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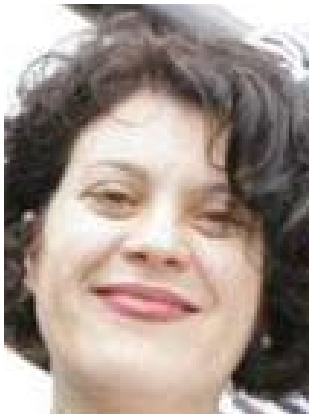
Intrauterine infection: preterm birth and pulmonary impact



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… chorioamnionitis is a condition that cannot be diagnosed accurately until after the event, its cause appears multifactorial and non-specific, and treatment cannot be designed until after the cause is found – and then it is too late. Where are we going wrong? There is a long road ahead that must be taken because, in a time of low perinatal morbidity and mortality, the disorder is rapidly assuming an important role, if only by default. No longer is chorioamnionitis merely an interesting finding for pathologists to demonstrate to their colleagues [1].

This is an excerpt from a letter published anonymously in the *Lancet* in 1989. Acute chorioamnionitis is the histological hallmark of intrauterine infection and remains today the focus of intense, and increasing, research interest. This interest is underpinned by the association of chorioamnionitis with preterm delivery. Extreme prematurity is the fundamental, unresolved problem in perinatal medicine, has associated high morbidity and mortality, and accounts for a significant proportion of the health expenditure in the developed world [2]. The preterm delivery rate is increasing in Australia, from 6.8% in 1991 to 8.1% in 2005 [1]. Advancement in intensive care practice has increased survival of very preterm neonates, and this has meant an increase in diseases that are directly related to prematurity, such as cerebral palsy and neonatal chronic lung disease (CLD).

Epidemiology

Histological studies of the placentae of live-born infants consistently report chorioamnionitis to be most common in preterm populations, with the highest rates in the lowest gestational age groups, and the predominance in pregnancies less than 32 weeks' gestation. A recent Australian study of 3928 preterm infants between 20 -34 weeks' gestation demonstrated the clear inverse relationship between histological chorioamnionitis and gestation, with the incidence of chorioamnionitis in those born at 20-24 weeks 66%, decreasing to 16% at 34 weeks [2].

Pathogenesis of intrauterine infection

There are four potential pathways for intrauterine infection. The first and most common route is ascending infection from the lower genital tract. Infrequently, infection can occur via retrograde passage of organisms from the peritoneal cavity via the fallopian tubes, haematogenously from the maternal circulation and from invasive antenatal diagnostic procedures, such as amniocentesis [2].

Ascending intrauterine infection

After overgrowth in the vagina and cervix, organisms gain access to the space between the amniotic membranes and the uterus to cause localised inflammation, and this can cause rupture of the membranes. Further extension of infection may

follow, and/or the organisms can cross the amniotic membranes (intact or ruptured) to infect the amniotic fluid. Membrane rupture can also occur at this point, when there is infection and inflammation on both sides of the membranes [2]. Histologically this initial inflammatory response to ascending infection is seen as infiltration of predominantly maternal polymorphonuclear leucocytes (PMNLs) into the membranes (chorion and amnion). This is termed chorioamnionitis.

A fetal inflammatory response occurs in response to exposure of the umbilical cord to infected amniotic fluid. The infecting bacteria and bacterial products in the amniotic fluid activate the fetal white cells in the blood vessels in the umbilical cord. This results in PMNLs migrating from the intravascular space of the umbilical vessels into the vessel walls, and potentially beyond the vessel walls to the cord stroma. This fetal inflammatory response to infected amniotic fluid can occur without fetal infection and contributes to labour onset and delivery. Less commonly, fetal infection may occur via by aspiration or ingestion of infected amniotic fluid. Alternatively, skin or mucous membrane infection can occur in the fetus after contact with infected amniotic fluid, with the potential for the development of fetal systemic infection. It is also possible for fetal infection to occur via spread from the decidual layers to the intervillous space [2].

Thus the inflammatory responses to ascending intrauterine infection are of both maternal and fetal origin and occur as part of a continuum, with the initial inflammatory response of maternal origin and a fetal inflammatory response subsequent. This explains the relationship of preterm rupture of membranes (PROM) with intrauterine infection. Evidence supports the relationship of intrauterine infection as a likely cause and not an effect of prematurity and PROM. This hypothesis, based on an understanding of pathogenesis, is a departure from the earlier and largely discarded supposition that chorioamnionitis is a complication of both preterm labour and PROM.

Microbiology

The microbiological findings are discussed in this issue by Dr Helen McDonald.

Diagnosis

The clinical hallmarks of chorioamnionitis include uterine tenderness, tachycardia, fever and a raised maternal white cell count. However, in the majority chorioamnionitis is asymptomatic until labour onset or rupture of membranes. In the current clinical setting, histological examination of the placenta, extra-placental membranes and umbilical cord is often the mainstay of diagnosis.

Clinical implications

Intrauterine infection is known to be associated with the onset of preterm labour and delivery and with a decreased incidence of neonatal respiratory distress syndrome (RDS). RDS occurs in preterm infants because of structural and functional lung immaturity. RDS occurs in 60-80% infants born at <28 weeks' gestation, and 10-15% of infants 32-36 weeks' gestation at delivery [2]. Treatment for RDS includes mechanical ventilation which can result in lung injury from a combination of barotrauma and oxygen toxicity. This lung injury predisposes the infant to CLD. Further, there is a reported association of intrauterine infection and CLD which is controversial and discussed briefly below. Intrauterine infection is also reported to be associated with sepsis in the newborn, as are adverse neurological outcomes which will not be discussed here.

Intrauterine infection and preterm labour

Intrauterine bacterial invasion triggers preterm labour via a number of interacting pathways [2]. The bacterial endo and exotoxins stimulate the uterine lining (decidua) and fetal membranes to produce a range of proinflammatory cytokines including tumour necrosis factor (alpha), interleukin-1, interleukin-6, interleukin-8 and granulocyte colony stimulating factor. Both the bacterial products and the proinflammatory cytokines induce prostaglandin production by the chorioamnion, placenta and decidua, and recruit and activate PMNLs. These activated PMNLs synthesise and release a range of bioactive products including collagenases and elastases that degrade connective tissue [3].

The combined effect of prostaglandins and collaganase and elastase play a key role in initiation of both labour at term [4], and preterm labour and delivery [2] via a similar final common pathway. Increased prostaglandin concentration stimulates uterine contractions and the collagenases and elastases weaken the chorioamnionitic membranes and remodel and soften the cervical collagen [2, 3].

It is thought that spontaneous term labour is initiated via the fetal hypothalamic-pituitary-adrenal axis (HPA) [4]. Studies in humans indicate that the fetal HPA axis is activated by intrauterine infection [4]. The HPA axis is part of the peripheral stress system. Interleukin-1, interleukin-6 and tumour necrosis factor (alpha) independently and, in combination synergistically, activate the HPA axis during the stress of inflammation.

The end products of HPA activation are glucocorticoids which inhibit the production and effect of inflammatory cytokines [5]. Glucocorticoids also accelerate maturation of the fetal lung physiologically, morphologically and biochemically [6]. This is the biological rationale for both the reduction of RDS in the presence of intrauterine inflammation, and therapeutic maternal antenatal steroid administration in preterm labour.

Intrauterine infection and pulmonary implications

In 1969 Liggins demonstrated that glucocorticoids decreased RDS and enhanced survival in preterm lambs [3]. Studies have shown that the presence of chorioamnionitis is associated with a significant decrease in the incidence of RDS. A very recent study of preterm newborns investigated the impact of fetal versus maternal inflammatory responses on the incidence of RDS. A greater reduction in odds for RDS with found with a fetal inflammatory response (adjusted OR 0.23, 95% CI 0.15-0.35) than with a maternal inflammatory response (chorioamnionitis) (adjusted OR 0.49, 95% CI 0.31-0.78) [4]. This indicates a dose response relationship between the degree of inflammatory response and reduction in RDS [4].

Early studies showed chorioamnionitis to be associated with CLD; however, recent studies in the current clinical context have

shown no relationship or a protective effect [3-6]. The postulation that intrauterine infection reduces RDS but increases CLD is difficult to reconcile biologically, as RDS and its treatment, and mechanical ventilation and oxygen therapy independently, are on the causal pathway for CLD [6].

Intrauterine infection, neonatal sepsis and CLD

An immature immune system predisposes the preterm infant to infection. Neonatal sepsis is defined as early or late onset. This is because infection occurring early after delivery is often associated with transmission from the mother (vertical transmission), whereas late onset neonatal sepsis is generally nosocomially acquired. Australian multi-centre data show the incidence of late onset sepsis in infants <1000 grams to be 22.6%, and decreasing with increasing gestation [7].

There is conflicting evidence regarding the association of intrauterine infection and neonatal sepsis, regardless of onset. However, neonatal sepsis has been shown to be an independent risk factor for CLD. This has significant implications given that the majority of neonatal sepsis is nosocomially acquired.

Future research

Many questions remain regarding intrauterine infection and its impact on the fetus and neonate. What is clear is that the most crucial relate to primary prevention of this disease, and to the improvement in infection control in the newborn intensive care.

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Call for Nominations – President-Elect

Associate Professor Keryn Christensen's term as Immediate Past President concludes at the Annual General Meeting which will be held in July 2009. In accordance with the ASM Constitution, nominations are invited for the position of President-Elect of the Society, to take office in July 2009 following the Annual General Meeting. The President-Elect will hold office until the next Annual General Meeting, to be held in July 2010, at the conclusion of which he or she will become President.

Candidates for election to the position of President-Elect shall be Honorary Life Members, Financial Fellows, Members or Senior Associate Members of the ASM and be proposed and seconded by Honorary Life Members, Financial Fellows, Members or Senior Associate Members of the Society. Nominations must have the written consent of the candidate.

Nominations must be received by the ASM National Office Manager before 5pm Wednesday 31 December 2008. Please use the nomination for the position of President-Elect form, which is set out opposite.

Nomination for the position of President-Elect of the Australian Society for Microbiology Inc

We the undersigned wish to nominate:

_____

of: _____

for the position of President-Elect of the Australian Society for Microbiology Inc.

Proposer (FASM / MASM / SASM / Honorary Life Member)

Name: _____

Signature: _____

Seconder (FASM / MASM / SASM / Honorary Life Member)

Name: _____

Signature: _____

I accept this nomination for the position of President-Elect of the Australian Society for Microbiology Inc.

Name: _____

Signature: _____

Date: _____

Address your envelope as follows:
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