Antibiotics for Preventing Preterm Labour; an Umbrella Review

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Abstract

Preterm birth causes 60% to 80% of neonatal deaths whilst survivors may experience life-long complications. Infection is thought to be present in 30% to 50% of preterm births, raising the possibility of prevention by antibiotic treatment.
To evaluate the effectiveness of using antibiotics at any time during pregnancy to prevent preterm birth, we searched databases with no language restrictions. We included both reviews and RCT's.
RCT's: 56 Randomized controlled trials considered, 45 were included and 11 excluded.
There is an average 9% decrease in the incidence of preterm birth with the use of antibiotics {RR 0.91, 95%CI 0.84, 0.97}.
Reviews: 33 reviews were considered, 18 included and 14 excluded. There is an average 30% decrease in the incidence of neonatal morbidity with antibiotics {RR 0.70, 95%CI 0.59, 1.00}.
Antibiotic treatment had little impact on preterm birth before 34 weeks [RR 1.03, 95%CI 1.00, 1.06] but associated with a modest but statistically significant decrease in preterm birth before 37 weeks [RR 0.97, 95% CI 0.95, 0.99].
Metronidazole may increase the risk of preterm birth [RR 1.16, 95% CI 1.00, 1.35].

1. 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 [1, 2, 3, 4].

Preterm birth is one of the most important problems in medicine today with an alarming frequency and economic impact [5]. 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 [4]. 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 [3, 6]. 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 [4, 6].

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 [7, 8]. The risk for these morbidities is directly related to the gestational age and birth weight [9]. The lifetime costs per preterm birth have been estimated at £511,614 [10].

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 [11. 12. 13. 14]. 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 [15, 16]. 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 [15, 17].

Ascending intrauterine infection is considered to have four stages {Figure 1}. 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 (choriovasculitis) or proceed through the amnion (amnionitis) into the amniotic cavity, leading to microbial invasion of the amniotic cavity (stage III) or an intra-amniotic infection [18, 19].

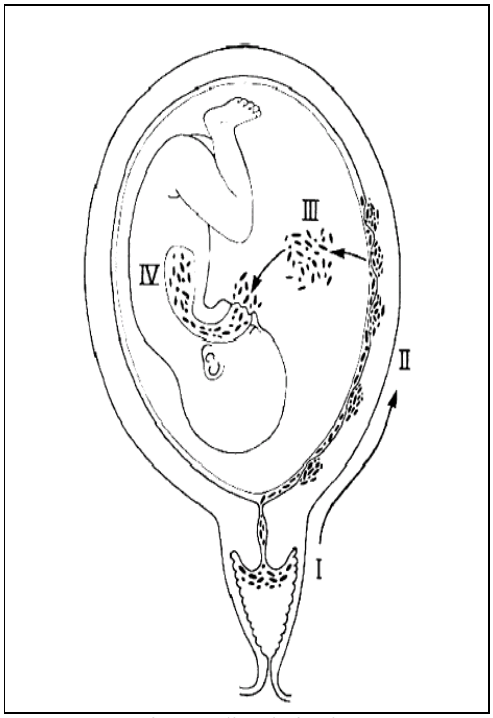

Figure 1: stages of ascending infection

Microorganisms produce different bioactive substances helping them to induce preterm labour and the pathway can be summarized as follows: 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. Similarly, protease toxins activate the deciduas

and fetal membranes to produce Cytokines such as Tumour Necrosis Factor (TNF), Interleukin (IL1a, IL1b, IL6, IL8), and Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF). In response to the activation of local inflammatory reaction Prostaglandins synthesis and release are stimulated leading to stimulate uterine contractions. Moreover, in infected foetus, there is an increase in both fetal hypothalamic and placental production of corticotrophin releasing hormone leading to increase in fetal corticotrophin secretion, which in turn increases fetal adrenal cortisol production leading to 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 [19, 20, 21].

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 [20, 21]. 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 [21].

2. Objective

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

3. Criteria for considering studies for this review

3.1 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.

3.2 Types of participants

Pregnant women.

3.3 Types of interventions

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

4. 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).

5. 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.

6. 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** (Table 1);

Group	Antibiotics
Penicillins and Cephalosporins	Benzylpenicillin Ceftriaxone Cefpirome Ampicillin Cefradin Amoxicillin Co-Amoxiclav Cefalexin (cephalexin) Cefuroxime axetil Co-Fluampicil Cefadroxil Cefixime Cefaclor Cefprozil Ceftazidime axetil Cefpodoxime pro Phenoxymethylpenicillin Ceftriaxone Flucloxacillin Cefradine Ceftazidime Cefuroxime Cefotaxime
Macrolide antibiotics	Clindamycin Clarithromycin Erythromycin Spiramycin Azithromycin Telithromycin
Metronidazoles	Metronidazole Tinidazole
Others	Sodium fusidate Doxycycline Tetracycline Minocycline Lymecycline Oxyteracycline
Combination of two or more of the groups	

Table 1: Antibiotic groups

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

7. Description of studies

56 Randomised controlled trials published between 1966 and the present day were considered for this umbrella review, 45 were included and 11 excluded due to being a subgroup analysis of one of the included trials [Goldenberg 2001; Kigozi 2003; Rosenstein 2000], not using antibiotics in the trial [Lopez 2002], or not being a proper intention to treat analysis with the loss of more than 20% of the participants [Andrews 2005; Gordon 1995; Jacobson 2001; McCaul 1992; McGregor 1986; Paul 1998; Wing 1999].

33 reviews published between 1993 and the present day were considered for this umbrella review, 18 were included and 14 excluded due to poor quality [Carey 2001; Kirschbaum 1993; Klein 2004; Lewis 1995], synthesis of opinion based on different data and not on meta-analysis of studies [Gibbs 1997; Lamont 2003; Lamont 2005; Mertz 2001; Tebes 2003], using outcomes not included in this umbrella review [Orton 2005; Thorp 2002; Young 2001], or not including any studies [Peyron 1999; Walker 2001].

8. 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].

4 of the included reviews were not Cochran reviews [Egarter 1996; Guise 2001; Leitich 2003; Turrentine 1995].

9. Results

9.1 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}.

There is 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 {RR 0.67, 95%CI 0.50, 0.90, P 0.009 for all antibiotics versus placebo or no treatment and all indications versus placebo or no treatment, RR 0.64, 95% CI 0.49, 0.85, P 0.002 for all gestational ages versus placebo or no treatment}.

9.2 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 {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, RR 0.53, 95%CI 0.40, 0.70 for all gestational ages versus placebo or no treatment}.

There is an average 83% increase in the maternal adverse effects with the use of antibiotics compared to placebo or no treatment for all indications, and all gestational ages {RR 1.17, 95%CI 1.00, 1.37 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 84% but did not reach statistical significance {RR 1.16, 95%CI 1.00, 1.35, P 0.06}.

10. Discussion

By comparing the above results we can see that there is 34-45% decrease in the maternal infective morbidity with the use of antibiotics during pregnancy compared to placebo or no treatment 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 regardless of the antibiotic group, indication, and gestational age. 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. There is 83% increase in the maternal adverse effects with the use of antibiotics compared to placebo or no treatment regardless of the indication, and gestational age.

10.1 Reviewers' conclusions

The results of this umbrella review proves that the use of antibiotics during pregnancy will decrease the incidence of preterm birth and maternal infective morbidity regardless of the antibiotic group, indication, but only before 37 weeks and are accompanied by a large increase in the maternal adverse effects. Antibiotics are not effective in preventing preterm birth before 34 weeks and not effective in preventing prematurity associated neonatal morbidity.

10.2 Implications for practice

The result of this umbrella review do not support the use of antibiotics during pregnancy.

10.3 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.

11. References

[1] Chaim W, Mazor M, Leiberman JR. The relationship between bacterial vaginosis and preterm birth. Archives of Gynecology and Obstetrics 1997; 257:51-58.

[2] Cram LF, Zapata MI, Toy EC, and Baker B III. Genitourinary Infections and Their Association with Preterm Labor. American Family Physician 2002; 65(2):241-248.
[3] Epstein F. Intrauterine infection and preterm delivery. New England Journal of Medicine 2000; 342(20):1500-1507.
[4] Gibbs RS, and Esehenbaeh DA. Use of antibiotics to prevent preterm birth. American journal of obstetrics and gynaecology 1997; 177(2):375-380.
[5] Goldenberg RL. The Management of Preterm Labor. Obstetrics & Gynecology 2002; 100(5):1020-1037.
[6] Goldenberg RL, Culhane JF. Prepregnancy Health Status and the Risk of Preterm Delivery. Archives of pediatric and adolescent medicine 2005; 159:89-90.
[7] Gonc LF, Alves CT, and Romero R. Intrauterine infection and prematurity. Mental retardation and developmental disabilities 2002; 8:3-13.
[8] Haram K., Mortensen JHS And Wollen AL. Preterm delivery: an overview. Acta Obstetricia et Gynecologica Scandinavica 2003; 82:687-704.
[9] Hollier LM. Preventing Preterm Birth: What Works, what does not. Obstetrical and gynaecological survey 2005; 60(2):124-131.
[10] Klein LL, Gibbs RS. Use of microbial cultures and antibiotics in the prevention of infection-associated preterm birth. American Journal of Obstetrics and Gynecology 2004; 190:1493-1502.
[11] Kurki T. A survey of etiological mechanisms and therapy of preterm labor. Acta Obstetricia et Gynecologica Scandinavica 1998; 77:137-141.
[12] Lamont RF. The prevention of preterm birth with the use of antibiotics. European journal of paediatrics 1999; 158(1):2-4.
[13] 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.
[14] Mertz HL and Ernest JM. Antibiotics and Preterm Labor. Current Women's Health Reports 2001; 1:20-26.
[15] Riggs MA, Klebanoff MA. Treatment of vaginal infections to prevent preterm birth: a meta-analysis. Clinical Obstetrics and Gynaecology 2004; 47(4):796-807.
[16] Romero R., Espinoza J, Chaiworapongsa T and Kalache K. Infection and prematurity and the role of preventive strategies. Seminars in Neonatology 2002; 7:259-274.
[17] Taraa P.N., Thornton S. Current medical therapy in the prevention and treatment of preterm labour Current medical therapy in the prevention and treatment of preterm labour. Seminars in Fetal & Neonatal Medicine 2004; 9:481-489.
[18] Ugwumadu AHN, Hay P. Bacterial vaginosis: sequelae and management. Current Opinion in Infectious Diseases 1999; 12(1):53-59.
[19] Ville Y. Premature delivery and inflammation. Journal of Gynecology, Obstetrics and Biological Reproduction 2001; 30(1):12-16.
[20] Vaginal infections and prematurity study group. Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. New England Journal of Medicine 1995; 333(26):1737-1742.
[21] Weismiller DG. Preterm Labor. American family physician 1999; 59(3):3-11.