Antibiotics for preventing preterm labour; An umbrella review

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Abstract

The risk of preterm labour in the presence of maternal infection is 30% to 50%. Antibiotics may induce a significant 12-20% reduction in neonatal infections following preterm rupture of the membranes and also may prolong pregnancy significantly. Aiming to evaluate the effectiveness of using antibiotics at any time during pregnancy to prevent preterm birth, we searched the Cochrane Library, MEDLINE, BIOSIS, EMBase, and CINAHL and we applied no language restrictions. We selected reviews and RCT's assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth.

45 randomised controlled trials published between 1966 and the present day were included, showing mild decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics and an average 34% less maternal infective morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages.

18 reviews published between 1993 and the present day were included, showing an average 30% decrease in the incidence of neonatal morbidity, 45% less maternal infective morbidity and an average 17% increase in the maternal adverse effects with the use of antibiotics compared to placebo or no treatment for all indications and all gestational ages.

In both trials and reviews, there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment.

The result of this umbrella review does not support the use of antibiotics during pregnancy except when there is a clear evidence of infection with extreme caution, regular follow ups and monitoring of the patient.

We do not support the use of metronidazole during pregnancy.

Background

Preterm labour is a clinical syndrome characterized by regular uterine contractions, cervical ripening with progressive changes, and/or membrane rupture occurring after the gestational age of viability (20 weeks, 500 grams weight) and before 37 completed weeks (259 days) of pregnancy [Cram 2002; Gonc 2002; Haram 2003; Taraa 2004]. Preterm birth is one of the most important problems in medicine today with an alarming frequency and economic impact [Hollier 2005]. With an incidence in most developed countries of 5-10% prematurity has major neonatal implications and is the single most common cause of perinatal death with an overall neonatal mortality rate of 41/1000 live births [Taraa 2004]. In spite of the advances in obstetric care, the rate of prematurity has not decreased over the past 40 years. In fact, most studies in the industrialized countries states that preterm labour and delivery has increased slightly. Neonatal mortality rates have declined in recent years largely because of improved neonatal intensive care and better access to these services [Goldenberg 2002; Haram 2003]. With appropriate medical care, neonatal survival dramatically improves as gestational age progress, with over 50% of neonates surviving at 25 weeks gestation, and over 90% surviving by 28-29 weeks gestation. However, these premature infants are often left with long term neurological impairment [Goldenberg 2002; Taraa 2004]. Short term morbidities associated with preterm delivery include respiratory distress syndrome, intraventricular haemorrhage, periventricular leuckomalacia, necrotizing enterocolitis, bronchopulmonary dysplasia, sepsis, and patent ductus arteriosus. Long term morbidities include cerebral palsy, mental retardation, and retinopathy of prematurity [Cram 2002; Goldenberg 2002]. The risk for these morbidities is directly related to the gestational age and birth weight. For example, cerebral palsy, defined as non progressive motor dysfunction with origin around the time of birth, complicates around 2/1000 of all live births. The relative risk for a preterm infant to develop cerebral palsy is 40 times that for term infants. Approximately 8-10% of surviving newborns weighing less than 1000 grams at birth will develop cerebral palsy. These infants also have substantial higher rates of mental retardation and visual disabilities, as well as neurobehavioral dysfunction and poor school performance [Goldenberg 2002]. Economically preterm birth account for 57% of the initial care of the USA neonates or nearly $6 billion annually [Hollier...
The lifetime costs per preterm birth have been estimated at £511,614 [Riggs 2004].

Preterm labour has 3 obstetrical antecedents:

1. Spontaneous preterm labour which accounts for 50% of cases.
2. Spontaneous membrane ruptures which almost always result in delivery within 1 week and account for 30% of cases.
3. Indicated preterm birth which is the decision of the obstetrician to induce labor or perform a caesarean section because of fetal or maternal indication, and this accounts for 20% of cases [Goldenberg 2002; Goldenberg 2005; Hollier 2005].

Infection has emerged during the last 20 years as an important and frequent mechanism of disease in preterm labour. Indeed, it is the only pathological process for which a firm causal link with prematurity has been established and for which a defined molecular pathophysiology is known. Moreover, fetal infection has been implicated in the genesis of fetal and neonatal injury leading to cerebral palsy and chronic lung disease [Kurki 1998; Lamont 2003a; Mertz 2001; Romero 2002].

The following evidence implicates infection as the cause of almost 40-50% of preterm birth:

1. Histological chorioamnionitis is consistently increased in cases of preterm birth.
2. Clinical infection is increased in the infant and the mother after preterm birth.
3. Several genital tract isolates are associated with preterm birth.
4. 10-15% of amniotic fluid cultures from preterm labour patients are positive for microorganisms.
5. Infection cause cytokines and prostaglandin production

The infection may be either generalized or more commonly a local urogenital tract infection. Generalized infections (for example; pneumonia, pyelonephritis, malaria, typhoid fever, periodontal disease, etc.) has been associated with preterm labour and delivery. Yet, many of these conditions are rare in developed countries. Thus, the risk attributable to systemic maternal infection for prematurity is considered to be low [Kurki 1998; Romero 2002]. It has been estimated that at least 40% of all preterm births occur to mothers with intrauterine infection. Moreover, the lower the gestational age at delivery the greater the frequency of intrauterine infection (Figure 1) [Gonc 2002; Romero 2002].

Microorganisms may gain access to the amniotic cavity and the fetus through the following pathways:

1. Ascending from the vagina and the cervix.
2. Haematogenous dissemination through the placenta.
3. Retrograde seeding from the peritoneal cavity through the fallopian tubes.
4. Accidental introduction at the time of invasive procedures, such as amniocentesis, percutaneous fetal blood sampling, chorionic villous sampling or shunting [Gonc 2002; Romero 2002; Ville 2001].

The most common pathway of intrauterine infection is the ascending route. Evidence in support of this includes:

1. Histological chorioamnionitis is more common and severe at the site of membrane rupture than in other locations, such as the placental chorionic plate or the umbilical cord.
2. In virtually all cases of congenital pneumonia chorioamnionitis is present.
3. Bacteria identified in cases of congenital infections are similar to those found in the lower genital tract.
4. In twin gestations, histological chorioamnionitis is more common in the firstborn twin and has not been demonstrated only in the second twin, as the membranes of the first twin are generally opposed to the cervix, this is taken as evidence in favour of an ascending infection [Gonc 2002; Romero 2002].

Ascending intrauterine infection is considered to have four stages (Figure 2).

Stage I consists of a change in the vaginal/cervical microbial flora or the presence of pathologic organisms in the cervix, bacterial vaginosis may be an early manifestation of this initial stage. Once microorganisms gain access to the intrauterine cavity, they reside in the decidua (stage II). A localized inflammatory reaction leads to deciduitis. Microorganisms may then reside in the chorion and amnion. The infection may invade the fetal vessels (choriovascuclitis) or proceed through the amnion (amnionitis) into the amniotic cavity, leading to microbial invasion of the amniotic cavity or an intra-amniotic infection (stage III). Rupture of the membranes is not a prerequisite for intraamniotic infection, as microorganisms are capable of crossing intact membranes. Once in the amniotic cavity, the
bacteria may gain access to the fetus through various ports of entry (stage IV). Seeding from any of these sites to the fetal circulation may result in fetal bacteraemia and sepsis [Epstein 2000; Gonc 2002; Romero 2002]. Stage IV is the most advanced and serious stage with overall mortality rate ranges between 25% and 90% [Gonc 2002; Romero 2002]. The mean rate of positive amniotic fluid cultures for microorganisms in patients with preterm labour and intact membranes is 12.8%, and those inpatients with preterm premature rupture of membranes is 32.4% [Romero 2002].

Microorganisms produce different bioactive substances helping them to induce preterm labour and the pathway can be summarized as follows (Figure 3):

The presence of sialidases facilitates bacterial attachment and break down of mucin while mucinases assist microbial ascent into the decidua (uterine tissue). Metalloproteolytic enzymes and other microbial bioactive substances act directly on cervical collagen and amnionchorion leading to premature cervical ripening and weakening the fetal membranes with subsequent preterm premature rupture of the membranes. Microorganisms stimulate the maternal monocytes and macrophages resulting in the production of phospholipase A2 which is an enzyme that liberate arachidonic acid from the phospholipids of the membranes leading to the synthesis of prostaglandins E2 and F2α by the placental membranes. Moreover, in infected foetuses, there is an increase in both fetal hypothalamic and placental production of corticotrophin releasing hormone leading to increase in fetal adrenal cortisol production with increased production of prostaglandins. Also, when the fetus is infected, there is a high increase in the production of cytokines and marked decrease in the delivery time [Epstein 2000; Goldenberg 2002; Keelan 1997; Klein 2004; Mertz 2001; Romero 2002].

In pregnancy, the genital tract flora is more abundant progressively more benign, until at term, the upper vaginal flora is composed mainly of organisms of low virulence which threaten no significant hazard to the fetus [Lamont 1999]. Bacterial vaginosis is a polymicrobial condition caused by the increased prevalence of anaerobes including Gardnerella vaginalis, Bacteroides spp., and Mobiluncus and Mycoplasma hominis. There is an associated reduction in hydrogen peroxide producing Lactobacilli and a dramatic increase in the anaerobe to aerobe ratio.

The criteria used to diagnose bacterial vaginosis are:

a. Vaginal PH >4.5.
b. Grey homogenous vaginal discharge.
c. Presence of clue cells in a wet mount preparation of vaginal fluid.
d. Positive amine test in which a fishy odour is released after the addition of 10% potassium hydroxide (KOH) to the vaginal fluid [Chaim 1997; Cram 2002; Haram 2003; Lamont 2003a; Taraa 2004; VIPS 1995].

The current recommendation by the centre for disease control and prevention (CDC) {Atlanta, GA, USA} and the UK drug and therapeutics bulletin is to screen and treat bacterial vaginosis in high risk pregnancies [Ugwumadu 1999]

Asymptomatic bacteriuria, defined as more than 100,000 colonies of a single bacterial species per ml of urine, cultured from midstream sample, is present in 2-7% of pregnant women. The most commonly isolated bacteria are escherichia coli. Pregnancy does not increase the incidence of asymptomatic bacteriuria; however, pyelonephritis develops in 20-40% of pregnant women with untreated asymptomatic bacteriuria and if not treated will cause preterm labour [Cram 2002; Weismiller 1999].

The centers for disease control and prevention (CDC) recommends that pregnant women with bacteriuria be treated at the time of diagnosis [Cram 2002].

Because infection is clearly associated with preterm births, it has been logical to ask whether antibiotics can prevent prematurity. Antibiotics may induce a significant 12-20% reduction in neonatal infections following preterm rupture of the membranes and also may prolong pregnancy significantly [Kurki 1998; Lamont 2003a]. Moreover antibiotics may be used prophylactically for those women at high risk of preterm birth, or may be given as adjuvant therapy.
with tocolytics for those women who are in preterm labour [Lamont 2003a].

Objectives

To evaluate the effectiveness of using antibiotics at any time during pregnancy to prevent preterm birth.

Criteria for considering studies for this review

**Types of studies**
All reviews assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth.

Also, all randomised clinical trials assessing the use of antibiotics during pregnancy with outcome data on preterm labour and birth.

**Types of participants**
Pregnant women.

**Types of interventions**
Antibiotics versus placebo, no treatment, or any other intervention to prevent preterm labour and birth.

**Types of outcome measures**
Main;
1. Preterm birth before 34 weeks.
2. Neonatal morbidity (includes; intraventricular haemorrhage, neonatal sepsis, pneumonia, ophthalmia neonatorum, and necrotizing enterocolitis).

Other outcomes of interest;
1. Preterm birth before 28 weeks.
2. Preterm birth before 37 weeks.
3. Maternal infective morbidity (includes; any infection diagnosed by fever, blood culture, urine culture, high vaginal swab, or any other method of diagnosis and classified by author as infective morbidity).
4. Maternal adverse effects (includes; palpitation, flushes, nausea, vomiting, diarrhoea, abdominal pain, rashes, headache, and dizziness).

**Search strategy for identification of studies**
We searched the Cochrane Library, MEDLINE, BIOSIS, EMBase, and CINAHL.

Reviews and Randomised clinical trials identified through the searching activities and fit to the criteria for selecting studies mentioned above included. We did not apply any language restrictions.

Methods of the umbrella review

**Methods for the reviews**

**Selection of reviews:** We assessed for inclusion all potential reviews we identify as a result of the search strategy. We resolved any disagreement through discussion.

**Data extraction and management:** We designed a form to extract data from the reviews. Two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. When information regarding any of the above is unclear, we attempted to contact authors of the original studies to provide further details.

**Measures of treatment effect:** We carried out a statistical analysis using fixed effect meta-analysis for combining data in the absence of heterogeneity if reviews are sufficiently similar. Heterogeneity was found and explored by sensitivity analysis followed by random effect meta-analysis.

**Assessment of methodological quality of included reviews:**
Methods used in each review and its quality was described. We assessed the validity and quality of each study using the following criteria;
1. Quality assessment: We designed a form to assess the quality of the reviews based on the QUOROM reviews quality checklist [Moher 2000], with score of 1 point for each yes and 0 score for each no (with the exception of restriction of search where no scores1 and yes scores 0) the maximum score is 27. We will assign each review using the following criteria;
   A. Excellent quality: score of 24 or more (out of 27 points).
   B. Good quality: score of 20 to 23.
   C. Fair quality: score of 16 to 19.
   D. Poor quality: score of 15 or less.
2. Presence of studies assessment: (as stated in the inclusion and exclusion criteria of the review e.g. randomised controlled trials, observational studies).

We assessed the presence of studies in each review using the following criteria:
1. There are studies included in the review.
2. There are no studies included in the review.

**Assessment of heterogeneity:** We applied tests of heterogeneity between reviews, using the I² statistic.
We identify high levels of heterogeneity among the reviews, (exceeding 50%); a random-effects meta-analysis was used as an overall summary. We carried out sensitivity analysis to explore the effect of reviews quality. This involved analysis based on an A, B, C, or D rating of quality assessment and 1, or 2 in the presence of studies assessment. Reviews of poor quality (those rating D) or with no studies included (those rating 2) were excluded in the analysis, in order to assess for any substantive difference to the overall result.

**Methods for the randomised clinical trials.**

**Selection of studies:** We assessed for inclusion all potential studies we identify as a result of the search strategy.

**Data extraction and management:** We designed a form to extract data. At least two review authors extracted the data using the agreed form. We resolved discrepancies through discussion. When information regarding any of the above is unclear, we attempted to contact authors of the original reports to provide further details.

**Assessment of methodological quality of included studies:** Methods used for generation of the randomisation sequence was described for each trial. We assessed the validity of each study using the following criteria;

1. Selection bias (randomisation and allocation concealment) We assigned a quality score for each trial, using the following criteria:
   - A. Adequate concealment of allocation: such as telephone randomisation, consecutively numbered sealed opaque envelopes;
   - B. Unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
   - C. Inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.
   - D. Randomisation not used.

2. Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations). We assessed completeness to follow up using the following criteria:
   - A. less than 5% loss of participants;
   - B. 5% to 9.9% of loss of participants;
   - C. 10% to 19.9% loss of participants;
   - D. More than 20% loss of participants.

3. Performance bias (blinding of participants, researchers and outcome assessment) We assessed blinding using the following criteria:
   - 1. Blinding of participants (yes/no/unclear);
   - 2. Blinding of caregiver (yes/no/unclear);

**Measures of treatment effect:** We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials are sufficiently similar. Heterogeneity was found this was explored by sensitivity analysis followed by random effect meta-analysis.

**Unit of analysis issues:** We planned to include cluster-randomised trials in the analyses along with individually randomised trials. Their sample sizes was to be adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICC’s from other sources are used, this was to be reported and sensitivity analyses conducted to investigate the effect of variation in the ICC. If we identify both cluster randomised trials and individually randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely.

We also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis. Therefore the meta-analysis was to be performed in two parts as well.

**Dealing with missing data:** We analysed data on all participants with available data in the group to which they are allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants are not analysed in the group to which they were randomised, and there is sufficient information in the trial report, we attempted to restore them to the correct group.

**Assessment of heterogeneity:** We applied tests of heterogeneity between trials, using the I² statistic. We identified high levels of heterogeneity among the trials, (exceeding 50%); a random-effects meta-analysis was used as an overall summary. We carried out sensitivity analysis to explore the effect of trial quality. This involved analysis based on an A, B, C, or D rating of selection bias and attrition bias. Studies of poor quality were excluded in the analysis (those rating D) in order to assess for any substantive difference to the overall result.

**Subgroup analyses**

We carried out the following subgroup analyses;
According to the indication for the use of the antibiotics:
- Dental indications.
- Genital infections including sexually transmitted diseases.
- Urinary tract infections.
- Other indications.

According to the antibiotic group:
- Penicillins and Cephalosporins.
- Macrolide antibiotics.
- Metronidazole.
- Other antibiotics.
- Combination of two or more of the groups mentioned above.

According to the stage of pregnancy
- Less than 16 weeks.
- 16 weeks or more.
- Mixed or not stated.

Results

Results of included randomised controlled trials meta-analysis:
There is an average 9% decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {Risk Ratio (RR) 0.93, 95% Confidence Interval (95%CI) 0.89, 0.98, and Probability (P) 0.003 for all antibiotics versus placebo or no treatment, RR 0.90, 95%CI 0.84, 0.97, P 0.006 for all indications versus placebo or no treatment, RR 0.90, 95%CI 0.84, 0.97, P 0.005 for all gestational ages versus placebo or no treatment}.

Although not statistically significant, (Figure 5), there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment {RR 1.19, 95%CI 0.88, 1.61, P 0.26 before 37 weeks, RR 1.17, 95%CI 0.90, 1.51, P 0.24 before 34 weeks, RR 2.61, 95%CI 0.71, 9.62, P 0.15 before 28 weeks}.

Results of included reviews meta-analysis:
There is an average 30% decrease in the incidence of neonatal morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages {Risk Ratio (RR) 0.70, 95% Confidence Interval (95%CI) 0.58, 0.85, P 0.002 for all gestational ages versus placebo or no treatment}. For the rest of the outcomes in the subgroups analysis the results are not statistically significant.

Methodological quality of included studies

26 of the included trials were multicenter trials. Only one randomised trial used antibiotic control to compare the use of 3 antibiotics versus 2 antibiotics [Maberry 1991]. For detailed description of the included trials see (Figure 4).

4 of the included reviews were not Cochran reviews [Egarter 1996; Guise 2001; Leitch 2003; Turrentine 1995]. For detailed description of the included reviews see (Figure 4).
groups, all indications, and all gestational ages (RR 0.77, 95% CI 0.59, 1.00 for all antibiotics versus placebo or no treatment; RR 0.69, 95% CI 0.53, 0.89 for all indications versus placebo or no treatment; RR 0.64, 95% CI 0.51, 0.81 for all gestational ages versus placebo or no treatment).

There is an average 45% less maternal infective morbidity with the use of antibiotics compared to placebo or no treatment for all antibiotic groups, all indications, and all gestational ages (RR 0.59, 95% CI 0.47, 0.70 for all antibiotics versus placebo or no treatment; RR 0.53, 95% CI 0.40, 0.70 for all indications versus placebo or no treatment and all gestational ages versus placebo or no treatment). In the case of all antibiotics versus placebo or no treatment maternal adverse effects increased with antibiotics to 16% but did not reach statistical significance (RR 1.16, 95% CI 1.00, 1.35, P 0.06).

For the rest of the outcomes in the subgroups analysis the results are not statistically significant.

Although not statistically significant, (Figure 5), there is a noticeable increase in preterm births with the use of Metronidazole compared to placebo or no treatment (RR 1.02, 95% CI 0.89, 1.17, P 0.81 before 37 weeks, RR 1.07, 95% CI 0.79, 1.45, P 0.66 before 34 weeks, no studies compared metronidazole to placebo or no treatment before 28 weeks).

Discussion

By comparing the above results we can see that regardless of the antibiotic group, indication, and gestational age there is 39% decrease in the maternal infective morbidity with the use of antibiotics during pregnancy compared to placebo or no treatment, which is accompanied by 17% increase in the maternal adverse effects.

Again regardless of the antibiotic group, indication, and gestational age there is 9% decrease in the incidence of preterm birth before 37 weeks with the use of antibiotics compared to placebo or no treatment, but there is no significant effect for antibiotics use to prevent preterm birth before 34 weeks which is more important clinically.

There is 30% decrease in the incidence of neonatal morbidity with the use of antibiotics compared to placebo or no treatment regardless of the antibiotic group, indication, and gestational age. This Decrease in neonatal morbidity is noticed in infants up to the age of 6 weeks, but recent study [Kenyon 2008b] followed up the long-term effects on children after exposure to antibiotics that were given to there mothers when they were in spontaneous preterm labour with intact membranes and without overt signs of clinical infection, in this follow up study they found that the prescription of antibiotics for these women was associated with an increase in functional impairment among their children at 7 years of age and The risk of cerebral palsy was increased.

There is a positive association between using metronidazole and increase the incidence of preterm labour this results supports the previous findings by other researchers [Carey 2000, Kigozi 2003, Klebanoff 2001, Shennan 2005, Simcox 2007].

Conclusion

The results of this umbrella review proves that the use of antibiotics during pregnancy have no effect in preventing preterm labour before 34 weeks, but also may increase the risk of preterm labour specially metronidazole, and this is accompanied by an increase in the maternal adverse effects including palpitation, flushes, nausea, vomiting, diarrhoea, abdominal pain, rashes, headache, and dizziness.

Implications for practice

The result of this umbrella review does not supports the use of antibiotics during pregnancy except when there is a clear evidence of infection with extreme caution, regular follow ups and monitoring of the patient.

We do not support the use of metronidazole during pregnancy.

Implications for research

There is a real need for a randomised controlled trial designed to test antibiotics versus antibiotics, the trials should be appropriately sized and Outcomes should include preterm labour and birth at clinically significant gestational ages, neonatal and maternal infective morbidity and adverse effects.

Effects of metronidazole on pregnancy needs further investigation.

Long term effects of antibiotics on infants and children needs further investigation.
References

References to included randomised controlled studies

Andrews 2003 {published data only}

Antsaklis 1997 {published data only}

Carey 2000 {published data only}

Cox 1996 {published data only}

Elder 1971 {published data only}

Eschenbach 1991 {published data only}

Gray 2001 {published data only}

Guaschino 2002 {published data only}

Hauth 1995 {published data only}

Hawkinson 1966 {published data only}

Jeffcoat 2003 {published data only}

Joesoef 1995 {published data only}

Kekki 2001 {published data only}

Kenyon 2001a {published data only}
Kenyon 2001b [published data only]

Keuchkerian 2004 [published data only]

Kiss 2004 [published data only]

Klebanoff 1994 [published data only]

Klebanoff 2001 [published data only]

Kurkinen-Raty 2000 [published data only]

Lamont 2003 [published data only]

Little 1966 [published data only]

Maberry 1991 [published data only]

Martin 1997 [published data only]

McDonald 1997 [published data only]

McGregor 1990 [published data only]

McGregor 1991 [published data only]

McGregor 1994 [published data only]

Morales 1988 [published data only]

Morales 1994 [published data only]

Newton 1989 [published data only]

Newton 1991 (published data only)

Norman 1994 (published data only)

Odendaal 2002 (published data only)

Ogasawara 1999 (published data only)

Oyarzun 1998 (published data only)

Purwar 1997 (published data only)

Romero 1993 (published data only)

Saez-Llorens 1995 (published data only)

Shennan 2005 (published data only)

Svare 1997 (published data only)

Thomsen 1987 (published data only)

Ugwumadu 2003 (published data only)

Vermeulen 1999 (published data only)

Watts 1994 (published data only)

References to included reviews
Brocklehurst 1998 (published data only)

Brocklehurst 2002 (published data only)
* Brocklehurst P. Antibiotics for gonorrhoea in...

Egarter 1996 (published data only)

Flenady 2002 (published data only)

Garner 2002 (published data only)

Guise 2001 (published data only)

Gülmezoglu 2002 (published data only)

Hopkins 2002 (published data only)

Kenyon 2003 (published data only)

King 2002 (published data only)

Leitch 2003 (published data only)

McDonald 2005 (published data only)

Raynes-Greenow 2004 (published data only)

Smaill 2001 (published data only)

Thinkhamrop 2002 (published data only)

Turrentine 1995 (published data only)

Vazquez 2003 (published data only)

Villator 2000 (published data only)

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Kigozi 2003 (published data only)

Lopez 2002 (published data only)

McCaul 1992 (published data only)

McGregor 1986 (published data only)

Paul 1998 (published data only)

Rosenstein 2000 (published data only)

Wing 1999 (published data only)

References to excluded reviews

Carey 2001 (published data only)

Gibbs 1997 (published data only)

Kirschbaum 1993 (published data only)

Klein 2004 (published data only)

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* Lamont RF. Infection in the prediction and antibiotics in the prevention of spontaneous preterm labour and preterm birth. BJOG 2003; 110(20):71-75.

Lamont 2005 (published data only)

Lewis 1995 (published data only)

Mertz 2001 (published data only)

Orton 2005 (published data only)

Peyron 1999 (published data only)

Tebes 2003 (published data only)

Thorp 2002 (published data only)
* Thorp JM Jr, Hartmann KE, Berkman ND, Carey TS,

Walker 2001 {published data only}

Young 2001 {published data only}

References to ongoing reviews
Crowther 2005 {published data only}

* indicates the primary reference for the study

Other references
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Cram 2002

Epstein 2000

Gibbs 1997

Goldenberg 2002

Goldenberg 2005

Gonc 2002

Haram 2003

Hollier 2005

Keelan 1997

Klein 2004

Kurki 1998

Lamont 1999

Lamont 2003a
Lamont RF. Infection in the prediction and antibiotics in the prevention of spontaneous preterm labour and preterm birth. BJOG: an international journal of obstetrics and gynaecology 2003; 110(20):71–75.

Mertz 2001

Moher 2000
Riggs 2004

Romero 2002

Taraa 2004

Ugwumadu 1999

Ville 2001

VIPS 1995

Weismiller 1999
Illustrations

Illustration 1

Microorganisms isolated from the amniotic cavity of patients with preterm labour

<table>
<thead>
<tr>
<th>Family</th>
<th>Microorganisms</th>
</tr>
</thead>
</table>
| Genital Mycoplasma    | Ureaplasma urealyticum  
Mycoplasma hominis            |
| Aerobes               | Group B streptococci  
Enterococci              |
| Viridans streptococci | Gardnerella vaginalis  
Hemophilus influenza  
Pseudomonas species  
Lactobacilli  
Coliforms  
Corynebacterium  
Moraxella  
Staphylococci  
Acinetobacter wolffi  
Bacillus cereus  
Capnocytophaga species  
Diphtheroids  
Enterobacter cloacae |
| Anaerobes             | Fusobacterium species  
Veillonella parvula  
Peptostreptococcus species  
Propionobacterium species  
Peptococcus species  
Bacteroides species  
Neisseria species       |
| Yeasts                | Candida species                                                             |
Illustration 2

Stages of ascending infection Adapted from Romero 1988 with permission
Illustration 3

Potential pathway for bacteria to initiate preterm labour Adapted from Goldenberg 2000 with permission
**Illustration 4**

Characteristics of excluded randomised controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldenberg 2001</td>
<td>This is a subgroup analysis of Carey 2000.</td>
</tr>
<tr>
<td>Gordon 1995</td>
<td>This is not a proper intention to treat analysis as 47% of the participants are lost to follow up, protocol violations, and withdrawals</td>
</tr>
<tr>
<td>Jacobson 2001</td>
<td>This is not a proper intention to treat analysis as 30% of the participants are lost to follow up, protocol violations, and withdrawals.</td>
</tr>
<tr>
<td>Kigozi 2003</td>
<td>This is a subgroup analysis of Gray 2001.</td>
</tr>
<tr>
<td>Lopez 2002</td>
<td>There is no use of antibiotics in this trial, just periodontal treatment.</td>
</tr>
<tr>
<td>McCaul 1992</td>
<td>This is not a proper intention to treat analysis as 34% of the participants are lost to follow up, protocol violations, and withdrawals.</td>
</tr>
<tr>
<td>McGregor 1986</td>
<td>This is not a proper intention to treat analysis as 71% of the participants are lost to follow up, protocol violations, and withdrawals.</td>
</tr>
<tr>
<td>Paul 1998</td>
<td>This is not a proper intention to treat analysis as 26% of the participants are lost to follow up, protocol violations, and withdrawals</td>
</tr>
<tr>
<td>Rosenstein 2000</td>
<td>This is a subgroup analysis of a cohort study.</td>
</tr>
<tr>
<td>Wing 1999</td>
<td>This is not a proper randomised controlled clinical trial, the same antibiotics used for the in patient group and the out patient group with no control group.</td>
</tr>
</tbody>
</table>
### Illustration 5

Results of randomised controlled trials random effect meta-analysis

<table>
<thead>
<tr>
<th>Comparison</th>
<th>RR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antibiotics versus placebo or no treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth before 34 weeks</td>
<td>1.03</td>
<td>1.00, 1.06</td>
<td>0.07</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>0.90</td>
<td>0.77, 1.05</td>
<td>0.18</td>
</tr>
<tr>
<td>Preterm birth before 28 weeks</td>
<td>0.96</td>
<td>0.83, 1.12</td>
<td>0.63</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
<td>0.93</td>
<td>0.89, 0.98</td>
<td>0.003</td>
</tr>
<tr>
<td>Maternal infective morbidity</td>
<td>0.67</td>
<td>0.50, 0.90</td>
<td>0.009</td>
</tr>
<tr>
<td>Maternal adverse effects</td>
<td>1.24</td>
<td>0.96, 1.61</td>
<td>0.10</td>
</tr>
<tr>
<td>All antibiotics versus antibiotics control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preterm birth before 34 weeks</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>1.39</td>
<td>0.24, 8.06</td>
<td>0.71</td>
</tr>
<tr>
<td>Preterm birth before 28 weeks</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
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<td>0.37, 2.33</td>
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<tr>
<td>Maternal infective morbidity</td>
<td>1.86</td>
<td>0.67, 5.14</td>
<td>0.23</td>
</tr>
<tr>
<td>Maternal adverse effects</td>
<td>*</td>
<td>*</td>
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<td>0.99, 1.07</td>
<td>0.18</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>0.84</td>
<td>0.69, 1.04</td>
<td>0.10</td>
</tr>
<tr>
<td>Preterm birth before 28 weeks</td>
<td>1.02</td>
<td>0.80, 1.30</td>
<td>0.88</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
<td>0.90</td>
<td>0.84, 0.97</td>
<td>0.006</td>
</tr>
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<td>0.88</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
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<td>0.84, 0.97</td>
<td>0.005</td>
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<td>Maternal infective morbidity</td>
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<td>0.49, 0.85</td>
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<td>Maternal adverse effects</td>
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<td>0.85, 1.63</td>
<td>0.34</td>
</tr>
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<td>All gestational ages versus antibiotic control</td>
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<tr>
<td>Preterm birth before 34 weeks</td>
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Illustration 6

Results of reviews random effect meta-analysis

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<td></td>
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<tr>
<td>Preterm birth before 34 weeks</td>
<td>1.07</td>
<td>0.79, 1.45</td>
<td>0.66</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>0.77</td>
<td>0.59, 1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Preterm birth before 28 weeks</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
<td>0.95</td>
<td>0.89, 1.02</td>
<td>0.15</td>
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<tr>
<td>Maternal infective morbidity</td>
<td>0.59</td>
<td>0.47, 0.74</td>
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<td>Maternal adverse effects</td>
<td>1.16</td>
<td>1.00, 1.35</td>
<td>0.06</td>
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<tr>
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<td></td>
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<td>0.005</td>
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<td>0.88, 1.04</td>
<td>0.27</td>
</tr>
<tr>
<td>Maternal infective morbidity</td>
<td>0.53</td>
<td>0.40, 0.70</td>
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<tr>
<td>Maternal adverse effects</td>
<td>1.17</td>
<td>1.00, 1.37</td>
<td>0.04</td>
</tr>
</tbody>
</table>
### All indications versus antibiotic control

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth before 34 weeks</td>
<td>*</td>
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<td>*</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
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<td>0.29, 1.35</td>
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<td>*</td>
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</tr>
<tr>
<td>Preterm birth before 37 weeks</td>
<td>0.99</td>
<td>0.96, 1.03</td>
<td>0.73</td>
</tr>
<tr>
<td>Maternal infective morbidity</td>
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<td>0.68, 1.51</td>
<td>0.97</td>
</tr>
<tr>
<td>Maternal adverse effects</td>
<td>0.27</td>
<td>0.16, 0.46</td>
<td>&lt;0.00001</td>
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</tbody>
</table>

### All gestational ages versus placebo or no treatment

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth before 34 weeks</td>
<td>1.07</td>
<td>0.79, 1.45</td>
<td>0.66</td>
</tr>
<tr>
<td>Neonatal morbidity</td>
<td>0.64</td>
<td>0.51, 0.81</td>
<td>0.0003</td>
</tr>
<tr>
<td>Preterm birth before 28 weeks</td>
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<td>*</td>
<td>*</td>
</tr>
<tr>
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<td>0.88, 1.04</td>
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<td>0.40, 0.70</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>Maternal adverse effects</td>
<td>1.17</td>
<td>1.00, 1.37</td>
<td>0.04</td>
</tr>
</tbody>
</table>

### All gestational ages versus antibiotic control

<table>
<thead>
<tr>
<th>Condition</th>
<th>Risk Ratio</th>
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<tr>
<td>Preterm birth before 37 weeks</td>
<td>0.99</td>
<td>0.96, 1.03</td>
<td>0.73</td>
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