Royal College of Obstetricians & Gynaecologists

Preterm Labour, Antibiotics, and Cerebral Palsy

Scientific Impact Paper No. 33
February 2013

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1. Introduction

The rate of preterm birth (pregnancy under 37^{+0} weeks of gestation) is 5–9% of all births in Europe, and 12–13% in the United States of America (USA); the rates in both continents increased up to 2008, partly due to the higher number of multiple births associated with assisted conceptions.[1] Recent data from Scotland shows nearly a quarter of these births are medically induced with the aim of improving maternal or fetal outcome.[2] Most (62%) of the remainder involve premature delivery after spontaneous preterm labour without premature rupture of membranes and a few (15%) are premature delivery following premature membrane rupture, although rates may vary between populations. For families struggling to cope with having a baby in special care, this will be one of the most difficult, emotional and stressful times of their lives,[3] regardless of the longer term outcome. The sequelae of preterm birth also pose significant challenges. Children born preterm are at increased risk of major disabilities such as cerebral palsy. The risk of cerebal palsy increases as gestation at birth decreases.[4] Many children who were born preterm without disability develop significant behavioural and educational difficulties.[5]

This paper will examine the evidence for:

- Prescribing antibiotics to symptomatic women and women with no evidence of infection in preterm labour (with and without ruptured membranes)
- The effects in both the short and longer term
- Whether there is a plausible link between infection and cerebral palsy
- The clinical implications of any findings
- Implications for the design of future maternity trials.

2. Cerebral palsy

Cerebral palsy is a group of disorders that can involve brain and nervous system functions such as movement, learning, hearing, seeing, and thinking. It is the most common cause of motor disability in childhood, with a prevalence of 1.5–3 cases per 1000 births.[6] The risk of cerebral palsy is inversely proportional to gestational age; the prevalence of cerebral palsy is 80 times higher in infants born prior to 28 weeks of gestation compared to those born at term. Currently, preterm birth is the strongest known risk factor for cerebral palsy.[7]

3. The link between infection and cerebral palsy

Infection/inflammation is commonly associated with preterm birth (particularly when the membranes have ruptured) especially less than 30 weeks of gestation[1] and must therefore be considered to contribute, either directly or indirectly, to the high mortality and neurological morbidity in this group.[1,8] The high risk of brain injury in preterm infants could be directly related to the intrauterine hostile inflammatory environment,[9,10] in addition to the effects of the complicated period of neonatal intensive care following preterm birth. Although a number of studies do not report that infection/inflammation is associated with central nervous system injury and cerebral palsy,[11,12] a direct effect of intrauterine infection/inflammation is supported by studies showing a higher risk of brain injury in infants born preterm with spontaneous onset of labour (high frequency of infection) compared with physician–initiated delivery (low frequency of infection).[13,14] Furthermore, funisitis (inflammation of the connective tissue of the umbilical cord)[15,16] high cytokines (IL–6, IL–8, TNF–α, IL–1β) in amniotic fluid and fetal blood are associated with white matter injury and cerebral palsy.[17–19] A recent systematic review demonstrated that clinical chorioamnionitis is associated with white matter injury and cerebral palsy (12 studies included, RR 1.9, 95% CI 1.5–2.5), and histological chorioamnionitis with periventricular leukomalacia (3 studies, RR 1.6, 95% CI 1.0–2.5).[20,21] Infection/inflammation may not exert adverse effects alone but experimental

and clinical studies suggest that it may sensitise the immature brain to hypoxia–ischemia and other insults demonstrating the complexity of this process.[22,23] Furthermore, recent work suggests there may be a link between fetal infections and other neurological and psychiatric conditions during childhood and even in adults.[24] Although a causal link has been proposed between antibiotics and cerebral palsy, no direct association has been demonstrated.[25]

4. Short term effect of antenatal antibiotics on preterm birth

Subclinical infection is implicated in a large proportion of preterm births, so theoretically, the acute use of antibiotics could eradicate the infection, prolong the pregnancy and improve neonatal outcome. Alternatively, antibiotics might suppress the infection, thus prolonging the pregnancy, but leaving the fetus in a hostile inflammatory environment.

4.1 Asymptomatic women at risk of preterm labour

A recent meta–analysis of antibiotic treatment during the antenatal period for asymptomatic women at risk of preterm birth showed no reduction in preterm delivery.[26] 17 trials were included; 12 trials identified women at risk by abnormal vaginal flora, 3 trials studied women at high risk from a previous preterm birth and 2 trials recruited women based on positive fetal fibronectin status. There has been the suggestion that antibiotics may increase preterm birth in these circumstances,[27] and routine treatment is therefore not recommended.

Bacterial vaginosis has been confirmed as a risk factor for preterm birth and maternal infectious morbidity and a strong risk factor for miscarriage,[28] yet clinical trials of antibiotic therapy during the antenatal period to reduce these complications have yielded conflicting results;[29] antibiotic therapy is not routine practice.

In summary, the current evidence (which excludes long term follow up of the children) does not support the routine use of antibiotics in the antenatal period for asymptomatic women.

4.2 Symptomatic women in preterm labour

Evidence of the effects of administration of antibiotics in the acute situation, after the diagnosis of preterm labour (with or without preterm premature rupture of membranes [pPROM]), came from two Cochrane reviews which were dominated by the Overview of the Role of Antibiotics in the Curtailment of Labour and Early Delivery (ORACLE) studies. These studies randomised 4826 women with pPROM[30] and 6295 women with suspected preterm labour from 15 countries.[31]

The review of antibiotics for women with preterm rupture of the membranes was updated in 2010[32] and included 22 trials, involving 6800 women and babies. The use of antibiotics following pPROM is associated with statistically significant reductions in chorioamnionitis (RR 0.66, 95% CI 0.46–0.96) and a reduction in the numbers of babies born within 48 hours (average RR 0.71, 95% CI 0.58–0.87) and 7 days of randomisation (RR 0.79, 95% CI 0.71–0.89). The following markers of neonatal morbidity were reduced: neonatal infection (RR 0.67, 95% CI 0.52–0.85), use of surfactant (RR 0.83, 95% CI 0.72–0.96), oxygen therapy (RR 0.88, 95% CI 0.81–0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.81, 95% CI 0.68–0.98), although no reduction in perinatal mortality was observed (RR 0.93, 95% CI 0.76–1.14) Co–amoxiclav was associated with an increased risk of neonatal necrotising enterocolitis (RR 4.72, 95% CI 1.57–14.23).[32]

The second Cochrane review of the routine use of antibiotics for women with spontaneous preterm labour (with intact membranes) was updated in 2002.[33] Meta–analysis of 11 included trials (7428 women enrolled) showed a reduction in maternal infection with the use of prophylactic antibiotics (RR 0.74, 95% CI 0.64–0.87) but failed to demonstrate benefit or harm for any of the pre–specified neonatal outcomes. Indeed, there was a suggestion of harm with a near significant increase in neonatal mortality in the antibiotic group (RR 1.52, 95% CI 0.99–2.34).[33]

5. Longer term effects of antibiotics on childhood outcomes

The most robust evidence on the role of antibiotics (administered in pregnancy) on longer term childhood outcomes comes from the ORACLE Children Study (OCS) which followed–up surviving children at 7 years of age in the UK using a parent–report postal questionnaire.[34] The primary outcome was defined as the presence of any level of functional impairment using the Multi Attribute Health Status (MAHS) classification system.[35] Secondary outcomes included a range of medical and behavioural outcomes. Educational attainment of children at 7 years of age was assessed for those residents in England using results from National Curriculum tests at Key Stage 1.

For children whose mothers had pPROM, the prescription of antibiotics seemed to have little effect on the health and educational attainment of children at 7 years[36] which was surprising since antibiotics might have been expected to improve clinical outcomes in this group as positive amniotic fluid cultures are found in 32% of women at presentation,[37] and in as many as 75% during subsequent labour.[38] The reasons for this are not clear but might be linked to the length of antibiotic exposure which in this group of women was fairly short, since about 60% gave birth within a week.[30] There is also evidence that antibiotics neither eradicate nor prevent intra–amniotic infection.[39]

For children whose mothers had spontaneous preterm labour the prescription of erythromycin (with or without co-amoxiclav) was associated with an increase in the proportions of children with any level of functional impairment from 38% to 42% (OR 1.18, 95% CI 1.02–1.37). Similarly proportions of children with cerebral palsy increased from 1.7% to 3.3% (OR 1.93, 95% CI 1.21–3.09) associated with erythromycin and from 1.9% to 3.2% (OR 1.69, 95% CI 1.07–2.67) with co–amoxiclav. There was a suggestion that more children who developed cerebral palsy had been born to mothers who had received both antibiotics.[40]

It is not clear why receipt of antibiotics increased the risk of functional impairment and cerebral palsy. Rates of subclinical infection in this group are found to be relatively low at 13–22%, and an absence of benefit is therefore not unexpected, but evidence of harm is surprising.

A number of pathways have been suggested but none is established. The most obvious is a direct effect of the antibiotics, but this seems unlikely as it was not seen in the pPROM group. Length of exposure to antibiotics to this group was fairly long, with only 15–20% giving birth within 7 days.[31] An episode of preterm labour which settles could reflect an infective episode, where maternal defences – facilitated by the antibiotics – overcome the insult, thus prolonging the pregnancy, but not necessarily resolving the associated intrauterine and fetal inflammation. A continuing inflammatory environment could lead to fetal brain injury and thereby cerebral palsy. Finally, it is also possible that the episode of spontaneous preterm labour was not associated with infection, but with other pathologies associated with the so called 'preterm parturition syndrome'.[38]

A recently published nested study[41] investigated the profile of impairment, recorded by parents and physiotherapists, for children in the OCS, and contrasted outcomes with those in a population cerebal palsy registry called *4*Child (Four countries database of cerebral palsy, vision loss and hearing loss in Children).[42] Cerebral palsy was more prevalent among OCS children compared to *4*Child (standardised morbidity ratios: spontaneous preterm labour group: 3.12, 95%CI 2.47–3.87); preterm rupture of membranes (pPROM) group: 1.56 (95% CI 1.24–1.92). Of the children with cerebral palsy in the spontaneous preterm labour group, more were born >32 weeks of gestation (71%), compared to pPROM (30%); prevalence was higher in this spontaneous preterm labour group than pPROM or *4*Child. OCS children with cerebral palsy tended to have similar distributions of neuroimpairment but with less severe motor impairment or associated vision and hearing problems compared to *4*Child. The pattern of cerebral palsy for both pPROM and spontaneous preterm labour groups was similar and milder than in the general population, but with increased risk independent of gestation. These results have led to further speculation that, for the antibiotic treated spontaneous preterm labour group; this is

related to an ongoing low–grade antenatal neurological insult. This is because despite later birth, the injury is consistent with a more preterm origin.

6. Opinion

6.1. Clinical implications in practice

The evidence relates to women with subclinical infection and it is important that women with clinical evidence of infection are treated with antibiotics since clinical chorioamnionitis remains an important cause of maternal, fetal and neonatal death. The evidence reviewed suggests that women with spontaneous preterm labour with intact membranes and no evidence of overt infection should not routinely be prescribed antibiotics because there is evidence that antibiotics given under these circumstances increase the risk to their offspring of functional impairment and cerebral palsy.

The decision to prescribe antibiotics routinely for women with pPROM and without evidence of overt infection is not clear cut, although current guidance endorses the routine use of antibiotics for women with pPROM[43] in the acute situation. Benefits in some short–term outcomes (prolongation of pregnancy, reductions in infection, need for surfactant, oxygen therapy and fewer babies with abnormal cerebral ultrasound before discharge from hospital) should be balanced against a lack of evidence of benefit for others, including perinatal mortality, and longer term outcomes. Given the lack of any long–term demonstrable benefit, a decision not to prescribe antibiotics to women with pPROM without evidence of infection would also be reasonable, especially in a high-income setting where support is available. There may be a stronger argument for routine antibiotic treatment in low income settings, where access to other interventions (antenatal steroids, surfactant therapy, ventilation and antibiotic therapy) may be low.

Subgroup comparisons undertaken as part of the Cochrane review[32] did not indicate a particular antibiotic to be the more effective. On the other hand, erythromycin has been recommended as an antibiotic of choice after being tested by the ORACLE.[43] Co–amoxiclav should be avoided in women at risk of preterm delivery due to increased risk of neonatal necrotising enterocolitis. Indeed, where organisms are sensitive to other antibiotics, it would seem sensible to avoid using co–amoxiclav in pregnancy. Antibiotics should not be prescribed unless a definite diagnosis of pPROM has been made. The diagnosis of pPROM is not always clear cut; a policy to prescribe antibiotics for all women with suspected pPROM will inevitably lead to some women with spontaneous preterm labour, but with intact membranes, being prescribed antibiotics in the belief that their membranes have ruptured. Consequently, these women would be given antibiotics which would then expose their child to an increased risk of cerebal palsy.

Women with spontaneous preterm labour and intact membranes may be considered at increased risk of Group B Streptococcus infection (GBS). However, the RCOG[44] does not recommend routine prophylaxis in this situation. These women are not dissimilar to the women in the ORACLE study; they are admitted in spontaneous preterm labour and at the time of assessment, it is unclear whether they will go on to give birth.

6.2. Implications for the design of further obstetric trials

The ORACLE studies strengthen the argument that short–term outcomes are not sufficient to assess the full impact of the interventions given to pregnant women to improve outcome. The need for more comprehensive, longer and more detailed follow–up of such interventions needs to be the default position for both clinicians and funders, with clear justification given for follow–up not being required. Given its importance to parents and clinicians, assessment of neurodevelopment of the child, including rates of cerebral palsy are key outcome measures.

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This Scientific Impact Paper was produced on behalf of the Royal College of Obstetricians and Gynaecologists by:
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Conflicts of interest: Dr S Kenyon RM PhD led the ORACLE Trial and Children Study and leads the Cochrane review of Antibiotics for preterm rupture of the membranes.

The Scientific Advisory Committee lead reviewer was: Mr JP Ash MRCOG, Exeter.

The final version is the responsibility of the Scientific Advisory Committee of the RCOG.

The reviewing process will commence in 2016, unless otherwise indicated.

