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Review

Inflammation-induced preterm lung maturation: lessons from animal experimentation

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EDUCATIONAL AIMS

The reader will better appreciate that:

- Intrauterine inflammation mediates its effects on the preterm lungs via a mechanism independent to glucocorticoid signalling.
- Intrauterine inflammation does not increase fetal cortisol levels enough to improve preterm lung function.
- Intrauterine inflammation-induced increases in surfactant proteins are much greater, occur sooner and last longer than those induced by glucocorticoids.
- Inflammatory mediators act directly on the fetal lungs to elicit developmental changes that alter preterm lung function, rather than by systemic signals.
- PGE_2 is a likely candidate for mediating inflammation-induced effects on the preterm lungs.

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ABSTRACT

Intrauterine inflammation, or chorioamnionitis, is a major contributor to preterm birth. Prematurity *per* se is associated with considerable morbidity and mortality resulting from lung immaturity but exposure to chorioamnionitis reduces the risk of neonatal respiratory distress syndrome (RDS) in preterm infants. Animal experiments have identified that an increase in pulmonary surfactant production by the preterm lungs likely underlies this decreased risk of RDS in infants exposed to chorioamnionitis. Further animal experimentation has shown that infectious or inflammatory agents in amniotic fluid exert their effects on lung development by direct effects within the developing respiratory tract, and probably not by systemic pathways. Differences in the effects of intrauterine inflammation and glucocorticoids demonstrate that canonical glucocorticoid-mediated lung maturation is not responsible for inflammation-induced changes in lung development. Animal experimentation is identifying alternative lung maturational pathways, and transgenic animals and cell culture techniques will allow identification of novel mechanisms of lung maturation that may lead to new treatments for the prevention of RDS.

PRETERM BIRTH

Intrauterine inflammatory processes likely underlie the majority of preterm births [1], which account for 10-15% of live births worldwide, albeit with considerable geographic variability [2]. Preterm infants constitute ~75% of all neonatal deaths, largely due to lung immaturity and the consequent increased risk of potentially fatal respiratory disease [3].

Intrauterine inflammation

Intrauterine infection or inflammation has been recognised for over a decade as the principal contributor to preterm birth [4]. The incidence of intrauterine infection increases as gestational age at delivery decreases [4,5]. Evidence of intrauterine infection is present in ~70% of deliveries before 28 weeks' gestational age (GA),

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but only ~15% of deliveries at 34-36 weeks GA [5]. More than half of infants born prior to 30 weeks gestation were exposed to intrauterine inflammation [5]. The reason for the inverse relationship between the incidence of intrauterine inflammation and preterm birth is not completely understood, partly because intrauterine infection is predominantly a clinically silent syndrome [6,7], which makes its investigation difficult.

Intrauterine inflammation most commonly presents as chorioamnionitis (inflammation of the fetal membranes; the chorion and amnion). The clinical diagnosis of chorioamnionitis is most frequently made near term labor when a pregnant woman has symptoms including fever, a tender uterus and preterm or prolonged rupture of membranes [7,8]. Histologic chorioamnionitis, on the other hand, is more prevalent and is a silent, indolent process that is only diagnosed by measuring bacteria and/or inflammatory cells in amniotic fluid or upon histological examination of the placenta, chorioamnion and umbilical cord after delivery [8]. In cases of histological chorioamnionitis, the most commonly identified microorganisms (using whole-genome sequencing) are *Ureaplasma parvum*, *Fusobacterium nucelatum* and *Streptococcus agalactiae* [9]. However, in nearly one-third of pregnancies with evidence of intra-amniotic inflammation, no bacteria or viruses were identified (using culture and PCR/Mass spectrometry techniques) [10].

Consequences of preterm birth

The outcome for infants born preterm primarily depends on the extent of prematurity, with infants born at earlier gestations more likely to experience complications after delivery. In addition to having a higher mortality rate after birth, infants born preterm have increased risks of gastrointestinal problems [11], visual impairments [12], and intracranial hemorrhage and periventricular leukomalacia, which are strong predictors of mental retardation and cerebral palsy [13]. However, respiratory disease is the major source of morbidity and mortality in preterm infants, especially those born earlier than 28 weeks of gestation [14–16].

Neonatal respiratory problems are common in preterm infants because their lungs generally have a smaller surface area for gas exchange, a thicker blood-gas barrier and fewer differentiated type-II alveolar epithelial cells (the surfactant-producing cells of the lungs) compared with their term counterparts [17]. The structural immaturity of the terminal airspaces and a lack of surfactant can render the immature lungs unconducive to efficient gas exchange [18,19]. These characteristics of the immature lungs render preterm infants vulnerable to respiratory distress syndrome (RDS).

LUNG MATURATION PRIOR TO PRETERM BIRTH

Corticosteroid-induced lung maturation

The most effective clinical intervention for preventing RDS is antenatal corticosteroid therapy. Glucocorticoids were first trialled as a medical intervention in women at risk of preterm delivery [20] after groundbreaking studies using fetal sheep, conducted by Sir Graham "Mont" Liggins in the late 1960s [21]. The most recent Cochrane systematic review demonstrates clearly the respiratory benefit antenatal corticosteroid therapy [22]. Current clinical guidelines recommend antenatal corticosteroids for women at risk of preterm birth between 24 and 34 weeks of gestation [23,24]. Efficacy at very young gestational ages is questionable [25].

Animal experiments show that the beneficial respiratory effects of antenatal corticosteroid treatment are achieved principally through effects on lung structure rather than the pulmonary surfactant system [26]. This is consistent with the role of glucocorticoids in lung development revealed by studies using transgenic mice with defective glucocorticoid signalling [27].

The optimal glucocorticoid dose, timing of use, frequency of administration and the gestational age at which antenatal corticosteroid treatment is beneficial remain unclear [28–30], and remain the subject of animal experimentation [31,32] years after their introduction into clinical use. In experimental animals and in humans, fetal responses to corticosteroids are inconsistent and can be adverse [33,34]. Corticosteroids only protect infants from the development of RDS in ~1/3 of cases, and do not protect against bronchopulmonary dysplasia (BPD) [35].

Initial concerns about safety of repeated doses of antenatal glucocorticoids appear refuted by clinical trials [36], although effects on head and body growth were observed in a recent clinical trial [37]. Repeated antenatal corticosteroid treatments reduce the incidence of RDS by only 17% compared to a single treatment if birth is delayed [38].

Inflammation-induced lung 'maturation'

It has been known for almost two decades that preterm infants exposed to chorioamnionitis have a reduced risk of RDS [7,39,40]. For example, Ammari *et al.* [41] observed that in cases of chorioamnionitis, 31% of infants born at 23-25 weeks and 78% of infants born at 26-28 weeks could be managed with only CPAP and without surfactant treatment or mechanical ventilation, indicating that these infants have advanced biochemical maturation of the lungs and improved lung mechanics for their gestational age.

The mechanism whereby inflammation leads to functional 'maturation' of the preterm lungs is not completely understood. Initially it was proposed that increases in corticosteroid levels, owing to fetal stress induced by chorioamnionitis, resulted in lung maturation [40]. However, this simple scenario is likely incorrect [42,43]. Animal experiments describe a myriad of effects of intrauterine inflammation within the fetal lungs [44–46] but the key to unlocking the 'maturation' that underlies the reduced risk of RDS is yet to be found.

Despite reducing the incidence of RDS, intrauterine inflammation may increase the incidence of BPD [47–49]. Indeed, an increased risk of BPD was associated with the presence of *Ureaplasma urealyticum* or mycoplasmas in cord blood [50], and with chronic colonization by *Ureaplasma urealyticum* [51]. Variables such as the severity and duration of inflammation, the organisms responsible for intrauterine infection, and other antenatal exposures likely interact to modulate the risk of BPD.

GLUCOCORTICOIDS AND INFLAMMATION ACT VIA DIFFERENT MECHANISMS

Temporal difference in the effects of corticosteroids and inflammation on the developing lungs

The underlying mechanisms whereby inflammation protects against the development of RDS are not known. Inflammation threatens homeostasis and can activate a stress response in the fetus, which was proposed to stimulate production of endogenous glucocorticoids and potentially induce lung maturation [52]. However, available evidence from animal experiments indicates that inflammation-induced lung maturation occurs via a mechanism independent of glucocorticoids.

Intra-amniotic (IA) injection of lipopolysaccharide (LPS) in experimental animals induces an intrauterine and fetal pulmonary inflammatory response that shares many characteristics with human cases of histologic chorioamnionitis, including the developmental consequences for the fetus [53]. However, IA LPS injection in sheep elicits effects on fetal lung development that