks of gestation, low birthweight, very low birthweight, admission to NICU, stillbirth, peripartum infection, and adverse effects, although these outcomes were recorded in only 1 or 2 trials.

Larsson et al[86] demonstrated that the mean number of days spent in the NICU was 45 for those in the control group compared with 18 for those who received clindamycin ($P = .14$) and the cumulative days were 223 and 70, respectively. With an estimated cost of $1602 per day in the NICU, the additional cost for the control group was approximately $245,136.

Clindamycin appeared to be most effective the greater the degree of abnormal flora. In women with the highest Nugent score (10), those who received clindamycin had a 5.4% rate of PTB and LM, compared with 35.7% in those who received placebo.[87]

TABLE 3
Effect of clindamycin on spontaneous preterm birth and perinatal/maternal outcomes

Outcome	Number of trials	Number of events/total number or total number		Relative risk or mean difference (95% CI)	I^2, %
		Clindamycin, n/N (%)	Placebo, n/N (%)		
Spontaneous preterm birth <37 weeks of gestation	5[80,85-87,145]	44/1183 (3.7)	72/1163 (6.2)	0.60 (0.42–0.86)[a]	41
Late miscarriage	2[86,87]	2/639 (0.3)	12/631 (1.9)	0.20 (0.05–0.76)	0
Spontaneous preterm birth <37 weeks of gestation or late miscarriage	2[86,87]	24/639 (3.8)	50/631 (7.9)	0.53 (0.20–1.40)	73
Spontaneous preterm birth <33 weeks of gestation	2[86,87]	4/639 (0.6)	9/631 (1.4)	0.44 (0.14–1.41)	0
Gestational age at delivery, wks	2[85,87]	442	434	0.64 (0.28–1.01)	0
Low birthweight	2[85,87]	38/444 (8.6)	38/420 (9.0)	0.95 (0.62–1.45)	0
Very low birthweight	2[85,87]	13/444 (2.9)	8/420 (1.9)	1.54 (0.64–3.67)	37
Birthweight, g	1[80]	244	241	−12.0 (−128.6 to 104.2)	NA
Admission to neonatal intensive care unit	1[80]	18/238 (7.6)	23/228 (10.1)	0.75 (0.42–1.35)	NA
Stillbirth	2[85,87]	2/386 (0.5)	4/381 (1.0)	0.49 (0.09–2.67)	0
Peripartum infection	1[80]	21/187 (11.2)	33/188 (17.6)	0.64 (0.38–1.06)	NA
Adverse effects	2[80,87]	23/426 (5.4)	14/427 (3.3)	1.65 (0.86–3.16)	11

CI, confidence interval; *NA*, not applicable.

[a] Fixed effects model.

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TABLE 4
Sensitivity and subgroup analysis of the effect of clindamycin on spontaneous preterm birth at <37 weeks of gestation

Subgroup	Trials, n	Clindamycin, n/N (%)	Placebo, n/N (%)	Relative risk or mean difference (95% CI)	I^2, %
Statistical analysis					
Fixed effects	5[80,85-87,145]	44/1183 (3.7)	72/1163 (6.2)	0.60 (0.42–0.86)	41
Random effects	5[80,85-87,145]	44/1183 (3.7)	72/1163 (6.2)	0.64 (0.39–1.05)	41
Route of administration					
Vaginal	4[80,85,86,145]	33/939 (3.5)	44/922 (4.8)	0.73 (0.47–1.14)	31
Oral	1[87]	11/244 (4.5)	28/241 (11.6)	0.39 (0.20–0.76)	NA
Use of placebo					
Yes	3[80,85,87]	28/639 (4.4)	54/630 (8.6)	0.55 (0.27–1.11)	55
No	2[86,145]	16/544 (2.9)	18/533 (3.4)	0.87 (0.45–1.68)	0
Re-treatment					
Yes	3[85,86,145]	24/752 (3.2)	37/734 (5.0)	0.63 (0.38–1.04)	27
No	2[80,87]	20/431 (4.6)	35/429 (8.2)	0.67 (0.21–2.18)	75

CI, confidence interval; *NA*, not applicable.

Lamont. Clindamycin for the prevention of preterm birth. Am J Obstet Gynecol 2011.

In one study, BV persisted in 31% (115 of 375) and recurred in 7% (26 of 375) of the study population.[80] The overall rate of PTB and peripartum infection was almost 3 times higher in women in whom BV persisted or recurred during pregnancy (40 of 141; 28%) compared with those in whom BV was cured (12 of 121; 10%; odds ratio, 2.9; 95% CI, 1.3–5.2). Excluding women with intermediate Gram stain findings and including only those who attended both follow-up visits, the rate of PTB was 15% (4 of 26) in the subgroup in which BV was first cured but later recurred, compared with only 2% (2 of 121) in the subgroup in which BV did not recur (odds ratio, 9.3; 95% CI, 1.6–53.5). Kekki et al[80] rescreened 1 week after treatment and again between 30 and 36 weeks of gestation but did not re-treat. Nevertheless, 21 women (6%) were given additional CVC for what they described as "suspected symptomatic BV during the rest of the pregnancy," although this was not defined. Kiss et al[145] found that BV alone persisted in approximately 10% of women (44/447). After rescreening at 23 weeks, Larsson et al[86] found that BV had resolved in 70% of women; therefore, 30% of the women were re-treated. At 31 weeks of gestation, 10% of the women had experienced relapse and were again re-treated.

One study reported on long-term outcomes of preterm (but not term) infants.[86] Twenty-one preterm infants were followed up to 4 years. Among children in the control group, 1 child had retrolental fibroplasia that required strong eyeglasses, and 1 child was diagnosed with bronchopulmonary dysplasia in the neonatal period, but persisted at 4 years of age. No severe treatment-related adverse events were noted.[86] All funnel plots showed no asymmetry, either visually or in terms of statistical significance ($P > .10$ for all, by Egger test[143]).

Comment

Principal findings of the study

This systematic review and metaanalysis of randomized clinical trials shows that when clindamycin is administered to pregnant women with evidence of BV before 22 weeks of gestation: (1) the rate of PTB before 37 weeks of gestation is significantly lower than in the control group. The reduction in the risk of PTB before 37 weeks of gestation was only statistically significant for oral clindamycin but not for vaginal clindamycin; (2) the mean gestational age at delivery was significantly higher in women treated with clindamycin than those allocated to the control group; and (3) the rate of LM was lower (clindamycin vs control group) than in the control group.

Strengths of the study

This study used rigorous methods for performing a systematic review of randomized controlled trials, used a broad literature search, assessed the quality of the studies and is based on studies that have low-to-moderate statistical heterogeneity. Moreover, the robustness of the results for the primary outcome of spontaneous PTB before 37 weeks was examined after performing a sensitivity analysis by adding hypothetical data from 2 excluded studies.

Metronidazole vs clindamycin for the treatment of BV

Although both antibiotics have been recommended for the treatment of symptomatic BV,[147] their antimicrobial spectrum is not identical. Clindamycin and other macrolides have a broader antimicrobial activity against organisms involved in BV, including *Mobiluncus spp.*

and mycoplasmas.[98,148-151] Importantly, these antibiotics have antiinflammatory properties.[152-156] Patients with the highest Nugent score (who have the most serious disruption in the microbial ecosystem of the vagina, and in which *Mobiluncus spp.* is frequently found) had a significantly lower rate of PTB when treated with clindamycin, in comparison with those in the placebo group (5.4% vs 35.7%).[87] Such observation is in keeping with a subgroup analysis of another study,[85] in which women with a grade III Gram stain (Nugent score, 7-10) responded better to clindamycin than those who had intermediate flora (grade II Gram stain, Nugent score 4-6).[157]

The cure rate of BV after treatment with oral clindamycin has been reported to be as high as 90%,[158] while the cure/improvement rate for CVC is 70.8%.[134] The 70.8-90% appears better than the 40-77% cure rate after a 2-day course of metronidazole,[78,159] or the use of clindamycin cream late in pregnancy.[74,160] Two factors seem to influence response to therapy: (1) choice of antibiotic; and (2) gestational age at which it is administered.

Another issue which has not received full attention is whether there is a need to follow patients, confirm that treatment has been effective and the detection of recurrence and appropriate retreatment. Both antimicrobials can cure BV in a large number of women, but the condition can recur, and a second treatment 3-6 weeks after eradication is still able to cure or improve BV in 50% of the patients in whom the condition persisted or recurred (Lamont RF, Taylor-Robinson D, unpublished personal communication, 2009). However, there is no solid evidence that this can lead to a reduction in the rate of spontaneous PTB.

The route of administration of clindamycin appears to be important. Vaginal administration delivers the highest concentration of the antibiotic to the site in which the vaginal ecosystem has changed. If microorganisms have gained access to the endometrium/decidua, CVC may not be effective at this site, and oral therapy may be beneficial. It is noteworthy that, in this review, CVC administration was not associated with a statistically significant reduction in the rate of PTB.

A potential drawback of clindamycin treatment is the risk for *C. difficile*; however, this complication has also been reported with other antibiotics.[161] The vaginal preparation of clindamycin has limited systemic absorption (only 4%),[162] and therefore, appears to be safer than oral clindamycin.[134]

Insofar as metronidazole, in vitro studies have demonstrated that metronidazole and other nitroimidazoles are largely inactive against *Gardnerella vaginalis*, *Mycoplasma hominis*, *Ureaplasma urealyticum*,[163,164] and *Atopobium vaginae*.[165,166] Similarly, these compounds have little or no activity against streptococci or *Staphylococcus aureus*.[167] Yet, metronidazole administration to women with symptomatic BV is associated with a treatment success rate similar to clindamycin.[168] This has been attributed to the activity of the hydroxy metabolite of the drug in vivo, which is effective against the organisms involved in BV. Another potential explanation is that the administration of metronidazole changes the microbial flora by eradicating bacteria susceptible to it (eg, anaerobes and other organisms), and this favors cure of BV.[169]

The need to examine the potential value of clindamycin

The role of antibiotics in the prevention of PTB was considered to have promise nearly 2 decades ago. However, the results of several studies in which antibiotics were administered to patients whose genital tract was colonized with particular microorganisms (eg, GBS, *Ureaplasma urealyticum*, Chlamydia trachomatis, *Trichomonas vaginalis*) yielded largely negative results. We believe that the primary reason for this is that colonization with GBS,[170] *Ureaplasma urealyticum*,[171,172] or infection of the endocervix with Chlamydia trachomatis[173] in the absence of a systemic adaptive immune response is not a risk factor for preterm delivery. Therefore, treatment with antibiotics of patients colonized or infected with these organisms should not be expected to reduce the rate of preterm delivery, and that has been proven to be correct.[90-93] In the case of BV in which there is an increased risk for preterm delivery, such risk is modest and is now known to be affected by gene-environment interactions.[114-116] For example, patients with symptomatic BV who carry a polymorphism for the tumor necrosis factor-α receptor gene have a significantly increased risk of preterm delivery;[114-116,174] yet, randomized clinical trials have not taken into consideration the maternal genotype that may confer risk.

Results of clinical trials of antibiotics in patients with BV did not provide clear evidence of benefit,[73-81] and in some cases, the administration of metronidazole was associated with adverse pregnancy outcome (an excess rate of PTB).[88] Alternatively, clindamycin administration early in pregnancy has yielded more promising results.[87] Yet, when systematic reviews and metaanalyses have been conducted, all trials have either not been included or the studies have considered metronidazole and clindamycin as equivalent, and gestational age at the initiation of therapy has not always been taken into account. We conducted this metaanalysis to explore whether clindamycin treatment of BV in early pregnancy could be of value for the prevention of PTB.

Does clindamycin prevent PTB and late spontaneous miscarriage in patients with BV?

The findings of this study (Figure 2 and Table 3) suggest that clindamycin administration before 22 weeks reduces the rate of PTB at <37 weeks. However, sensitivity analysis performed according to the statistical model indicated that the reduction in PTB (<37 weeks) was only detected using a fixed effect model (relative risk [RR], 0.60; 95% CI, 0.42–0.86), but not when using a random effect model (RR, 0.64; 95% CI, 0.39–1.05). Although the point estimates of the relative risk are quite similar, the results are not significant in both analyses, and this suggests some instability in the results, probably attributed to heterogeneity of clinical trials (heterogeneity, $I^2 = 41$).

When the outcome was spontaneous PTB <33 weeks of gestation, the reduc-

tion in PTB was not statistically significant (0.6% [4/639] vs 1.4% [9/631]). This may reflect a limitation in sample size as treatment was associated with a 2 fold decrease in the rate of PTB. This particular endpoint is important because early PTB is expected to be associated with infection more frequently than late PTB, and most morbidity of preterm neonates is found among those born before 33 weeks of gestation.

Of major interest, is that treatment with clindamycin before 22 weeks was associated with a significant reduction in late spontaneous miscarriage (0.31% [2/639] vs 1.9% [12/631]). Nevertheless, these results are only based on 2 studies (Table 3).

Subgroup analysis indicated that the route of administration of clindamycin is important. Oral clindamycin was associated with a significant 61% reduction in the rate of PTB <37 weeks (4.5% [11/244] vs 11.6% [28/241]). However, this is only based on 1 study.[87] Vaginal clindamycin was associated with a nonsignificant 27% reduction in the rate of PTB at <37 weeks (3.5% [33/939] vs 4.8% [44/922]; RR, 0.73; 95% CI, 0.47–1.14; 4 trials).[80,85,86,145]

Finally, retreatment of BV was not found to have a significant effect on the rate of spontaneous PTB (<37 weeks). This was based on the results of 3 studies, which use retreatment and 2 in which retreatment was not employed (Table 4).

BV as a syndrome

BV has traditionally been considered a single condition in which the vaginal microbial ecosystem has changed, and its presence is associated with a greater risk of adverse pregnancy outcome, and specifically, PTB. However, a number of questions remain about the etiology, pathophysiology, diagnosis and treatment of BV. We have recently proposed that BV is a syndrome, and not a single condition.[175] This is based on observations which indicate that the profile of proinflammatory cytokines varies among women with BV diagnosed with a Gram stain. Some women have high concentrations of proinflammatory cytokines, and others do not.[118,119,176] The outcome of pregnancy in this subset of patients may vary. Such differences may account, in part, for the negative results of clinical trials. It is possible that the predictive value of the Nugent score for spontaneous PTB may be improved by studying the inflammatory response of patients with BV, or the genotype of the mother for genes involved in the inflammatory response or the microbiome of the vagina.[175]

Future studies

The results of this systematic review and metaanalysis suggest that some patients with BV may benefit from early treatment with clindamycin. It would seem that oral treatment is superior to vaginal treatment. Additional randomized clinical trials are required to confirm the findings of this metaanalysis. However, a much deeper knowledge of the biology, diagnosis, taxonomy, and response to therapy are required to design such trials. An important conclusion of this review is that some late spontaneous miscarriages may be prevented by treatment with clindamycin. This endpoint should be included in future studies. ■

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