Neonatal morbidity associated with chorioamnionitis in premature under 1,500g

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Respiratory distress syndrome (RDS), neurological damage ((intraventricular haemorrhage (HIV), periventricular leukomalacia LPV, cerebral palsy (CP)), sepsis, poor neurological outcome and increased rate of perinatal deaths have been related to the presence of Chorioamnionitis (CA). Chorioamnionitis activates the inflammatory pathway and the biochemical mediators would be associated with the premature labour and may cause the possible damage of the foetus and newborn infant. These mediators could be found in other situations: premature rupture of membranes (PROM) and premature labour, which can be confounding factors.

To find out if there is any correlation between maternal clinical chorioamnionitis and acute morbidity and mortality in premature newborn infants, a multicentre prospective case-control study was designed with premature infants ≤ 1500g matched by gestational age. There were 165 cases and 163 controls. A significantly higher percentage of cases than controls required intubation (53% vs. 35.8%), had normal intrauterine growth (98.1% vs. 84.7%), were born in the tertiary centre (inborn) (95.1% vs. 89.1%), from single gestations (76.4% vs. 65.6%) and vaginal delivery (47.3% vs. 33.3%), showed a lower Apgar score at 5 min, and presented a higher rate of early-onset sepsis (10.4% vs. 1.2%). Older maternal age (32.5 vs. 30.8 years), premature labour (67.3% vs 25.8%), premature rupture of membranes (61.3% vs. 25.8%), and antibiotic treatment (88.5% vs 52.3%) were significantly more frequent among cases than controls.

Follow up during 2 years is being performed in both groups to compare neuropsychological development.

In summary if gestational age is controlled, chorioamnionitis is associated with neonatal depression and early sepsis but not with other complications of the prematurity.
Mechanisms of infection-associated preterm labor: Influences of fetal sex

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Preterm birth is clearly recognized as a syndrome characterized by different pathophysiologic pathways which have a temporal dependency. Stress pathways involving activation of the maternal and/or fetal hypothalamic-pituitary-adrenal axis appear to predominate later in gestation whereas preterm birth associated with inflammation or infection has a higher incidence earlier in gestation. The infection-driven pathway involves up-regulation of the prostaglandin-cytokine cascade, and we have recently shown suppression of key steps in this pathway by probiotic lactobacilli GR-1 supernatant. It has been reported that the incidence of preterm birth, and preeclampsia are higher in pregnancies carrying a male fetus. We found that effects of lipopolysaccharide (LPS) on placental trophoblast cells from pregnancies carrying a male fetus were greater than cells carrying a female fetus and this correlated with enhanced expression of prostaglandin synthase-2 enzyme. Conversely, expression of the prostaglandin metabolizing enzyme (PGDH) and the anti-inflammatory cytokine (GCSF) was greater in cells from pregnancies carrying a female fetus. While this information suggests the mechanism of a gender-associated effect on the incidence of preterm birth, the impact of other factors on these pathways and the temporal dependence of the gender-related incidence of preterm birth requires further elucidation.
Antibiotics for the prevention of preterm birth

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The ORACLE study, its seven year follow up, the meta-analyses and systematic reviews which include it, together with a number of editorials and commentaries, often suggest that antibiotics used to prevent preterm birth (PTB) are ineffective and may cause more harm than good. This conclusion is incomplete. A more accurate conclusion would be that the use of erythromycin or co-amoxiclav, or both, given to women in threatened preterm labor (PTL) with intact membranes, without evidence of infection as a cause of the PTL, may decimate normal genital tract flora late in pregnancy and therefore cause more harm than good for the following reasons:

a) Erythromycin and co-amoxiclav are ineffective against those organisms (bacterial vaginosis [BV] and its related organisms) known to be associated with PTL and PTB.

b) It is a self fulfilling prophecy that antibiotics would be ineffective under such circumstances since those women who were in genuine PTL which led to PTB were not infected (no objective evidence of abnormal colonization was sought; women with clinical infection were excluded from the study; by the investigators own estimate, only 13-22% of participants had what they considered sub-clinical infection).

c) The antibiotics were administered at a time in pregnancy when the inflammatory cascade which constitutes the labor process will have resulted in irreversible changes in the cervix and myometrium.

In contrast, a number of studies using an antibiotic active against BV or BV revealed organisms (clindamycin) given to women with objective evidence of abnormal genital tract colonization (BV on gram stain), early in pregnancy, before infection and inflammation have caused irreversible damage, (the majority of women were treated before 20 weeks gestation) have demonstrated a 40-60% reduction in the incidence of PTB. Less harm will be done by correcting abnormal colonization in early pregnancy than by causing decimation of normal flora late in pregnancy.

Nevertheless, the long term effects of antibiotics remains unknown and the use of antibiotics in pregnancy should be strictly monitored.
Perinatal antibiotics and nosocomial infections in very low birth weight infants

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The reduction of neonatal group B streptococcal early-onset infections by intrapartum antibiotics and the association between chorioamnionitis and cerebral palsy in preterm infants have increased the popularity of administration of antibiotics to pregnant women with preterm labor, as well as to preterm infants born after preterm labor. There are, however, points of concern:

(1) Prepartum antibiotics are effective against group B streptococcal bacteremia but there is no evidence for an effect of antibiotics given prior to delivery on gram-negative or enterococcal bacteremia (Gilbert-RE BJOG 2005)

(2) In preterm infants, rates of infections with gram-negative enterobacteriaceae increase alongside increased prepartum administration of ampicillin (Bizzarro-MJ Pediatrics 2008)

(3) In preterm infants, there is an emergence of infections with gram-negative enterobacteriaceae resistant to ampicillin alongside increased prepartum administration of ampicillin (Bizzarro-MJ Pediatrics 2008)

(4) Beta-lactam antibiotics given prior to birth appear to increase the risk of neonatal necrotizing enterocolitis (Kenyon-SL Lancet 2001).

(5) Prolonged duration of empirical antibiotics after birth is associated with increased rates of necrotizing enterocolitis or death (Cotton-CM Pediatrics 2009)

(6) Empiric use of third-generation cephalosporins is associated with increased neonatal death (Clark-RH Pediatrics 2006).

(7) Antibiotics given to women with preterm labor may increase the risks cerebral palsy and functional impairment of children assessed at school age (Kenyon-SL, Lancet 2008)

These data call for the judiciously restricted use of antibiotics both in women with preterm labor and in infants born preterm.