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Clinical and experimental information indicate that fetal exposure to inflammation can induce lung maturation. This inflammation may be chronic and indolent.

Intrauterine inflammation most commonly presents as chorioamnionitis, which is defined as inflammation caused usually by bacterial infection of the chorion, amnion, and placenta. Intrauterine inflammation is one of the most common antecedents of premature birth [20]. This is likely to be a conservative estimate due to the difficulty associated with detecting chorioamnionitis using conventional culture techniques [20]. Chorioamnionitis Chorioamnionitis may manifest as a clinical condition defined by maternal fever, leukocytosis, tachycardia, uterine tenderness, and preterm rupture of membranes [25 , 26]. The diagnosis of clinical chorioamnionitis is most commonly made during labour near or at term. Highly virulent organisms likely cause clinical chorioamnionitis [27]. Before 30 weeks of gestation, clinical chorioamnionitis is usually diagnosed after attempting to delay preterm delivery or with preterm prolonged rupture of the fetal membranes [27]. Alternatively, chorioamnionitis can be subclinical, which is considered the most common manifestation and is defined histologically by inflammation of the chorion, amnion, and placenta [26 , 28]. Histological chorioamnionitis is associated with organisms considered to be of low virulence. Deliveries prior to 30 weeks of gestation are typically associated with histological chorioamnionitis [22]. Histological diagnosis occurs after delivery and is based on a semiquantitative assessment of inflammatory cells in the chorioamniotic membranes, umbilical cord in cross-section , and placental disc. However, variability in the assessment criteria for the diagnosis of histological chorioamnionitis exists within the literature [29]. This may influence the results of studies of histological chorioamnionitis, preterm delivery, and outcomes. The majority of fetuses exposed to chorioamnionitis develop a systemic inflammatory response known as the fetal inflammatory response syndrome FIRS [30 , 31]. FIRS can itself be categorised as clinical or subclinical. LPS is capable of inducing an inflammatory cascade which is the dominant feature of clinical and subclinical chorioamnionitis , in the absence of bacterial infection. Intracervical LPS administration to pregnant rats and rabbits has been used to model clinical chorioamnionitis [33 , 34]. Injection of LPS into the cervix causes high-grade placental inflammation [33 , 34] associated with a maternal systemic inflammatory response that extends to the fetus and causes moderate to high rates of fetal loss [34 â€” 37]. The consequences of this experimental intervention mimic the most severe forms of clinical chorioamnionitis. Other models of clinical chorioamnionitis include intravenous and intraperitoneal administration of LPS to pregnant animals. Intra-venous administration of LPS to pregnant sheep causes maternal pyrexia, septicaemia, and increased uterine contractility [38]. The effects on the fetus include systemic inflammation, increased serum cortisol levels, preterm delivery, and death [38 , 39]. In mice, maternal intravenous LPS exposure causes systemic and placental inflammation and altered placental vascular function [41 , 42]. Fetal demise due to administration of LPS to pregnant mice is dose dependant [42]. Intraperitoneal injection of LPS to pregnant rodents elicits a maternal systemic inflammatory response that causes placental inflammation, FIRS [43 â€” 45], and, in some cases, fetal death [46]. Interestingly, rats seem to be more resistant to inflammation-induced preterm birth than mice [46]. This does not present with clinical symptoms in the pregnant animal and causes a low-grade FIRS that is usually tolerated without fetal demise [47 , 50 , 51]. Microbial Invasion of the Amniotic Cavity Microbiota may invade the amniotic cavity via several pathways, outlined previously [20 , 23 , 52]. Microbes proliferate in the amniotic fluid and subsequently invade the amnion. In severe cases choriodecidual invasion may occur [53]. Thus, microbial invasion of the amniotic cavity precedes widespread infection of the chorioamniotic membranes. Other modes of microbial invasion of the amniotic cavity include contamination during invasive obstetric procedures such as amniocentesis or

chorionic villous sampling; haematogenous dissemination through the placenta; and retrograde invasion from the peritoneal cavity through the fallopian tubes. Traditionally, the microorganisms most commonly associated with infection of the amniotic cavity were species of Ureaplasma and Mycoplasma such as Ureaplasma urealyticum, Ureaplasma parvum, and Mycoplasma hominis [54 , 55]. Due to recent advances in microbial detection, the range of microbial colonies in the amniotic cavity is now regarded as more diverse. Fusobacterium, Sneathia, and Leptotrichia have each been identified as novel and highly prevalent bacterial antecedents of chorioamnionitis [56 , 57]. Whilst there is a wide range of data describing the role of bacterial invasion of the intrauterine space in premature labour, data describing the role of viruses and fungi in premature labour are limited. There is some evidence demonstrating viral and fungal invasion of the amniotic cavity in the pathogenesis of intrauterine inflammation. Specifically, cytomegalovirus, parvovirus, adenovirus, and the fungal phenotype Candida albicans have been detected in amniotic fluid samples [58 â€” 60]. There are data to suggest pregnant women with hepatitis B virus are at increased risk of premature labour [61 , 62]. Furthermore, intrauterine injection of polyinosinic-cytidylic acid Poly I: C , a viral mimetic, causes preterm birth in rodents [63], whereas no effects of intra-amniotic Poly I: C were observed in sheep [64]. Bacteria that invade the choriodecidual space release endotoxins and exotoxins, which are recognised by Toll-like receptors TLRs on the surface of leukocytes, and dendritic, epithelial, and trophoblast cells [65 , 66]. Inflammatory cytokines stimulate the production of prostaglandins and initiate neutrophil chemotaxis, infiltration, and activation, resulting in the synthesis and release of metalloproteases [54]. Prostaglandins stimulate uterine contractions while metalloproteases cause cervical ripening and degrade the chorioamniotic membranes causing them to rupture [67]. Prostaglandins produced in the amnion are normally inactivated by prostaglandin dehydrogenase released by the chorionic tissue, thus preventing prostaglandins reaching the myometrium and causing uterine contractions [23]. Infection of the chorion inhibits the activity of prostaglandin dehydrogenase, thereby allowing prostaglandins to reach the myometrium and cause premature contractions [68]. In human pregnancies affected by chorioamnionitis, FIRS increases the production of corticotrophin releasing hormone CRH from both the fetal hypothalamus and the placenta [23]. Increased CRH causes the fetal adrenal glands to increase cortisol production, which stimulates placental prostaglandin synthesis and myometrial contractility [69]. However, in studies using a sheep model of histological chorioamnionitis that displays many characteristics of the human condition, Nitsos et al. Chorioamnionitis Affects Multiple Organ Systems Chorioamnionitis, together with the associated FIRS, is an antecedent of preterm labour and a major contributor to neonatal morbidity [23 , 54 , 55 , 70 , 71]. The consequences of intrauterine inflammation on fetal and neonatal cardiopulmonary, cerebral, and renal systems are described in the following sections. Heart Evidence from humans and experimental models of chorioamnionitis suggest intrauterine inflammation results in abnormal fetal cardiac function. These clinical observations are supported by animal studies that have demonstrated reduced descending aorta blood flow velocities in fetal rats following intracervical administration of LPS to pregnant dams [33]. In fetal mice intra-amniotic LPS exposure caused inflammation and impaired contractility and relaxation of the myocardial tissue [75]. Increased cardiac afterload and reduced cardiac output have also been observed in fetal mice after maternal LPS administration [41]. Collectively these studies indicate that exposure to inflammation in utero not only impairs cardiac function but may also impair development of the myocardium, with likely long-term deleterious consequences. Given the evidence from human and animal studies, investigation of the long-term cardiovascular consequences of exposure to intrauterine inflammation is warranted. Lungs In , Watterberg et al. RDS is caused primarily by a lack of pulmonary surfactant and its incidence is inversely associated with gestational age at delivery [10]. It is characterised by tachypnoea, chest wall retraction, cyanosis, and a ground glass appearance of the chest on X-ray [78]. BPD is defined as the need for supplemental oxygen beyond one month of postnatal age [79 , 80] and is most commonly observed in extremely preterm infants [

79]. BPD is characterised by impaired vascularisation and alveolarization of the developing lung, whereby pulmonary microvascular angiogenesis is disrupted and alveoli are fewer in number and larger in size [27 , 80]. An increased risk of BPD in preterm neonates exposed to chorioamnionitis may be mediated by other postnatal events such as mechanical ventilation and oxygen exposure [80]. Since the initial description by Watterberg et al. In contrast, infants diagnosed with chorioamnionitis but without accompanying FIRS had less severe RDS than infants who were not exposed to chorioamnionitis. Recent studies have been unable to demonstrate an independent association between chorioamnionitis and the development of BPD in preterm infants [82 , 83], likely because of the complex variety of prenatal inflammatory stimuli and their interaction with ventilatory management of neonates [84]. Animal studies clearly indicate that fetal lung development is altered by intrauterine inflammation. The increase in surfactant protein production is thought to be associated with an increase in type 2 alveolar epithelial cells because in vivo and in vitro studies of fetal mice show that intra-amniotic LPS exposure increases type 2 alveolar epithelial cell numbers [86]. We have recently demonstrated that the fetal lung response to intrauterine inflammation is mediated, at least in part, by prostaglandins [90]. Inflammation-induced alterations to fetal pulmonary vascular development include smooth muscle hypertrophy and deposition of collagen in the adventitial layer of pulmonary resistance arterioles [92]. We have recently observed that these alterations to the pulmonary vasculature are associated with an increase in pulmonary vascular resistance and subsequent reduction in pulmonary blood flow in the fetus at 2 and 4 days, respectively, after intra-amniotic LPS exposure [93]. One of the postnatal consequences of inflammation-induced vascular remodelling of the fetal lungs is persistent pulmonary hypertension of the newborn PPHN. This condition is characterised by increased resistance to pulmonary blood flow and right-to-left shunting across the foramen ovale FO and ductus arteriosus DA , resulting in decreased left ventricular output [94 , 95]. Preterm lambs exposed to a single injection of intra-amniotic LPS 7 days prior to delivery showed increased pulmonary vascular resistance and right-to-left shunting of blood through the DA within 30 minutes after delivery [97]. LPS exposure 2 or 4 days prior to delivery does not have such profound effects on pulmonary haemodynamics of preterm lambs, suggesting that the full extent of vascular remodelling had not occurred by that time [98]. Considering the pulmonary vascular and alveolar remodelling demonstrated in fetal lambs exposed to intra-amniotic LPS [88 , 92], a causative link between chorioamnionitis, BPD, and PPHN becomes increasingly apparent. Brain In preterm infants, perinatal brain damage is a major cause of developmental delay and lifelong neurological impairments such as mental retardation, cerebral palsy, and learning, and behavioural deficits [99 â€”]. There is robust epidemiological evidence linking perinatal brain injury, in particular cerebral palsy, periventricular leukomalacia, and intraventricular haemorrhage, with intrauterine inflammation [25 , â€”]. Exposure to histological chorioamnionitis combined with impaired placental perfusion has been demonstrated to increase the risk of poor neurological and neurocognitive outcomes at 2 years of corrected age in children born very preterm [99]. Similar observations were made at 8 years of age in children exposed to severe histological chorioamnionitis [ ]. Histological chorioamnionitis is also associated with an increased incidence of speech delay and hearing loss at 18 months of corrected age in infants born very preterm [ ]. Furthermore, histological chorioamnionitis caused by bacterial and viral infection has been associated with an increased risk of autism spectrum disorders [ ] and schizophrenia [,]. Recent work suggests that persistent inflammation is responsible for phenotypic abnormalities observed in autism, whereas a latent inflammatory process in utero appears responsible for schizophrenia-specific brain and behavioural abnormalities [ ]. A number of clinical studies have identified potential mechanisms for associations between chorioamnionitis and adverse neurological outcomes. A direct effect of immune activation is demonstrated by studies showing that intrauterine inflammation is linked with diffuse white matter injury in the brain of preterm neonates, due to activation of a systemic inflammatory cascade [99 , â€” ,]. Chorioamnionitis has been associated with impaired fetal and newborn cardiac function [

74 ,], which may compromise brain blood flow. Lower blood pressures and higher concentrations of inflammatory mediators have been demonstrated in the systemic circulation in very low birth weight infants exposed to chorioamnionitis [, ,]. Impaired cerebral autoregulation is considered one of the main contributors to brain injury in the preterm neonate [,] and has previously been demonstrated in preterm infants during the first hours after birth [,]. Impaired cerebral autoregulation may be more prevalent in neonates born after exposure to intrauterine inflammation [, , ,]; however there are limited data that directly support this contention. Data from animal experiments are consistent with human studies in showing effects of intrauterine inflammation on the developing brain. Rabbit pups exposed to a single intra-amniotic injection of E. In fetal sheep, chronic administration of intra-amniotic LPS derived from E. Recent experiments examining the effect of intrauterine inflammation on cerebral haemodynamics have shown that within 15 minutes after delivery carotid arterial blood flow and pressure are increased in preterm lambs 2 days after LPS exposure [98]. Additionally, carotid arterial pressure was shown to be increased 1 hour after preterm delivery of lambs 7 days after LPS exposure [97]. Such disturbances in cerebral haemodynamics may increase susceptibility to brain injury in the preterm neonate. We have demonstrated an increase in inflammatory cytokine mRNA expression in the periventricular and subcortical white matter and periventricular vascular damage and haemorrhage, 48 to 96 hours after exposure to intra-amniotic LPS [98], and increased cerebral perfusion after 4 and 5 days in preterm fetal sheep [93]. This finding is consistent with the observation that cerebral DO2 is increased in preterm fetal sheep exposed to intra-amniotic LPS, indicating an increased cerebral metabolic demand before birth [ ]. Inflammatory cytokines released during the course of intrauterine inflammation have been suggested as a possible cause of cerebral injury observed in animal studies [,].

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Epidemiological studies suggest that intra-uterine exposure to inflammation may prime postnatal immune responses. In fetal sheep, intra-amniotic injection of lipopolysaccharide (LPS) induced chorioamnionitis, lung inflammation and maturation, matured lung monocytes to macrophages and initiated.

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By exposing the fetal and maternal tissues to E. coli LPS, a number of investigators have studied the evolution and effects of intrauterine inflammation in animal models including mice, rabbits, nonhuman primates, and sheep. 14 We and others have clearly demonstrated that intra-amniotic administration of LPS induces chorioamnionitis.

Chapter 9 : The Newborn Lung: Neonatology Questions and Controversies

Moss TJM, Knox CL, Kallapur SG, Nitsos I, Theodoropoulos C, Ikegami M, Newnham JP, Jobe AH. Experimental amniotic fluid infection in sheep: effects of Ureaplasma parvum serovars 3 and 6 on preterm or term fetal sheep.