Lung development and inflammation

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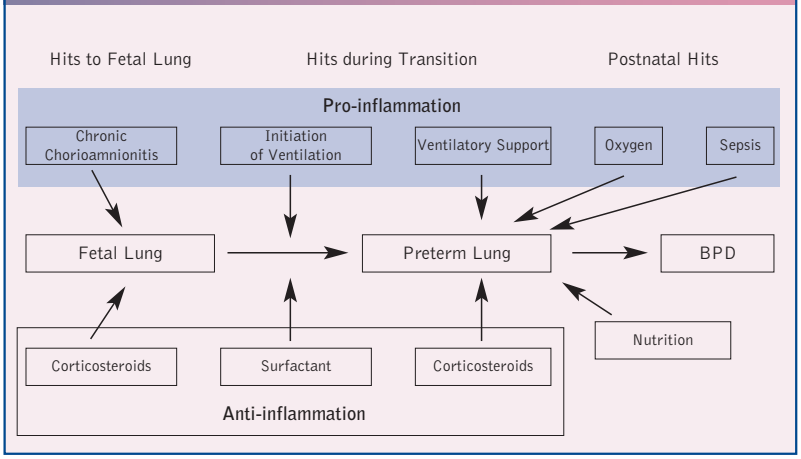
In the human fetus, airway branching occurs by 16 to 18 weeks and alveolarisation (alveolar duct branching) starts after 32 to 36 weeks. Little attention has been paid to the saccular divisions occurring between airway branching and alveolarisation. This may be due to current conceptual issues regarding the exact processes of lung injury in these preterm infants. This period of lung branching is critical to normal lung development or the pathophysiology of BPD. The preterm lung is susceptible to multiple different influences or 'hits' ranging from corticosteroid exposure or chorioamnionitis to more traditional injuries (e.g. sepsis) *[Figure 1]*.

Chorioamnionitis and fetal exposure to infection and inflammation

Figure 1. Multiple factors influence lung development in the preterm infant.



Recent evidence indicates that current assumptions regarding the sterility of the interamniotic cavity and fetal exposure to inflammatory mediators require reconsideration. Clinical studies demonstrated that the presence of micro-organisms in the amniotic fluid is not necessarily associated with preterm labour and delivery. At 3 months post-partum, positive microbial cultures were present in the endometrial cavity of approximately 80% of women irrespective of whether they had a normal delivery, spontaneous preterm delivery or indicated preterm delivery.[1] Furthermore, the presence of plasma cells within the endometrial cavity indicated the chronicity of these micro-organisms. These findings are supported by data from 254 asymptomatic women who had amniotic fluid collected at 15 to 17 weeks gestation.[2] A total of 11% of women had ureaplasma, 59% of these women had preterm labour but only 7% delivered at <34 weeks.
While the presence of infection/inflammation may not influence preterm delivery, it may have an impact on several infant outcomes. Controversial data support a correlation between histological chorioamnionitis and RDS and BPD in subselected ventilated infants.[3] The presence of inflammation prior to delivery decreased the incidence of RDS (33 vs 67% for those without inflammation) but increased the incidence of BPD (63 vs 37%, respectively). However, the association between chorioamnionitis and outcomes is not clear cut. In a study involving 446 consecutive singleton deliveries at <32 weeks gestation, ureaplasma and mycoplasma were present in 81% of infants with inflammation and 32% of those without any inflammation.[4] In this study, the incidence of RDS was decreased with no difference in the incidence of BPD or mortality. There was, however, an increased risk of necrotising enterocolitis associated with chorioamnionitis and an increased systemic inflammatory response following delivery. At present, there is a lack of understanding of chorioamnionitis including how it should be appropriately diagnosed and managed. It is possible that chorioamnionitis 'primes' the newborn to have an alternative response to any subsequent intervention.
Antenatal effects have the potential to change postnatal outcomes. In preterm infants exposed to chorioamnionitis,

ventilation and postnatal sepsis increased the risk of BPD *(Table 1)*.[5] In short, clinical reports demonstrate that fetal exposure to:

- organisms is probably common, and may cause preterm labour and delivery
- inflammation is associated with early lung maturation and adverse outcomes
- organisms/inflammation causes chorioamnionitis.

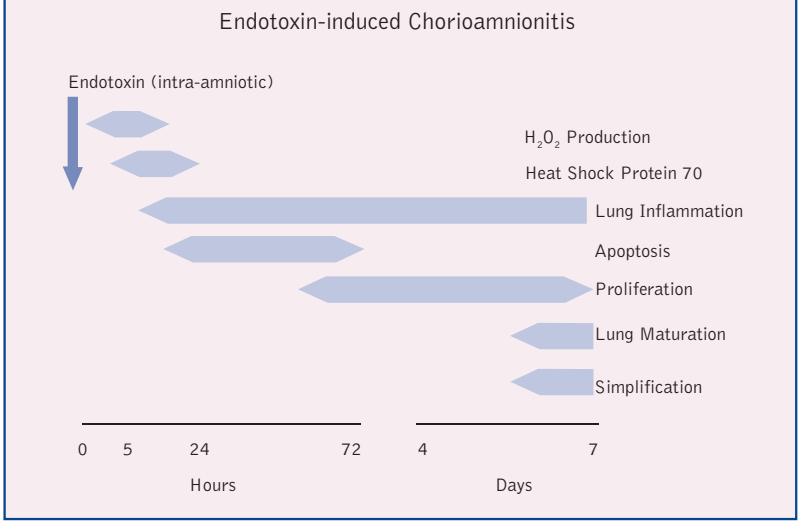
Table 1. The association between antenatal factors and the risk of BPD.[5]

	Multivariate Odds Ratio (OR)	
	OR	95% CI
Chorioamnionitis	0.2	0-0.5
Ventilation >7d plus chorioamnionitis	3.2	0.9-11
Postnatal sepsis plus chorioamnionitis	2.9	1.1-7.4

Fetal exposure to inflammation induces lung maturation

Antenatal exposure of the fetus to inflammation is undoubtedly associated with lung maturation but preclinical data suggest that inflammation itself may actually induce such maturation. In an experimental model, inflammatory mediators were introduced into the amniotic fluid/fetal trachea of sheep.[6,7] Fetal lung response to a 4 mg intra-amniotic injection of endotoxin demonstrated an increase in inflammatory cells within the BALF, cytokine release, apoptosis and proliferation within the lung and a protypic injury response in the lung. However, these changes were accompanied by improved lung compliance, gas exchange and CO_2, and in ventilated animals there was no change in plasma cortisol – indicating that lung maturation occurs independently of the adrenal axis.[8] Introduction of an endotoxin into amniotic fluid of pregnant animals causes an injury response followed by cellular proliferation and subsequent lung maturation, leading to a phenotype characteristic of BPD with simplification of microvascular and alveolar development *(Figure 2)*. Current evidence confirms that inflammation-mediated lung maturation is more potent and more consistent than that mediated by corticosteroid exposure. In addition, it is induced by intra-amnio *Escherichia coli* endotoxin, IL-1 and live ureaplasma, and requires direct contact of the agonist with the fetal lung and an inflammatory response.

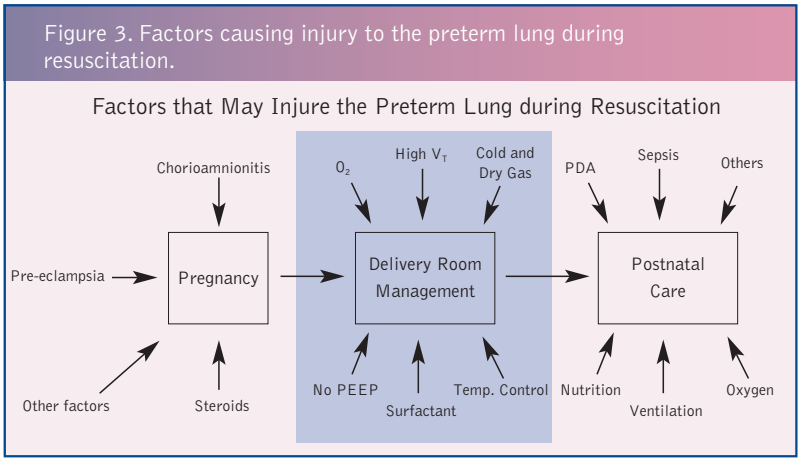
Figure 2. The effect of endotoxins on lung development.



Factors that cause preterm lung injury during resuscitation

Neonatal resuscitation provides ample opportunity for lung injury to occur *(Figure 3)*. Only 15 minutes of fetal ventilation has been shown to induce serum amyloid A in the liver, indicating the development of a systemic inflammatory response. Ventilation-mediated lung injury during resuscitation was investigated in an animal model (unpublished data). Fetuses were intubated with a target of V_T = 15 mL/kg at 15 minutes and were given heated

Figure 3. Factors causing injury to the preterm lung during resuscitation.



humidified air followed by 100 mg/kg surfactant (Survanta) after 15 minutes. They were then either returned to the uterus for 2 hours and 45 minutes or ventilated gently to a target $PaCO_2$ of 60 mm Hg and V_T ≤8 mL/kg for 2 hours and 45 minutes. Resuscitation was shown to induce lung injury and gentle ventilation amplified this injury. Fifteen minutes of resuscitation produced a large inflammatory response evidenced by the recruitment of monocytes and neutrophils, and 40- and 100-fold increase in the expression of IL-1β and IL-6, respectively (unpublished data). Furthermore, postnatal ventilation amplified the inflammatory response mediated via IL-6, IL-8 and neutrophils and resulted in systemic inflammation.

The current focus in preterm infants appears to be on issues such as ventilatory support and sepsis but other variables also require careful consideration in the diagnosis and management of BPD. Antenatal inflammation has potent effects on fetal lung development and may influence outcomes.

References

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