The role of infection in preterm labour and birth

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Preterm birth is the major cause of neonatal mortality and morbidity. Infection is a major cause of preterm labour. Abnormal genital tract flora in early pregnancy is predictive of preterm labour. Antibiotics may be of help in preventing preterm birth.

Preterm birth (PTB) is the major cause of death (Magowan et al, 1998) and handicap (Woods et al, 2000) in the developed world, accounting for 13 million births annually worldwide (Villar et al, 1994). In the USA, neonatal intensive care costs approximately US $5 billion per annum (Keirse, 1995) and the cost of hospital readmissions in the first 10 years of life is 20 times more expensive for those babies born before 28 weeks' gestation than those born after 37 weeks' gestation (Petrou, 2003). This article addresses the role of infection in the prediction and antibiotics in the prevention of PTB.

THE AETIOLOGY OF PTB

The aetiology of spontaneous preterm labour (SPTL) and PTB is multifactorial but there is overwhelming evidence that infection is an important cause (Lamont and Fisk, 1993), probably accounting for up to 40% of cases (Lettieri et al, 1993). By the time a woman is admitted in preterm labour, knowing that infection is a possible cause may be unhelpful since there may be irreversible changes in the uterine cervix, which render futile those attempts to inhibit the progress of labour.

Pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, IL-8 and tumour necrosis factor alpha (TNF-α) are found in significantly increased concentrations in the amniotic fluid of women in SPTL with infection compared to women without infection. The presence of these cytokines in amniotic fluid and fetal blood has been shown to be associated with fetal and neonatal tissue damage to the brain and lung, resulting in bronchopulmonary dysplasia and periventricular leucomalacia. Babies born preterm in the presence of increased concentrations of white blood cells, IL-6 or IL-8 in amniotic fluid or funisitis are statistically significantly more likely to develop cerebral palsy by the age of 3 years (Yoon et al, 2000).

THE PREDICTION OF PTB

Nine cohort studies from Europe, USA and the Far East and three case-controlled studies from USA, Sweden and Australia have examined the association between bacterial vaginosis (BV) or BV-related organisms and the adverse outcome of pregnancy (Lamont, 2001). The majority of these studies show a statistically significant association between abnormal genital tract flora and adverse pregnancy outcome. Most important is the observation that the earlier in pregnancy at which abnormal genital tract flora was detected, the greater was the risk of an adverse outcome. A positive result from screening at around 26 weeks' gestation is associated with a 1.4–1.9-fold increased risk of PTB, whereas a positive result for screening in the second trimester is associated with a 2.0–6.9-fold increased risk of an adverse outcome (Lamont, 2001). In a longitudinal study in Indonesia, the risk of PTB was almost double for women with BV in early pregnancy (21%) compared to those women who developed the condition later in pregnancy (11%).

In a non pre-specified subgroup analysis of a randomized placebo controlled trial of clindamycin vaginal cream (CVC) to treat BV in early pregnancy and to reduce the incidence of PTB, some women had abnormal vaginal flora which subsequently reverted to normal (revertants) (Rosenstein et al, 2000). As a result, they were not entered into the trial but were followed up. The incidence of adverse outcomes in revertants was similar to those women with BV who received placebo – nearly one-third delivered preterm or suffered a late miscarriage. This suggests that whatever damage was caused by abnormal flora, this occurred early in pregnancy even though genital tract flora subsequently reverted to normal, emphasizing that antibiotics would have to be used early in pregnancy to reduce the incidence of PTB.

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THE USE OF ANTIBIOTICS IN THE PREVENTION OF PTB

There are five areas in which antibiotics may be helpful in preventing PTB, as shown in *Table 1*.

Prophylactically for women at increased risk of SPTL and PTB

A number of studies have examined the use of antibiotics for prevention of PTB in women identified as at risk of SPTL and PTB as a result of infection. Unfortunately, these studies have used different doses of different antibiotics by different routes of administration and regimens to women of varying risk and not surprisingly varying outcomes (Lamont and Chin, 1998).

The route of administration may be important. There is merit in using intravaginal antibiotics, since with BV, the vagina contains 1000-fold increase in the number of organisms. If, however, the imbalance of genital tract flora has existed from early pregnancy, systemic therapy may be necessary to eradicate organisms which have already accessed the decidua by ascending colonization. As yet, no study has combined oral and intravaginal antibiotics and this may result in greater success. Since abnormal genital tract flora in early pregnancy is associated with the greatest risk of a subsequent adverse outcome (late miscarriage or PTB) (Lamont, 2001), the gestational age at the time of treatment is important. Treatment after 20 weeks' gestation is rarely associated with a reduced incidence of PTB (Lamont, 2001).

The largest study of prophylactic antibiotics (Carey et al, 2000) showed no benefit from oral metronidazole but was criticized (Lamont, 2000) for a number of reasons, not least that no patients were treated before 16 weeks' gestation and most were treated after 20 weeks' gestation. Only 20% of women with BV were included in the study and nearly 1000 women were excluded for 'other' reasons. Women symptomatic for BV were excluded. Nearly 8 weeks could elapse from diagnosis of BV to initiation of therapy by which time the assessment of the degree of abnormal flora had changed in 25% of women. The response to placebo was 47%, which is unexplained and in contrast to the 10% observed in many other studies. Finally, the choice of metronidazole has been criticized since this is inactive against more fastidious organisms such as *Mycoplasma* or aerobes, both of which are associated with BV.

Two recently published studies have emphasized the importance of early treatment showing that clindamycin used either vaginally (Lamont et al, 2003) or orally (Ugwumadu et al, 2003) in early second trimester can significantly reduce the incidence of PTB by around two-thirds. The degree of abnormality of genital tract flora is also potentially important. Women with grade 3 flora on Gram stain (BV) responded better to CVC than those women with either grade 2 (intermediate) or grade 2 and 3 combined (abnormal flora) resulting in a greater reduction in the incidence of SPTL and PTB (Rosenstein et al, 2000).

Prophylactically for prevention of preterm prelabour rupture of the membranes

The literature on preterm prelabour rupture of the membranes (PPROM) is voluminous but has been reviewed in two meta-analyses (Mercer and Arheart, 1995; Egarter et al, 1996). These concluded that the use of antibiotics following PPROM could prolong pregnancy but did not reduce perinatal mortality and morbidity. Many of the studies reviewed were conducted at late gestational ages where the incidence of respiratory distress syndrome was low and perinatal death too rare for any benefit to be seen. Conversely, other studies were conducted at gestational ages as low as 20–23 weeks, which was too close to the limit of viability for a reduced incidence of respiratory distress to be evident. In a study where antibiotics were used between 24 and 32 weeks' gestation following PPROM, a significant reduction in perinatal mortality and morbidity was found, together with a reduction in maternal infectious morbidity and an increased latency and delay in delivery (Mercer et al, 1997). In women at risk of PPROM, prophylactic antibiotics reduce the subsequent incidence of PPROM (McGregor et al, 1990).

Delaying delivery in women in SPTL

A number of studies have shown latency when antibiotics were used in women in SPTL whereas others have shown no latency (Lamont and Chin, 1998; Lamont, 2001). Of those studies that did show latency, it may be relevant that four used antibiotics active against anaerobes compared to only one of the studies that showed no latency. Two studies stopped antibiotic treatment when

TABLE 1.
Use of antibiotics in the prevention of preterm birth

Prophylactically for women at increased risk of spontaneous preterm labour and preterm birth as a result of abnormal genital tract flora
Prophylactically for the prevention of preterm prelabour rupture of the membranes (PPROM)
Therapeutically to delay delivery in women who present with PPROM
Therapeutically to delay delivery in women who present in spontaneous preterm labour
Prophylactically for the prevention of early onset group B neonatal sepsis (not strictly prevention of preterm birth but an important association between infection, antibiotics and preterm birth and the mortality and morbidity of preterm babies)

amniotic fluid cultures proved positive so it is not surprising that antibiotics showed no latency. In another study that showed no latency, despite a power calculation requiring 2000 women to be recruited, only 277 took part and only 60% completed study medication (Lamont, 2001).

No consistent benefit has been found between antibiotic treatment and pregnancy prolongation and a decrease in the rate of perinatal mortality or morbidity. This may be because pregnancy prolongation in the presence of infection is undesirable and a relative risk for the mother and the fetus, particularly at later gestations. The lack of consistent benefit may also be explained by the different antibiotics used. Clindamycin and metronidazole are effective against anaerobes, in contrast to erythromycin and ampicillin. While erythromycin may be partially active against BV-related organisms, it cannot be fully activated in vaginal fluid. The combination of erythromycin and co-amoxiclav may be ineffective since this is a combination of bactericidal and bacteriostatic antibiotics whose actions may cancel out each other's effectiveness.

The ORACLE study reported on the effect of antibiotics and adverse outcome of pregnancy (Kenyon et al, 2001). Co-amoxiclav alone or in combination with erythromycin failed to prolong pregnancy, without significant benefit for the neonate. When the multicentre study was conceived, *Ureaplasma* was considered important in the neonatal mortality and morbidity associated with SPTL and PTB and this probably influenced the choice of erythromycin, which is not advocated in BV and is ineffective against anaerobes and *Mycoplasma hominis*. When the study started in 1994, the detrimental influence of BV on the outcome of pregnancy was apparent but BV was not considered as part of the study. Co-amoxiclav is effective against some anaerobes but not useful in BV. Clindamycin has a better spectrum of activity and was reportedly considered for the trial but the reason for its dismissal was not given.

In the multicentre study, subjective assessment of the risk of PTB was used rather than any objective measure of risk resulting from infection, since no screen for BV or other infections was performed. The ORACLE study reported that 89.9% and 84.6% of women with SPTL and intact membranes remained undelivered after 48 hours and 7 days respectively. Only 41% required beta-agonist therapy. The median gestational age at delivery was more than 38 completed weeks. Since infection is thought to occur in up to 40% of cases of SPTL, it appears that most women were not in SPTL and of those who were, probably less than half were in labour as a result of infection. Consequently it is not surprising that antibiotics did not improve outcome. In the ORACLE study, it is likely that the wrong antibiotics were used in the wrong women too late in pregnancy.

If antibiotics are to be helpful in reducing the morbidity and mortality associated with late miscarriage and PTB, they should be given early in pregnancy (Lamont et al, 2003; Ugwumadu et al, 2003) to women with the greatest degree of abnormal genital tract flora (Rosenstein et al, 2000). The results suggest that *Ureaplasma* does not cause neonatal disease because erythromycin was of little benefit, albeit that ureaplasmal infection was not assessed in the study. It would have been helpful to determine the extent to which BV was associated with neonatal disease as this might have influenced the antibiotic regimen.

Intrapartum chemoprophylaxis

While a heavy growth of group B haemolytic streptococcus (GBS) is associated with low birth weight and PTB, most literature on GBS considers the use of intrapartum chemoprophylaxis for prevention of early onset GBS infection. UK data are sparse although there are efforts to gather data from multidisciplinary groups in the UK (Hughes and McCartney, 2001). Up to 30% of pregnant and non-pregnant women are colonized by GBS.

The Centers for Disease Control and Prevention (CDC) in Atlanta, USA, estimated that there were 7600 cases of GBS sepsis (1.8% per thousand live births) in the USA in 1990, resulting in 310 deaths. The American Academy of Pediatricians, the American College of Obstetricians and Gynecologists and the CDC published revised guidelines for use of intrapartum chemoprophylaxis to prevent early onset GBS infection in the neonate (American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn, 1997). They recommended either screening or treating on the basis of risk.

If screening is to be used to achieve the best possible isolation rates (up to 27%), the combination of a low vaginal swab and rectal swab should be cultured in selective broth medium. A high vaginal swab will only detect 5% of GBS colonization. Screening should only occur after 35 weeks' gestation since, before this time, swabs do not reflect the genital tract flora at term. If swab results are not available or labour occurs before this time, prophylaxis should be given on the basis of risk factors (pyrexia, duration of ruptured membranes, prematurity). Women with positive screening results, those with incidental findings of GBS colonization or those with a history of previous invasive GBS disease should be given intrapartum chemoprophylaxis without further screening or treatment during the pregnancy. The only situation

where antibiotics are recommended during pregnancy for GBS is following diagnosis of a GBS urinary tract infection or if the patient is at high risk of delivering preterm as a result of heavy colonization with GBS (and a GBS urinary tract infection is indicative of heavy colonization).

Intrapartum chemoprophylaxis should be intravenous penicillin given 4-hourly, rather than ampicillin, which is more likely to produce resistant strains. For women allergic to penicillin, a combination of erythromycin and clindamycin is recommended (American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn, 1997). A study assessing the effectiveness and feasibility of the screening-based protocol found the prevalence of early onset GBS sepsis was 1.16 per thousand live births before and 0.14 per thousand after the policy was implemented ($P<0.001$), an 88% reduction in early onset GBS sepsis (Brozanski et al, 2000).

CONCLUSIONS

Infection is an important cause of SPTL and PTB. Abnormal genital tract flora in early pregnancy is a useful predictor of subsequent pregnancy loss in the form of late miscarriage or SPTL and PTB. The earlier in pregnancy the abnormal colonization is detected, the greater the subsequent risk of SPTL and PTB. Antibiotics can prevent SPTL and delay PTB but the evidence shows lack of consistent benefit. If antibiotics are to be successful, it is likely that they should be administered early in pregnancy, be active against those organisms associated with BV and be used in those women likely to mount a damaging immune response and those women with the greatest degree of abnormal genital tract flora. HM

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KEY POINTS

- Infection is an important cause of spontaneous preterm labour and preterm birth (PTB) in up to 40% of cases.
- It is possible to identify women at risk and predict an increased risk of late miscarriage and PTB by detecting abnormal genital tract flora in early pregnancy.
- The earlier in pregnancy at which abnormal genital tract flora is detected, the greater is the risk of an adverse outcome.
- There are a number of ways in which antibiotics may help to reduce the incidence of mortality and morbidity in preterm infants born early in association with infection.
- Antibiotics used prophylactically to prevent PTB in women at high risk as a result of infection are far more likely to be helpful if used early in pregnancy and in women with the greatest degree of abnormal genital tract flora.