LONG-TERM EFFECTS OF PRETERM BIRTH AND EARLY NUTRITION ON PREDISPOSITION TO LATER LUNG DISEASE.

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Symposium title: "Early Origins of Respiratory Disease"
CIPP Conference, March 2008

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Short title: The early environment and lung development
It is now well established that lung development is affected by environmental as well as genetic factors. There is abundant evidence that exposure to a sub-optimal environment during either intrauterine and early postnatal life can lead to specific alterations in lung development that may persist into later life [1]. Common perinatal factors known to alter lung development and later lung function are low birthweight (due to fetal growth restriction or preterm birth), undernutrition and respiratory infections after birth. This brief review will focus on perinatal nutrition and growth, and on preterm birth, with particular emphasis on long-term alterations in lung structure, lung function and vulnerability to lung disease.

**Fetal growth restriction and lung development:** Intra-uterine growth restriction (IUGR) is most often caused by a restricted supply of nutrients and oxygen to the fetus; causes include placental insufficiency, maternal hypoxia and maternal undernutrition. IUGR has been associated with reduced respiratory function in the neonate and with persistent adverse effects during infancy and childhood [2]. In adults, low birthweight has been associated with reduced lung function [3]. Although it is apparent that IUGR has persistent effects on lung function, there are no human data on the effects of IUGR on lung structure.

Our understanding of how IUGR can alter structural development of the lung is derived mainly from animal studies. Fetal hypoxia, reduced nutrient availability, elevated circulating levels of corticosteroids and maternal smoking are associated with IUGR and have all been shown to alter lung development. The physical environment of the fetal lung, including its expansion with lung liquid, and fetal breathing movements (FBM) are also critical for normal lung development. FBM play an essential role in maintaining the basal level of fetal lung expansion and hence are necessary for normal lung growth [4]. As they are active processes, the secretion of lung liquid and FBM are inhibited by hypoxia, and probably by hypoglycemia. Both are reduced in IUGR fetuses, potentially contributing to impaired lung development.

Numerous animal studies have shown that factors associated with restricted growth (ie undernutrition, hypoxia and excess glucocorticoids) both before and after birth can alter lung architecture. Many of these studies were performed in rodents in which alveolarization occurs after birth; they show that alveolarization is adversely affected, but the long term effects are relatively unknown. We have used sheep to study the long-term effects of IUGR and other prenatal challenges on the structure of lung parenchyma; alveolarization in the sheep, as in humans, begins before birth and continues after birth. We have documented the immediate and long-term pulmonary effects of IUGR which was induced during the saccular-alveolar stages of lung development [5, 6]. Lung architecture was assessed at 3 life stages: the near-term fetus, 8-week old lamb and adult sheep. The total number of alveoli was reduced by 31% at 8 weeks of age in IUGR lambs, and a similar reduction was seen in IUGR adult sheep aged 2.3 years; the alveoli were enlarged at 8 weeks and also in adults. Alveolar septa were significantly thicker both at 8 weeks and adulthood as a result of increased
extracellular matrix deposition. The alveolar blood-gas barrier was 29% thicker in IUGR fetuses, and this difference increased in adults to 43%. As with the alveolar septa, the thicker blood-gas barrier was apparently due to altered extracellular matrix metabolism. These studies show that the prenatal environment is important for normal alveolar structure and that the adverse effects can persist into adulthood.

Development of the conducting airways is also affected by IUGR. In fetal sheep, IUGR led to altered tracheal wall structure with less cartilage, less mucosal folding, impaired development of submucosal glands and evidence of reduced epithelial ciliation [7]. In the bronchi and bronchioles of IUGR fetuses, the walls were thinner and submucosal glands were less developed; however airway wall thickness recovered by 8 weeks after birth but changes in mucus secretory structures persisted [8]. In adult sheep, the dimensions of the conducting airways were not different between IUGR and control groups; however the number of alveolar attachments to bronchioles per mm of basement membrane length (500-2000 µm) in the lung parenchyma was significantly reduced by 10% in adult IUGR sheep [9]. A reduction in bronchiolar tethering in IUGR adults, likely a result of a reduced number of alveoli [6], could contribute to the reduced lung function reported in adults born with low birthweight [3].

**Postnatal nutrition and lung development:** Little information is available regarding effects of postnatal nutrient restriction on lung development in humans. Undernutrition during critical stages of lung development may occur due to severe prematurity and infections, and likely contributes to reduced respiratory function later in life [10]. Animal studies have shown that early postnatal undernutrition impairs alveolar formation [11]. In postnatal rats, for example, intermittent starvation coinciding with the late saccular and early alveolar phases of lung development resulted in enlarged alveoli, thicker septa with reduced elastin deposition [12]. Even in long gestation species such as primates and sheep, postnatal nutrition may have persistent effects on distal lung development; this is because alveolarization continues after birth, for up to 6 months in sheep and 1.5 - 3 years in humans. In adult sheep we have recently shown that slow postnatal growth can result in a reduced final number of alveoli and a reduced surface area for gas exchange [13] as well as altered airway wall structure [14]. This observation concurs with human data showing impaired lung function in children who were undernourished from birth [15].

**Preterm birth and lung development.**

Another common cause of persistent alterations in lung development is preterm birth. It is well established that severe preterm birth can have serious pulmonary sequelae due to injury and inflammation caused by mechanical ventilation and elevated oxygen levels. Even mild-moderate preterm birth, which affects approximately 6% of all births and usually does not require assisted ventilation, has been associated with adverse respiratory effects. For example preterm infants born at
~30 weeks showed reduced lung compliance, impaired gas mixing efficiency and higher dead space [16], and preterm birth (~35 weeks) has been associated with wheeze and reduced expiratory flows in children [17].

Infants born at early gestational ages (23-26 weeks) with extremely low birthweight (<1000 gm) are prone to the development of bronchopulmonary dysplasia (BPD). Radiological and pathological findings include lung hyperinflation, emphysema, and dilated, simplified distal air sacs due to a failure of septation [18]. A consequence of failed septation is a reduced number of alveoli and hence a reduction in the area for gas exchange and the mechanical tethering of bronchioles, which may reduce lung function throughout life. Infants born very preterm are particularly prone to inadequate nutrition, which may contribute to the aetiology of bronchopulmonary dysplasia (BPD). Owing to ongoing lung development in preterm infants, undernutrition, or a lack of essential micronutrients, could have detrimental effects on lung anti-oxidant and defence mechanisms, surfactant production, as well as on structural maturation of alveoli and airways [18].

Airway resistance and reactivity may be increased in infants and children following severe prematurity. Ventilatory support carries an increased risk not only for BPD but for later diseases such as asthma and COPD [19]. Our studies using sheep have shown that preterm birth per se, coinciding with the early alveolar phase of lung development, is associated with increased pulmonary resistance and altered alveolar formation including thicker alveolar walls and type I alveolar epithelial cells; in addition the airway epithelium is thicker in preterm animals [20]. This moderate preterm birth also delayed the postnatal increase in the proportion of type II to type I alveolar epithelial cells [21]. In our adult sheep born prematurely there were no differences in alveolar number or dimensions; however, airway reactivity was increased, especially in those with reduced postnatal growth rates [22].

**Conclusions:** A sub-optimal environment coinciding with distal lung development can have lasting effects on lung structure, which may reduce lung function and increase disease susceptibility. Alveolarization can be impaired by a range of factors operating in early life, such as IUGR and preterm birth, after which there is limited potential for recovery. A reduced alveolar number could contribute to obstructive lung disease due to a smaller surface area for gas exchange and reduced tethering of small airways. Our studies suggest that IUGR largely affects alveolar number and structure, whereas preterm birth per se largely affects the conducting airways. Future studies should be directed towards determining the mechanisms by which each of these factors adversely affects lung development and whether such effects can be prevented or reversed.
References