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Review

# Small for gestational age birth weight: impact on lung structure and function

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SUMMARY

Accumulating data suggest that prenatal compromises leading to intrauterine growth restriction (IUGR) increase the risk for respiratory deficiencies after birth. In this respect, a growing body of epidemiological evidence in infants, children and adults indicates that small for gestational (SGA) birth weight can adversely affect lung function, thus questioning the widely accepted concept that IUGR accelerates lung maturation and improves outcome.

Although the mechanisms responsible for the relationship between SGA and later lung dysfunction remain poorly documented, animal data indicate that intrauterine lung development can be adversely affected by factors associated with IUGR, namely reduced substrate supply, fetal hypoxemia and hypercortisolemia. Thus, it is suggested that fetal adaptations to intrauterine undernutrition result in permanent changes in lung structure, which in turn lead to chronic airflow obstruction.

The purpose of this review is to describe and discuss the effects of IUGR on lung structure and function.



## INTRODUCTION

Epidemiological and experimental evidence indicates that the development and later function of several organs can be affected by prenatal compromises leading to intrauterine growth restriction (IUGR).[1] These organs have a limited capacity to recover from early developmental defects, which may persist and affect health during later life.[1] Recently, accumulating data suggest that the lung is an organ that can be detrimentally affected by adverse conditions during its early development, resulting in persistent alterations in lung structure and impaired respiratory function during postnatal life.[2]

In this respect, an increased risk for respiratory distress syndrome (RDS) and death in small for gestational age (SGA) preterm and term infants has been shown,[3–8] challenging the widely accepted concept that IUGR may accelerate lung maturation and pulmonary surfactant secretion at birth, thus leading to improved respiratory outcome.[9] Furthermore, respiratory compromise may persist during postnatal development, as children born SGA present with impaired airway function.[10–13] In addition, adults with low birth weight, and therefore most likely IUGR, have reportedly reduced lung function and increased risk for respiratory morbidity and mortality, independently of smoking and social class.[14–18]

Although the structural basis for a relationship between SGA and later lung dysfunction is poorly understood, animal data suggest that factors characterizing IUGR, such as undernutrition, hypoxemia, and elevated cortisol levels[19,20] can affect fetal lung development.[2]

The aim of the present review is to discuss older and recent epidemiological and experimental evidence showing that the lung is an organ that can be adversely affected by IUGR during critical periods of its early development, resulting in permanent alterations in lung structure that can impair respiratory function, and probably, lung health during postnatal life.

## FETAL LUNG DEVELOPMENT

In long-gestation species, such as humans, the development of lung architecture occurs during fetal and early postnatal life and can be influenced by a range of physical, metabolic, endocrine and inflammatory intrauterine factors.[2]

However, lung tissue growth does not occur at a constant rate during maturation.[21] The airways are formed during early fetal life and are completed by 16-20 weeks of gestational age.[21] Alveolar development, which begins at around 20 weeks of gestational age, is largely completed by the age of 2-3 years.[21] After this, lung growth mainly occurs by the enlargement of existing alveoli.[21]

Thus, it seems logical that any stimulus or insult imposed during fetal or early postnatal life could permanently alter the structure and physiology of the respiratory system with possible long-term consequences.[22]

An important determinant of fetal lung growth and structural maturation is the degree to which the lungs are expanded with

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lung liquid, which is actively secreted by the pulmonary epithelium.[23] It is well established that prolonged underexpansion of the fetal lungs results in pulmonary hypoplasia and structural immaturity.[23]

## PULMONARY SURFACTANT SYSTEM

The pulmonary surfactant stabilizes the lung by producing a surface-active monolayer at the air-liquid interface of the terminal airways, thus preventing alveolar collapse at the end of expiration, a function required for adaptation to air breathing after birth.[24] It is synthesized and secreted by alveolar type II epithelial cells (which account for 5% of the alveolus) and consists of approximately 90% lipids (70-80% of which is phosphatidylcholine and 10% neutral lipids, mainly cholesterol, by weight of pulmonary surfactant) and 10% proteins.[25] The pulmonary surfactant is unique in its abundance of dipalmitoylated phosphatidylcholine, which is the surface active component.[26] Four specific surfactant proteins (SP) have been identified, namely SP-A, -B, -C and -D.[27] Surfactant function is dependent upon the interaction among the hydrophobic proteins, SP-B and SP-C, and surfactant phospholipids that contribute to the structural organization, spreading, and stability of surfactant in the alveolus.[25] SP-B and SP-C enhance the absorption of lipids to the surface of the alveoli.[28] Combined deficiency of SP-B and mature SP-C is incompatible with life.[29] SP-A and SP-D belong to the group of collectins.[30] They are potential markers of fetal lung maturation[25] and participate in the innate host defense immune system against inhaled microorganisms and allergens.[31] SP-A is instrumental in surfactant storage in lamellar bodies and in the formation of tubular myelin and surfactant monolayer.[25] SP-D seems to regulate the surfactant pool size, by influencing the surfactant ultrastructure and its reuptake in type II cells.[32]

## OTHER LUNG SECRETORY PRODUCTS

Alveolar type I epithelial cells make up 95% of the alveolus and along with endothelial cells compose the gas exchange barrier.[33] Type I cells express a variety of proteins, which may be useful biochemical markers of the severity of alveolar epithelial damage in human lung diseases.[34]

Pulmonary neuroendocrine cells are granulated epithelial cells distributed throughout conducting airways.[35] Among the bioactive products identified within the secretory granules of these cells are potent mitogens, as well as broncho- and vaso-active agents.[35] Aggregate data suggest roles for the secretory substances of pulmonary neuroendocrine cells in the regulation of airway epithelial differentiation.[35]

Another major secretory protein of the lungs, clara cell protein (CC16),[36] is the predominant product of the non-ciliated, non-mucous clara cells lining the bronchial and bronchiolar epithelium.[36] CC16 has been implicated in fetal lung growth[37] and plays a vital role in postnatal pulmonary adaptation and in the development of lung injury associated with lung immaturity.[38]

## SMALL FOR GESTATIONAL (SGA) BIRTH WEIGHT AND THE LUNG

The "fetal origins hypothesis" proposes that an adverse intrauterine environment resulting in IUGR, may constrain airway growth and peripheral lung development, predisposing individuals to chronic obstructive pulmonary disease (COPD) in adult life.[14] In this respect, reduced lung function, respiratory illness and lower respiratory tract infections have been associated with low birth weight, regardless of gestational age and respiratory complications at birth in a number of epidemiological studies.[10–18] This hypothesis is further supported by animal data, which show that fetal undernutrition leads to marked lung structural and functional alterations.[2,39,40]

### *SGA and Lung Disease: Epidemiological Evidence*

A growing body of epidemiological data suggests that SGA can adversely affect lung function during infancy,[3–8] childhood[10–13] and adulthood.[14–18] This section includes studies referring to preterm or full-term SGA (comprising IUGR and/or constitutionally small) individuals.

#### *SGA and neonatal lung disease*

IUGR fetuses have previously been regarded as having accelerated lung maturation, compared to appropriately grown infants of the same gestational age.[39] In line with this concept, amniotic fluid biochemical markers of fetal lung maturity were found to be increased in human SGA fetuses,[41] supporting the hypothesis that placental insufficiency may accelerate pulmonary maturation through chronic intrauterine stress.

More recently this view has been challenged with studies showing that both preterm and term SGA infants are at increased risk for asphyxial events, RDS, respiratory failure, or death compared to appropriately grown ones matched for gestational age, sex and race.[3–6] Furthermore, a higher incidence of RDS has been demonstrated in infants with abnormal prenatal Doppler results.[7,8] These studies suggest that SGA infants present with impaired pulmonary gas exchange, the causes of which have not been identified.[3,4]

On the other hand, Tyson et al[3] suggested that preterm SGA neonates are at similar risk of RDS, compared with normal infants. Additionally, findings from human studies are confusing, showing both reduced[42] and increased incidence of chronic lung disease[43,44] in preterm IUGR neonates. Thus, on the basis of human clinical studies, the question of whether SGA infants present with enhanced fetal lung maturation is still controversial.

#### *SGA and lung disease in infancy and childhood*

Associations between SGA and lung function in infancy and childhood have been studied less extensively. Interpretation is often confusing, due to lack of a discrimination between SGA and prematurity,[45] which both affect lung function, but in different ways. Limited information exists about the former, while abundant evidence suggests dysregulation of alveolar development in the latter.[46]

Lower lung function has been reported in low compared with normal birth-weight infants.[47,48] Rona and colleagues reported that lung function measurements in children positively correlate with birth weight, but respiratory symptoms are associated with prematurity.[10] In a group of 5-14 year old children born SGA, decreased total lung capacity and peak respiratory flow rates, as well as increased bronchial reactivity and a higher incidence of asthma has been described.[11] A report in twin pairs at 7–15 years of age has shown that IUGR has the most pronounced effect on airway growth and no detectable influence on lung volumes,[12] confirming the crucial effect of appropriate intrauterine growth on subsequent growth of pulmonary airways.

Furthermore, very recent studies[13,49–51] investigated the association between fetal growth and respiratory function in childhood. In this respect, reported data suggested a clear difference for all spirometric measures of lung function in children born IUGR at term compared with controls.[13] However, this difference did not translate into clinical symptoms, i.e. greater airway reactivity, increased incidence of asthma or other respiratory illnesses. Similarly, both restricted and accelerated fetal growth during the second and third trimester of pregnancy were not associated with asthma symptoms until the age of 4