The Effect of Second-Trimester Antibiotic Therapy on the Rate of Preterm Birth

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Abstract

Objective: As many as 50% of spontaneous preterm births are infection-related, with *Mycoplasma* species being the most common microbial isolates from the amniotic cavity. The goal of our study was to evaluate the effect of macrolides, a specific group of antibiotics known to be effective against *Mycoplasma* species, on the rate of preterm births.

Methods: We performed a systematic review of the literature and a meta-analysis. We searched PubMed, Medline (1965–March 2006), Embase, and the Cochrane Library, using the key words "pregnancy," "macrolides," "erythromycin," "azithromycin," and "clarithromycin." The research was limited to randomized controlled trials and to human females. Studies included for analysis were of women in the second trimester of pregnancy who received either macrolides or placebo (or no treatment) in order to prevent preterm delivery with at least 95% of patient follow-up. We excluded studies involving women with preterm premature rupture of membranes or regular uterine contractions. Meta-analysis of the retrieved data was performed using RevMan 4.2.8 (Cochrane Collaboration) with dichotomous analyses and delivery prior to 37 weeks' gestation as the primary outcome. The analysis was subsequently repeated using the same methodology for clindamycin and metronidazole administered during the second trimester.

Results: Of the 61 articles yielded by our search, three original papers, investigating a total of 1807 women, examined macrolide utilization and met our criteria. Women included in our analysis were all considered to be at higher risk for preterm delivery (vaginal fetal fibronectin positivity, urogenital *Mycoplasma* infection, prior preterm delivery, and/or pregestational maternal weight < 50 kg). Compared with placebo, macrolides were associated with a lower rate of preterm births (odds ratio [OR] 0.72; 95% confidence intervals [CI] 0.56–0.93), as was clindamycin (OR 0.68; 95% CI 0.49–0.95). On the other hand, metronidazole (OR 1.10; 95% CI 0.95–1.29) was not linked with significant changes in the rate of preterm births. A higher rate of preterm delivery was found when mid-trimester metronidazole was the only antibiotic administered (OR 1.31; 95% CI 1.08–1.58).

Conclusion: Macrolides and clindamycin, given during the second trimester of pregnancy, are associated with a lower rate of preterm delivery, whereas second-trimester metronidazole used alone is linked with a greater risk of preterm delivery in a high-risk population. Use of metronidazole, a common treatment for bacterial vaginosis and *Trichomonas vaginalis,* should be avoided during the second trimester of pregnancy in this population.

Key Words: Infectious disease, obstetrics, gynaecology, women's health, pregnancy, prematurity, preterm birth, antibiotics, macrolides, erythromycin, clindamycin, metronidazole

Competing Interests: None declared.

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Résumé

Objectif : Pas moins de 50 % des naissances prématurées spontanées sont associées à la présence d'une infection, l'espèce *Mycoplasma* étant l'isolat microbien issu de la cavité amniotique le plus courant. Notre étude avait pour but d'évaluer l'effet des macrolides (un groupe particulier d'antibiotiques dont on connaît l'efficacité contre l'espèce *Mycoplasma*) sur le taux de naissance prématurée.

Méthodes : Une analyse systématique de la littérature et une méta-analyse ont été effectuées. Nous avons mené des recherches dans PubMed, Medline (1965–mars 2006), Embase et la Cochrane Library, au moyen des mots clés suivants : *pregnancy*, *macrolides*, *erythromycin*, *azithromycin* et *clarithromycin*. Nous avons limité nos recherches aux essais comparatifs randomisés et aux femmes. Les études sélectionnées aux fins de l'analyse portaient sur des femmes en étant au deuxième trimestre de la grossesse et à qui l'on administrait des macrolides ou un placebo (ou aucun traitement) afin de prévenir l'accouchement prématuré; de plus, ces études se devaient d'avoir mené un suivi auprès d'au moins 95 % des patientes. Nous avons exclu les études qui portaient sur des femmes présentant une rupture prématurée préterme des membranes ou des contractions utérines régulières. La méta-analyse des données sélectionnées a été menée au moyen de RevMan 4.2.8 (Cochrane Collaboration) à l'aide d'analyses dichotomiques; l'accouchement avant la 37e semaine de gestation en constituait le critère d'évaluation principal. L'analyse a par la suite été répétée, en respectant la même méthodologie, pour la clindamycine et le métronidazole administrés au cours du deuxième trimestre.

Résultats : Des 61 articles identifiés par nos recherches, trois articles originaux (se penchant sur un total de 1 807 femmes) examinaient le recours aux macrolides et répondaient à nos critères. Les femmes admises aux fins de notre analyse étaient toutes considérées comme courant un risque accru d'accouchement prématuré (présence de fibronectine fœtale dans le vagin, infection urogénitale à *Mycoplasma*, antécédents d'accouchement prématuré et/ou poids maternel prégestationnel < 50 kg). Par comparaison avec un placebo, les macrolides étaient associés à un taux inférieur de naissance prématurée (rapport de cotes [RC], 0,72; intervalles de confiance [IC] à 95 %, 0,56–0,93), tout comme la clindamycine (RC, 0,68; IC à 95 %, 0,49–0,95). Par contre, le métronidazole (RC, 1,10; IC à 95 %, 0,95–1,29) n'a pas été associé à des modifications significatives du taux de naissance prématurée. Un taux supérieur d'accouchement prématuré a été constaté lorsque le métronidazole était le seul antibiotique administré au cours du deuxième trimestre (RC, 1,31; IC à 95 %, 1,08–1,58).

Conclusion : Les macrolides et la clindamycine, administrés au cours du deuxième trimestre de la grossesse, sont associés à un taux inférieur d'accouchement prématuré, tandis que le métronidazole administré seul au cours du deuxième trimestre est lié à un risque accru d'accouchement prématuré, au sein d'une population à risque élevé. Chez cette dernière, le recours au métronidazole, traitement couramment mis en œuvre contre la vaginose bactérienne et *Trichomonas vaginalis,* devrait être évité pendant le deuxième trimestre de la grossesse.

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INTRODUCTION

Preterm birth complicates between 7% and 11% of all pregnancies, is the leading cause of perinatal morbidity and mortality, and is responsible for high health care costs.[1] Over the last decade, intra-amniotic infection and inflammation has been demonstrated to be one of the major causes of preterm births. Microbial invasion of the amniotic cavity (MIAC) has been reported in approximately 10% to 21% of women with preterm labour and in approximately 30% of women with preterm premature rupture of membranes (PPROM); the earlier the gestational age at delivery, the higher the frequency of intrauterine infection.[2–6]

Interestingly, intra-amniotic infection and inflammation has been noted as early as the beginning of the second trimester in women who will subsequently develop preterm labour or PPROM and preterm delivery.[6–8] Recently, mid-trimester intra-amniotic *Ureaplasma urealyticum* was identified by polymerase chain reaction in 29 of 254 asymptomatic women (11%) who underwent transabdominal amniocentesis at 15 to 17 weeks' gestation.[7] Of these *U. urealyticum*-positive women, 24% delivered before 37 weeks compared with 0.4% of *U. urealyticum*-negative women. Therefore, it is suggested that preterm labour may be the consequence and the ultimate end-point of a process involving early infection with inflammation. This long pathogenic process could explain why antibiotics are ineffective in reducing preterm birth and neonatal morbidity in women with MIAC and preterm labour.[9] Moreover, since the detection and successful treatment of intrauterine infection have been reported in asymptomatic women with a short cervix during the second trimester, early diagnosis and therapy should be evaluated as strategies for the prevention of preterm birth in high-risk women.[10–12]

The most recent review from the Cochrane Database of Systematic Reviews on prophylactic antibiotic administration in pregnancy to prevent infectious morbidity and mortality concluded that antibiotic prophylaxis, given routinely to pregnant women during the second or third trimester, reduces the risk of prelabour rupture of membranes.[13] However, several antibiotic classes and administration routes were used in the studies reviewed, including oral erythromycin, metronidazole, cefetamet-pivoxil, parenteral ceftriaxone, and clindamycin vaginal cream, so the conclusion of this systematic review does not allow specific guidelines to be developed. Because *Ureaplasma* and *Mycoplasma* species have been the microorganisms most commonly involved in MIAC in the second trimester and related to preterm birth, we hypothesized that macrolide therapy during the second trimester would be the most appropriate way to prevent adverse obstetrical outcomes.[7,8] Moreover, because a recent randomized controlled trial (RCT) concluded that administration of metronidazole in the second trimester could increase the risk of preterm delivery, we decided to evaluate the effect of clindamycin and metronidazole, two other antibiotics that have been largely studied for the prevention of preterm births.[14]

METHODS

In the first part of the study, the authors independently searched the computerized PubMed, Medline, and Embase databases for papers published from 1965 to March 2006, using the key words "pregnancy," "macrolides," "erythromycin," "azithromycin," and "clarithromycin." The online Cochrane Database of Systematic Reviews, including the Cochrane Pregnancy and Childbirth Group's specialized register of controlled trials and the Cochrane Controlled Trials Register, was also searched. The authors independently reviewed all abstracts for eligibility and independently determined whether the paper was eligible for inclusion in the analysis. Disagreements were resolved by consensus or by discussion with a third party. Reference lists from relevant papers and full articles were read to find other important, pertinent publications. Publications were limited to RCTs and to the human female population. The inclusion criteria were studies of women randomized to receive either macrolides or equivalent placebo (or no treatment), during the second trimester of pregnancy (between 12 and 28 weeks' gestation) in order to prevent preterm delivery. Studies including women with PPROM, preterm labour, or treatment beginning at less than 12 weeks' or at more than 28 weeks' gestation were excluded. Trials that did not include at least 30 patients, or did not report the rate of preterm delivery (i.e., delivery prior to 37 weeks' gestation) in each group, and those with more than 5% of women lost to follow-up were also excluded. Case reports, descriptive studies, trials published in abstract form only, commentaries, and letters to the editor were also excluded.

The primary outcome evaluated was delivery prior to 37 weeks' gestation. The secondary outcome was mean gestational age at delivery. Sub-analyses were performed

Figure 1. Selection of randomized, controlled trials using macrolides

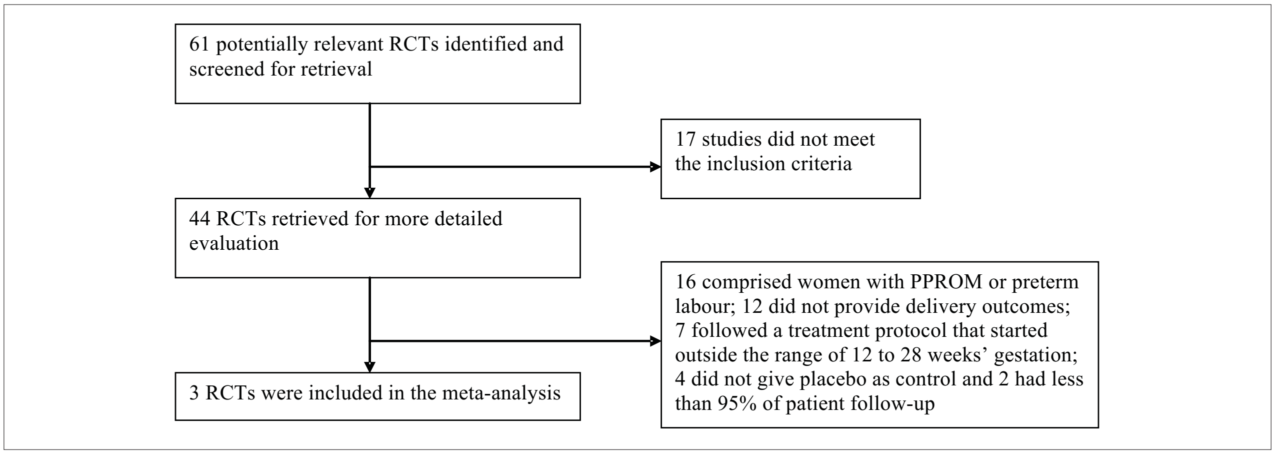


Table 1. Review of the studies using macrolides during the second trimester

Authors	n	Selection criteria	Treatment and dose	Primary outcome
Andrews et al. 2003	715	Cervico-vaginal fetal fibronectin positivity between 21 0/7 and 25 6/7 weeks' gestation	*Treatment group:* Metronidazole 250 mg three times daily by mouth and erythromycin 250 mg four times daily by mouth for 10 days *Controls:* Placebo	Incidence of spontaneous delivery < 37 weeks
Ye et al. 2001	488	Women with urogenital *Mycoplasma* infection at 28 weeks' gestation	*Treatment group:* Erythromycin 250 mg daily intravaginally for 6 weeks *Controls:* Placebo	Incidence of adverse perinatal outcomes (preterm labour, postpartum fever, puerperal infection and neonatal pneumonia)
Hauth et al. 1995	624	Healthy women between 22 and 24 weeks' gestation who had a previous spontaneous delivery or who weighed < 50 kg before pregnancy	*Treatment group:* Metronidazole 250 mg three times daily for 7days and erythromycin base 333 mg three times daily for 14 days *Controls:* Placebo	Incidence of preterm delivery < 37 weeks

according to three factors: (1) the route of antibiotic administration (intravaginal vs. oral), (2) the use of a single antibiotic versus a combination of antibiotics, and (3) the duration of treatment. Meta-analysis of the retrieved data was performed using RevMan 4.2.8 (Cochrane Library). In the second part of our study, a similar search and procedure were undertaken to analyze the effect of clindamycin and metronidazole administered during the second trimester.

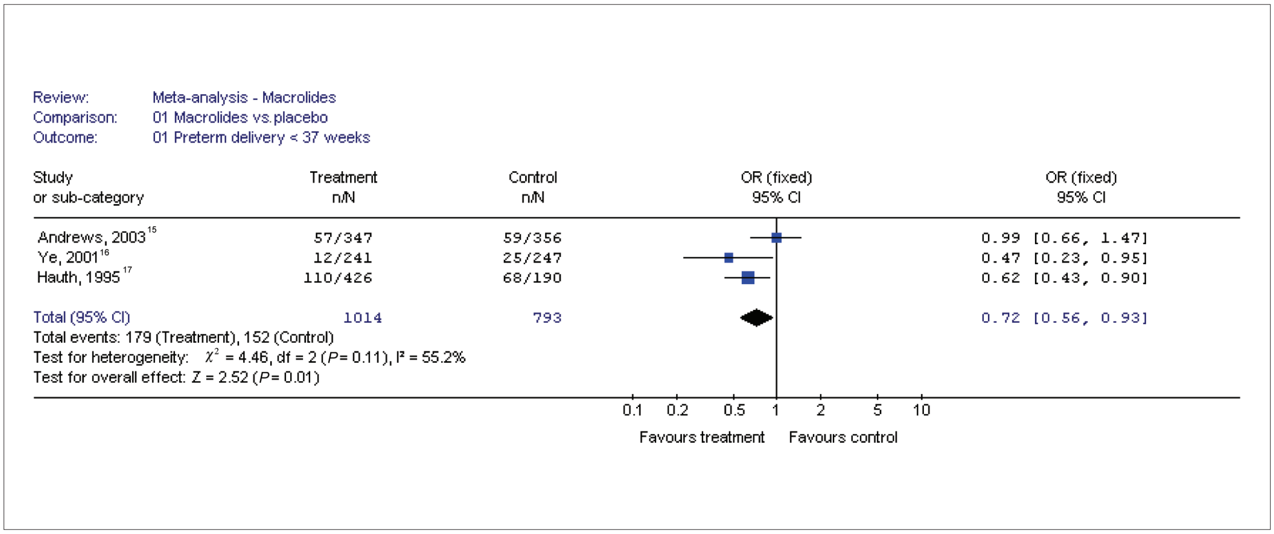
RESULTS

Macrolides

In the first part of our study, we analyzed the effect of macrolides used during the second trimester of pregnancy on the rate of preterm births. The search yielded 61 articles. Of these, three original papers met the inclusion criteria (Figure 1).[15–17] Details of each study can be found in Table 1. Erythromycin was the only macrolide given in these studies. In total, 1807 women were studied to detect the effect of prophylactic macrolide administration on pregnancy outcomes. All women were at higher risk for preterm delivery; the reasons for increased risk included having a prior preterm birth, a pregestational maternal weight of less than 50 kg, a urogenital *Mycoplasma* infection, or a positive vaginal fetal fibronectin test. From this total, 1014 women (56.1%) received antibiotics and 793 (43.9%) received placebo.

Compared with placebo, use of macrolides in mid-trimester was associated with a significantly lower rate of preterm births (odds ratio [OR] 0.72; 95% confidence intervals [CI] 0.56–0.93, P = 0.01) (Figure 2). The studies included women given oral and intravaginal antibiotic therapy. The sole trial employing intravaginal erythromycin showed significant improvement (OR 0.47; 95% CI 0.23–0.95, P =

Figure 2. Delivery before 37 weeks' gestation for each of the three included studies using macrolides with odds ratios (ORs) and 95% confidence intervals (CIs). The pooled ORs and 95% CIs are shown as totals. The size of the box at the point estimate of the ORs is proportional to the number of patients in the study and gives a visual representation of weighting of the study. Diamond represents point estimate of the pooled ORs from combining the primary studies. The length of the diamond is proportional to the 95% CIs. Bars represents 95%CIs



0.04),[16] whereas the combination of two trials with oral treatment did not demonstrate a statistically significant benefit (OR 0.77; 95% CI 0.59–1.01, *P* = 0.06).[15,17] The duration of treatment varied among the trials. The study that used a 10-day treatment did not reveal any difference,[15] whereas those including erythromycin treatment for more than 10 days were associated with significant benefits (OR 0.58; 95% CI 0.42–0.81, *P* = 0.001).[16,17] Only one of the three trials reported mean gestational age at delivery, and no difference was found between macrolide treatment and placebo (38.1 ± 3.0 vs. 38.1 ± 2.8 weeks, non-significant).[15] It is noteworthy that Andrews et al.,[15] who detected no benefit from second trimester antibiotic therapy, evaluated a combination of antibiotics including 10 days of metronidazole and 10 days of erythromycin, whereas Hauth et al. evaluated seven days of metronidazole and 14 days of erythromycin, with significant benefits, and Ye et al.[16] evaluated only erythromycin, with an even greater reduction in the rate of preterm births.

Four studies were excluded from analysis because treatment began between 26 and 30 weeks' gestation rather than between 12 and 28 weeks' gestation.[18–21] The 2600 patients included in these four excluded studies were treated with erythromycin or placebo for a period of between one and 10 weeks. If these patients treated late in pregnancy were included in the meta-analysis, erythromycin was no longer associated with a lower rate of preterm delivery (OR 0.85; 95% CI 0.71–1.01, *P* = 0.07), suggesting that benefits are associated with earlier treatment. Finally, two other studies were excluded because they were not published as full-length articles. The first study, by Hauth et al. (published abstract only),[22] reported that treatment with metronidazole (750 mg per day for 7 days) combined with azithromycin (1 g with a second dose given 4 days later) between 21 and 25 weeks' gestation did not improve the rate of preterm births compared with placebo (22.3% vs. 15.9%). The second study, reported by Odendaal et al.,[23] compared 244 women with bacterial vaginosis who were treated with metronidazole, metronidazole with erythromycin, or placebo (J. de Souza et al., unpublished data). The prevalence of preterm labour was 23.5%, 14.5%, and 17.1% respectively in the three groups (*P* values were not available).

Clindamycin

In the second part of our study, we analyzed the effect of second trimester clindamycin administration on the rate of preterm births. Five trials using clindamycin met the inclusion criteria out of a total of 62 that were retrieved from the literature (Table 2).[24–28] Second trimester clindamycin was significantly associated with a lower rate of preterm births (OR 0.68; 95% CI 0.49–0.95, *P* = 0.02) (Figure 3). Although studies investigating intravaginal treatment did not show any statistically significant benefits (OR 0.85; 95% CI 0.56–1.30), the only RCT that examined systemic treatment demonstrated a decrease in the rate of delivery prior to 37

Figure 3. Delivery before 37 weeks' gestation using clindamycin

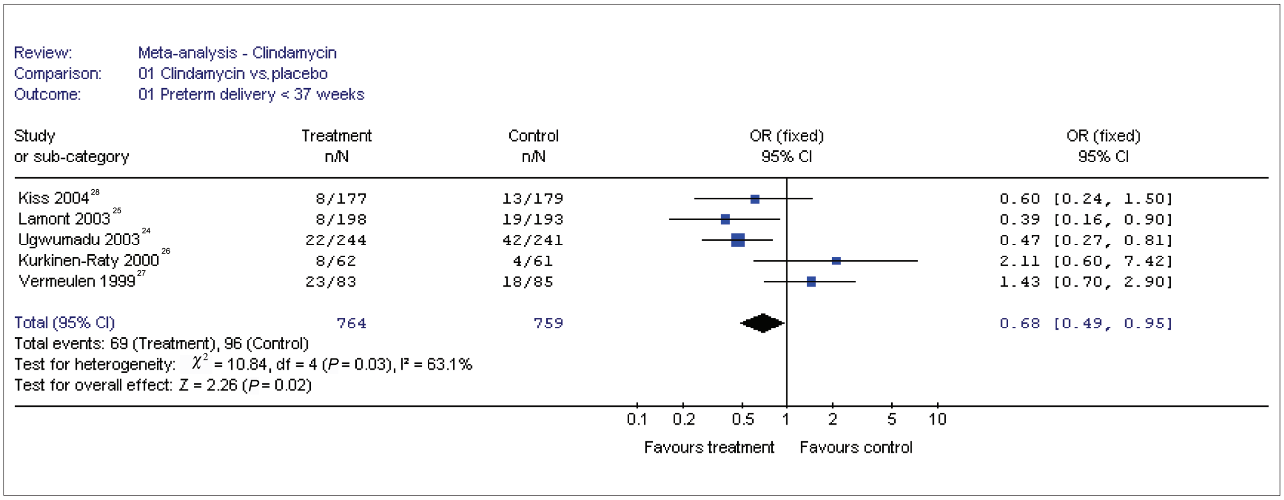


Table 2. Review of the studies using clindamycin during the second trimester

Authors	N	Selection criteria	Treatment and dose	Primary outcome
Kiss et al. 2004	356	Bacterial vaginosis between 15 0/7 and 19 6/7 weeks' gestation	*Treatment group:* Intravaginal clindamycin 2% daily for 6 days *Controls:* No treatment	Incidence of preterm delivery < 37 weeks
Lamont et al. 2003	409	Bacterial vaginosis between 13 and 20 weeks' gestation	*Treatment group:* Intravaginal clindamycin 2% 5 g per night for 3 nights *Controls:* Placebo	Incidence of preterm delivery < 37 weeks
Ugwumadu et al. 2003	494	Abnormal vaginal flora or bacterial vaginosis between 12 and 22 weeks' gestation	*Treatment group:* Clindamycin 300 mg twice daily for 5 days *Controls:* Placebo	Incidence of spontaneous preterm delivery (birth ≥ 24 but < 37 weeks) and late miscarriage (pregnancy loss > 13 but < 24 weeks)
Kurkinen-Raty et al. 2000	101	Bacterial vaginosis at 12 weeks' gestation	*Treatment group:* Intravaginal clindamycin 2% 5 g per night for 7 nights *Controls:* Placebo	Incidence of preterm delivery < 37 weeks
Vermeulen & Bruinse 1999	168	Women with previous spontaneous preterm delivery	*Treatment group:* Intravaginal clindamycin 2% daily for 7 days at 26 and 32 weeks *Controls:* Placebo	Incidence of preterm delivery < 37 weeks

weeks (OR 0.47; 95% CI 0.27–0.81, $P < 0.01$) and in the rate of late miscarriage (OR 0.19; 95% CI 0.04–0.88, $P = 0.03$).[24] There were some differences in the length of treatment (median 6 days, range 3–14 days) between the studies. Gestational age at delivery was analyzed in only one trial, showing a statistically significant difference (38.8 ± 3.6 vs. 38.0 ± 5.0, $P = 0.04$).[24]

Four studies, including a total of 1078 patients, were excluded because of a dropout rate greater than 5%, but less than 15% (8.6%, 9.2%, 10.7%, and 13.7%, respectively).[29–32] If these four studies had been included in the meta-analysis, clindamycin would have been shown to have no significant benefit over placebo on the rate of preterm births (OR 0.86; 95% CI 0.68–1.10, $P = 0.23$).

Metronidazole

Eight trials of second trimester metronidazole administration were included from a total of 62 retrieved from the literature (Table 3).[14,15,17,23,33–36] No significant change in the rate of delivery before 37 weeks was found in women treated with metronidazole (OR 1.10; 95% CI 0.95–1.29, $P = 0.21$) (Figure 4). Mean gestational age, reported in only

Table 3. Review of the studies using metronidazole during the second trimester

Authors	n	Selection criteria	Treatment and dose	Primary outcome
Shennan et al. 2006	100	Vaginal fetal fibronectin positivity between 23 0/7 and 24 6/7 weeks' gestation	*Treatment group:* Metronidazole 400 mg three times daily for 7 days *Controls:* Placebo	Incidence of preterm delivery < 30 weeks
Andrews et al. 2003	715	Cervico-vaginal fetal fibronectin positivity between 21 0/7 and 25 6/7 weeks' gestation	*Treatment group:* Metronidazole 250 mg three times daily by mouth and erythromycin 250 mg four times daily by mouth for 10 days *Controls:* Placebo	Incidence of spontaneous delivery < 37 weeks
Jeffcoat et al. 2003	366	Women with periodontitis between 21 and 25 weeks' gestation	*Treatment group:* Scaling and root planing + metronidazole 250 mg three times daily for 1 week *Controls:* Scaling and root planing + placebo capsule	Incidence of preterm delivery < 37 and < 35 weeks
Odendaal et al. 2002	277	Primigravidae or women with previous preterm labour or midtrimester miscarriage who had bacterial vaginosis between 15 and 26 weeks' gestation	*Treatment group:* Metronidazole 400 mg twice daily for 2 days *Controls:* Vitamin C 100 g bid for 2 days	*Primigravidae and Multigravidae:* Incidence of preterm delivery < 37, < 34 weeks and < 28 weeks
Klebanoff et al. 2001	615	Asymptomatic *Trichomonas vaginalis* between 16 and 23 6/7 weeks	*Treatment group:* Metronidazole 2 g by mouth twice, 48 hours apart, repeated at the follow-up visit between 24 and 29 6/7 weeks. *Controls:* Placebo (lactose)	Incidence of preterm delivery < 37 weeks
Carey et al. 2000	1953	Asymptomatic bacterial vaginosis between 16 and 23 6/7 weeks	*Treatment group:* Metronidazole 2 g by mouth twice, 48 hours apart, repeated at the follow-up visit between 24 and 29 6/7 weeks. *Controls:* Placebo (lactose)	Incidence of preterm delivery < 37 weeks
McDonald et al. 1997	879	Bacterial vaginosis between 16 and 26 weeks	*Treatment group:* Metronidazole 400 mg twice daily for 2 days at 24 weeks and 29 weeks if *G. vaginalis* was positive *Controls:* Placebo	Incidence of spontaneous preterm delivery < 37 weeks
Hauth et al. 1995	624	Healthy women between 22 and 24 weeks' gestation who had a previous spontaneous delivery or who weighed less than 50 kg before pregnancy	*Treatment group:* Metronidazole 250 mg three times daily for 7days + erythromycin base 333 mg three times daily for 14 days *Controls:* Placebo	Incidence of preterm delivery < 37 weeks

two trials (weighted mean difference -0.02; 95% CI -0.41–0.37, $P = 0.93$), was similar in the treatment and placebo groups.[15,23]

Considering the conclusion of Shennan et al.,[14] who suggested a higher rate of preterm births in women treated with metronidazole, we subsequently repeated the analysis of studies using second trimester metronidazole as the sole antibiotic administered (Figure 5). We found that metronidazole use was associated with a higher rate of preterm delivery (OR 1.31; 95% CI 1.08–1.58, $P = 0.005$).[14,23,33–36] The unpublished studies of J. de Souza et al. and J. Hauth et al., described earlier, are in agreement with this finding.[22,23]

DISCUSSION

Our meta-analysis evaluated the effects of three antibiotics, administered during the second trimester of pregnancy, on the rate of preterm delivery. Although mid-trimester administration of macrolides or clindamycin was associated with a reduction of delivery prior to 37 weeks' gestation, mid-trimester metronidazole was not linked with significant improvement. However, mid-trimester metronidazole, administered alone, was associated with a higher rate of preterm births.

Previous meta-analyses from the Cochrane Database of Systematic Reviews examined the relationship between antibiotic use during pregnancy and the rate of preterm births. Thinkhamrop et al.[13] analyzed RCTs that compared

Figure 4. Delivery before 37 weeks' gestation using metronidazole alone or in combination

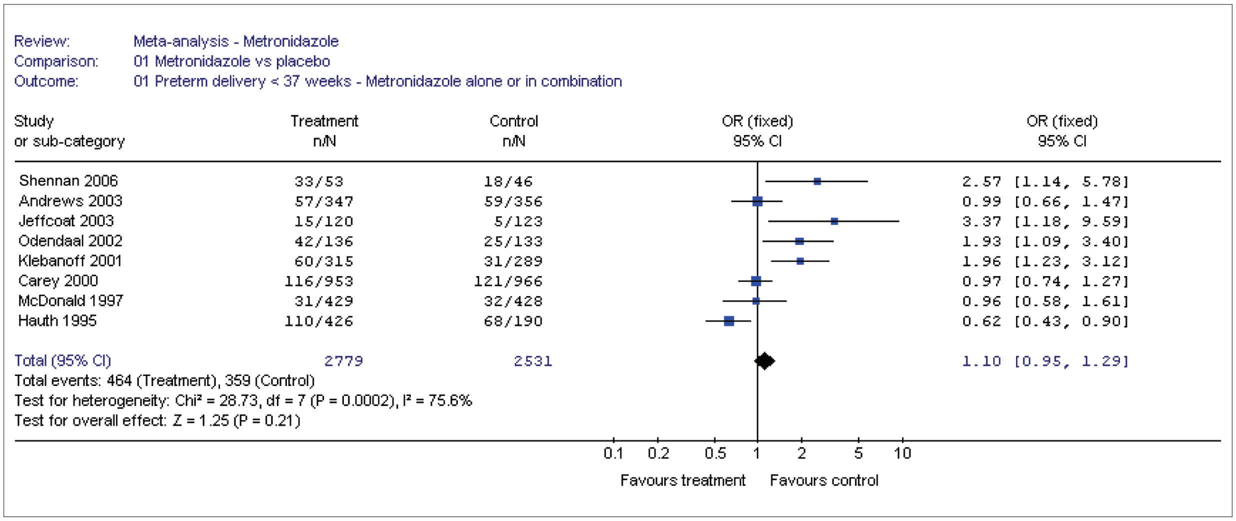
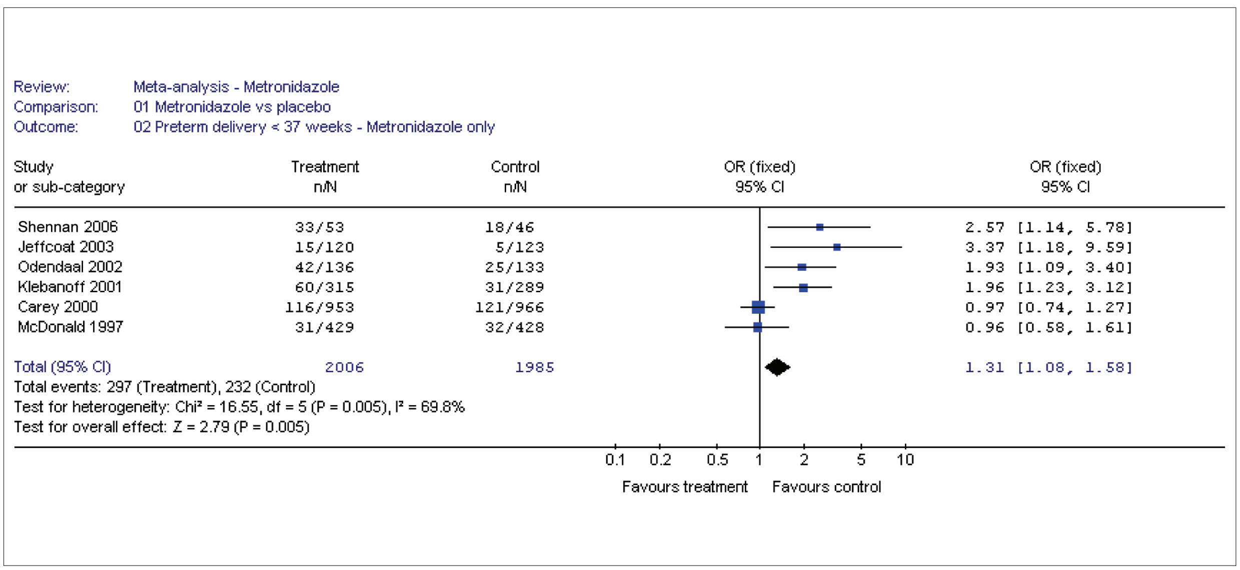


Figure 5. Delivery before 37 weeks' gestation using metronidazole alone



antibiotics with placebo or no treatment in the second trimester of pregnancy before labour and found a reduction in the risk of prelabour rupture of membranes with routine administration in pregnant women, but they did not find a significant decrease in the rate of preterm delivery. However, their analysis included trials using second-trimester and third-trimester antibiotics of all kinds, such as erythromycin, metronidazole, cefetamet-pivoxil, ceftriaxone, and clindamycin, but did not analyze them individually.

In a second meta-analysis, King and Flenady[37] examined RCTs that compared antibiotics with placebo or no treatment of women in preterm labour (between 20 and 36 weeks' gestation) with intact membranes. They did not observe any significant benefit of antibiotic use in this group of patients. It has been suggested that antibiotics administered during preterm labour may be ineffective because the infectious process and its inflammatory cascade have progressed too far by the time treatment is initiated. Moreover, in this situation, antibiotics may, by lysing bacteria, set free endotoxins and even stimulate labour.[38]

Raynes-Greenow et al.[39] examined RCTs that compared the effects of macrolide antibiotics with placebo or no treatment in women who had vaginal cultures positive for *Ureaplasma* in any trimester of pregnancy. Only one trial was included, and no statistically significant reduction was seen in the rate of low birth weight neonates with the use of erythromycin (relative risk 0.70; 95% CI 0.46–1.07). The rate of preterm births was not reported in the trial.[40]

Finally, Okun et al. conducted a meta-analysis of RCTs in which the effects of antibiotic therapy were compared with no antibiotic or placebo, in women with bacterial vaginosis or *Trichomonas vaginalis*.[41] However, they included studies with up to 20% loss to follow-up and women whose treatment was randomized in the third trimester. Although these authors concluded that there was no evidence to support antibiotic treatment for bacterial vaginosis or *Trichomonas vaginalis,* they did not evaluate specific macrolides during the second trimester. In fact, they found that the only trial that combined erythromycin with metronidazole for that purpose was associated with a lower rate of preterm births.[41]

The current meta-analysis has some limitations. First, few RCTs met our inclusion criteria, which restricts the power of this analysis and the strength of the conclusions. Second, the trials included were heterogeneous in terms of study population and treatments. Even if the patients were all at high risk for preterm delivery, the risk factors (previous preterm birth, urogenital *Mycoplasma* infection, cervico-vaginal fetal fibronectin positivity, bacterial vaginosis) were quite different between studies. Third, arguments for and against our choice of studies can be made, especially our exclusion of trials with a high rate of patients lost to follow-up, but these criteria were predetermined and seemed reasonable to both authors. Finally, these trials did not use the same dosage, route of administration or duration of treatment.

Despite the limitations, all efforts were made to establish strict criteria regarding the original aims of the study and to obtain all the available publications. The rationale for this study derived from the following observations.

(1) *Mycoplasma* species (including *Ureaplasma*) are the microorganisms most frequently found in the amniotic fluid of women in preterm labour; (2) *Mycoplasma* species have been reported in the mid-trimester amniotic fluid of women who subsequently deliver before term; (3) macrolides (and clindamycin to a lesser degree) are the most effective antibiotics against *Mycoplasma* species; and therefore (4) macrolides (and clindamycin) are likely to be the most effective antibiotics for preventing preterm births.

To our knowledge, ours is the first meta-analysis to evaluate this specific hypothesis. It is noteworthy that only three RCTs evaluated the effect of macrolides during the second trimester, with only one using erythromycin as the sole antibiotic and all treatment beginning after the 21st week of gestation. The two other trials combined metronidazole with erythromycin, raising the possibility that the full benefit of erythromycin was reduced by a negative effect of metronidazole. In fact, no RCT evaluated the effect of erythromycin or other macrolide given prior to 21 to 24 weeks' gestation on pregnancy outcomes, and it is therefore difficult to speculate on the effect of these agents on the rate of preterm births prior to 28 to 32 weeks' gestation. The only trial that evaluated systemic clindamycin given prior to 20 weeks' gestation (usually at 14 weeks' gestation) found a decrease in the rate of late miscarriage (delivery between 13 and 24 weeks) in women treated with antibiotics compared with those given placebo.[24] Clindamycin has activity against *Mycoplasma* species, but, since erythromycin and clindamycin have mainly bacteriostatic activity, it is likely that prolonged and systemic treatment will be necessary to obtain significant benefit.

On the other hand, the mechanism underlying the observed increase in preterm delivery among the metronidazole-treated women remains unclear. Metronidazole could theoretically have an adverse influence on the normal vaginal flora, allowing colonization by opportunistic organisms.[14] However, we believe that the major reason for the difference found between the effect of macrolides (or clindamycin) and metronidazole lies in their mechanism of action. Macrolides are classical bacteriostatic antibiotics, but metronidazole is a very active bactericidal antibiotic. Treatment of bacterial vaginosis or *Trichomonas vaginalis* with metronidazole could be associated with the release of endotoxins or lipopolysaccharide from bacteriolysis, causing a cervico-vaginal inflammatory response. Further research is needed to answer this specific question.

On the basis of these findings, it is reasonable to ask if mid-trimester treatment with macrolides or systemic clindamycin should be recommended for all women at high risk for preterm birth, and, if so, what dosage should be given. Our meta-analysis cannot answer these specific questions, because the inclusion criteria and the dosage were heterogeneous among the trials we included. However, in light of our results, it is likely that patients with high risk factors for preterm birth would benefit from macrolides or clindamycin prophylaxis during mid-trimester. Further studies should be conducted to determine (1) the optimal group of patients who will benefit from such prophylaxis and (2) the optimal course of treatment and route of administration. We believe that this meta-analysis is another step towards an efficient research program of early prevention of preterm births, and trials should be performed towards this end.

CONCLUSION

Treatment with macrolide antibiotics and clindamycin during the second trimester of pregnancy in women at high risk for preterm births is associated with a reduction in the rate of delivery prior to 37 weeks' gestation. However, uncertainty remains about how erythromycin and clindamycin should be administered because of the different dosing regimens, different drug preparations, and different timing of administration included in our analysis More research is clearly required to define the target population and the optimal treatment that should be administered. In light of our findings, use of metronidazole, an antibiotic that is commonly used in the treatment of bacterial vaginosis and *Trichomonas vaginalis,* should be avoided during the second trimester of pregnancy in women at higher risk for preterm birth.

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