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Title: Long term respiratory consequences of intrauterine growth restriction.

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ABSTRACT

Epidemiological studies demonstrate that <u>in utero</u> growth restriction and low birth weight are associated with impaired lung function and increased respiratory morbidity from infancy, throughout childhood and into adulthood. Chronic restriction of nutrients and/or oxygen during late pregnancy causes abnormalities in the airways and lungs of off-spring, including fewer numbers of enlarged alveoli with thicker septal walls and basement membranes. The structural abnormalities and impaired lung function seen soon after birth persist or even progress with age. These changes are likely to cause lung symptomology through life and hasten lung aging.

KEY WORDS:

Intrauterine growth restriction, Lung, Fetal, Adult, Lung function, Lung maturation

Introduction (heading level A)

Next to preterm delivery, intrauterine growth restriction (IUGR) is one of the most important causes of perinatal morbidity and mortality[1]. In its simplest form, IUGR occurs when the growth restriction is pathologic (ie not constitutional), indicating that the fetus has failed to achieve its full growth potential[1]. Most commonly, IUGR results in an infant that is small for gestational age (SGA) with a birth weight less than the 10th centile at birth. However, as birth weight for any given gestation is largely normally distributed, an infant can be SGA without also having IUGR, whilst a small number of IUGR infants may have birth weights above the 10th centile, and therefore not be classified as SGA. The term low birth weight (LBW), which refers to any infant with a birth weight less than 2500 g, is often used erroneously as a proxy for IUGR as this classification does not adjust for maturation and is predominantly populated by infants with appropriate growth for gestation. The confusion between these three terms confounds the interpretation of the literature. The calculation of customised centile calculators that consider maternal height, weight, ethnicity and parity and the fetal sex (eg http://www.gestation.net/birth_weight_centiles/birth_weight_centiles.htm)[2], can improve distinction of true IUGR from the constitutionally small infant.

IUGR is often described as symmetric or asymmetric; whereas the whole body of an infant with symmetric IUGR is proportionately small, the infant with asymmetric IUGR preserves growth of critical organs, such as the brain and the heart, at the expense of liver, gut and fat. Asymmetric IUGR implies impaired nutrition and affected infants have substantially lower centiles for weight, length and body mass index compared to the proportions of the head. However, the distinction between asymmetric and symmetric IUGR may be less clear as arguments that symmetric IUGR represents both an early[3] and late form of asymmetric IUGR are proposed. The etiologic basis of IUGR may have maternal, placental, fetal or environmental origins (or a combination of any of these), as detailed in Figure 1. Approximately 80-90% of all cases of IUGR amenable to preventive and therapeutic management involve impaired transplacental supply of oxygen and nutrients to the fetus[4]. Pregnancy induced hypertension and its associated pathological uteroplacental circulation is the single most contributory factor to the development of IUGR[3], whereas maternal smoking accounts for up to 40% of IUGR in developed countries[5].

Interest in the long term effects of IUGR has gained momentum in recent years: signals related to poor placental nutrient transfer during critical periods of fetal development may promote adaptations to reduced nutrient transfer that are beneficial in the short term but which may lead to alterations of structure or function with adverse long term consequences. This process of 'programming'[6] is recognised as an important means by which perinatal events and the in utero environment contribute to disease susceptibility in later life.

Lung development occurs in several distinct stages: embryonic, pseudoglandular, canalicular, saccular and alveolar phases[7]. Impaired fetal nutrient and oxygen availability can impact on any of these phases, potentially affecting long term lung function and respiratory morbidity. Placental insufficiency primarily occurs in late pregnancy in parallel with acinar and alveolar development: IUGR will thus most likely affect the structure and function of the distal lung.

This review examines the effects of nutritional and oxygen restriction on lung development in utero. It considers epidemiological evidence suggesting changes in lung development not only impact on lung function and respiratory disease in early life, but also cause effects into late adulthood. Data from in vivo animal models support and explain the observational studies.

Effects of IUGR on Lung Development (heading level A)

Much of our understanding of the effects of IUGR on lung development has arisen from studies using animal models. Most animal models of IUGR have restricted fetal growth using a nutritional approach (limitation of maternal energy and/or protein intake), interference with placental function and uterine blood flow (embolectomy), or placental insufficiency resulting from pre-conception carunclectomy, arterial ligation or chronic hypoxia[8]. Other models have included exposure to tobacco smoke, late-gestation ischemia/reperfusion, partial nephrectomy, and repeat antenatal corticosteroids[8]. The pathophysiology and phenotype of the abnormalities in lung development resulting from these insults may vary according to species, timing, chronicity and intensity of the relevant exposure/insult, as well as analytical techniques[9]. Nonetheless, these studies largely confirm that normal lung development is critically dependent on the presence of appropriate oxygen tensions and nutrition[10] and that IUGR is

associated with persisting or developing abnormalities of structure and function in both the airways and parenchyma.

Lung Parenchyma (heading level B)

Impairment of fetal nutrition and oxygenation, as frequently occurs in association with IUGR, has wide-ranging effects on cellular and molecular events in the developing lung. These effects include reduced surfactant content/activity[11, 12], impaired Type II alveolar cell maturation[13], reduced alveolar cell formation[9, 14], diminished alveolar surface area, thickened alveolar walls and air-blood barriers[15, 16], as well as an overall reduction in lung weight, protein and DNA content[17].

Reduction in lung DNA content and impaired alveolarisation may arise in part from the diminished fetal breathing movements that are associated with IUGR given the known role of these breathing movements in maintaining fetal lung expansion and lung growth and development[14]. The reduced number of alveoli associated with IUGR at birth persists into adulthood, with no evidence of catch up in mature sheep[14], or rats[18].

Prepubertal and adult IUGR animals have increased alveolar size[14, 19], caused by enlargement of the existing airspaces. This increase in alveolar volume may be associated with the development of emphysema[14] and early lung aging. Although emphysema may arise from abnormal elastin expression and deposition, this remains uncertain: Whereas some have found elastin expression and deposition of elastic fibre is reduced in the IUGR rat lung, associated with increased static lung compliance at maturity[16, 20], Cock found no evidence of similar alterations in elastin in newborn, early weanling or adult sheep[17].

A study using umbilical-placental embolisation in late gestation, to coincide with saccular and alveolar stages of lung development, examined the effects of IUGR in pre-pubertal sheep at 8 weeks[19]: compared to controls, IUGR sheep had fewer alveoli, thicker intra-alveolar septa and persistent thickening of the basement membrane. Such changes that are likely to impair gas exchange and alter the mechanical properties of the lungs. It is unknown whether antenatal glucocorticoids rescue this

pulmonary dysmaturation in the IUGR fetus[21].   The abnormal pulmonary development was more prominent at 8 weeks than near term, indicating that not only do the lung effects of IUGR persist, but they become worse with age.   In a follow-up study into adulthood[14], the IUGR group had more pronounced abnormalities than at 8 weeks.   Comparisons of septal wall thickness at birth[19], 8 weeks[19] and 2 years[14], indicate that most changes occurred postnatally due to an accumulation of extracellular matrix.   Similar septal wall thickening has been described in mature rats whose mothers were nutritionally restricted in pregnancy[18].   The reason for the accumulation of extracellular matrix in the alveolar septa, and also in the thickened basement membrane, is unknown but several hypotheses have been advanced: The mild neonatal hypoxia associated with IUGR may exert a persistent alteration in the metabolic processes within the pulmonary cells; alternatively, increased alveolar wall tension during tidal breathing, due to reduced alveoli numbers, may cause an adaptive response of extracellular matrix deposition.   Additionally, the increased thickness and cellularity of the pulmonary mesenchyme commonly associated with IUGR may result from the increased presence of insulin-like growth factor 1 (IGF1)[22].   Through binding to its specific tyrosine kinase IGF-1 receptor (IGF1R), IGF1 initiates intracellular signalling pathways including the Akt (protein kinase B) signalling pathway which promotes cell growth and differentiation and inhibits programmed cell death.   Whereas in other tissues this process may promote accelerated growth, in the developing lung it represents a maladaptive response to the low placental substrate supply.   The transcription factor p53 also has a pivotal role in cellular responses to stress, lung mesenchymal thinning via apoptosis, regulation of cell cycles and angiogenesis.   The active (phosphorylated) form of p53 (serine-15P) was decreased in the distal air space mesenchyme of IUGR rat lungs[16].   Messenger RNA of downstream targets of p53 involved in apoptosis (Bax, Apaf), growth arrest (Gadd45) and angiogenesis (Tsp-1) were decreased whilst mRNA for an anti-apoptotic gene normally downregulated by p53 (Bcl-2) was increased.

The effects of IUGR on pulmonary development may be partly mediated by epigenetic mechanisms. Epigenetic modifications affect developmental processes by altering gene expression patterns of target genes.   In rats, IUGR decreases the transcription factor peroxisome proliferator activated receptor gamma (PPARγ), with an associated decrease in a PPARγ downstream target the histone methyltransferase enzyme, Setd8, and PPARγ specific histone methylation[23].   These changes are ameliorated by maternal docosahexaenoic acid (DHA) supplementation; maternal DHA is known to be

low in pregnancies complicated by IUGR[23]. Together, these data suggest a role for PPARγ in IUGR-induced epigenetic changes in the lung during development and a novel benefit of maternal DHA supplementation.

Airways (heading level B)

There are few data concerning the long term effects of IUGR on airway development. Systematic evaluation of airway samples from generation 0 (trachea) to generation 8 (smaller conducting bronchi) in sheep with IUGR following late (80% of gestation) umbilical-placental embolization showed no effect of IUGR on smooth muscle content but the IUGR group had thinner walls of the larger airways with reduced cartilage at birth, suggestive of more collapsible airways[24]. However, by 8 weeks after birth the airway morphometry was no different to the control group, although the number of bronchial submucosal gland profiles was reduced and epithelial mucin area increased in the IUGR group[25]. Tracheas of IUGR fetuses at near term also have thinner mucosal and submucosal layers, in addition to decreased epithelial ciliation and decreased mucosal folding[26].

Vasculature (heading level B)

An increase in the thickness of the air blood barrier is evident in term gestation lambs born after umbilico-placental embolisation[27]. Although abnormal pulmonary vascular development and function may in part explain increased oxygen requirements and bronchopulmonary dysplasia incidence in IUGR preterm infants, there are few studies that have explored this aspect of cardiopulmonary development in IUGR fetuses. A recent investigation showed that pulmonary artery endothelial cells from fetal sheep with IUGR due to chronic placental insufficiency have diminished in vitro function and reduced signalling through the Akt/eNOS pathway as well as decreased density of the pulmonary vessels[28]. These data are highly relevant as impaired pulmonary vascular development impedes alveolarisation.

Functional consequences of IUGR in the neonatal period (heading level A)

The impact of IUGR on the incidence of neonatal respiratory distress syndrome varies from an increased[29-31], decreased[32] or equivocal[33, 34] effect, most probably determined by the duration and nature of the insult causing IUGR. Similar variation in outcome can be observed in animal models.

A key feature of neonatal respiratory distress syndrome is endogenous surfactant deficiency. Several studies showed abnormalities of the surfactant system. In human infants, placental insufficiency is associated with increased lecithin/sphingomyelin ratios in the amniotic fluid, suggestive of accelerated lung maturation[35], contrasting with lower saturated phosphatidylcholine content of the lungs of newborn rat pups[11] and guinea pigs[12, 36] born to undernourished dams. Whereas surfactant protein synthesis was upregulated in fetal sheep after fetal/maternal hypoxia[37, 38], reduced surfactant protein and mRNA expression is more often reported in IUGR fetal sheep of carunclectomised ewes[39] and the hypoxic fetal mouse[40]. Hypoxia induced by incubation in 15 % O_2 from day 15 in fetal chickens increased disaturated phospholipids at day 19 compared to controls, whereas more chronic hypoxia extending from day 6 of hypoxia resulted in a borderline decrease in desaturated phospholipid content[41]. Ultimately, therefore, the effect of hypoxia in IUGR on alveolar surfactant production may be modulated by gestation, duration and timing of exposure as well as the availability of surfactant substrate[11]. Interestingly, pulmonary vascular endothelial growth factor, which is expressed in alveolar type II cells and a stimulant of surfactant synthesis, is also upregulated by acute hypoxia in the fetal chicken[41] due to upstream regulation by hypoxia-inducible factor 2α[42]. This highlights the key role of fetal oxygen tension in regulation of the surfactant system. PPARγ is a further primary driver of adipogenic differentiation in the lung. The alterations in lung structure associated with IUGR consequent to maternal food restriction are linked to disturbance of PTHrP/PPARγ signaling between alveolar epithelium and mesenchyme[18] which appears driven by epigenetic mechanisms in a sex-dependent manner[22].

Long term functional and clinical consequences of IUGR in animal models (heading level A)

The longer-term effects of IUGR on respiratory function and morbidity in later life are not yet fully understood. A small number of studies have characterised the changes in lung function into pre-puberty and adulthood using animal models.

Growth restriction caused by late gestational umbilical-placental embolisation results in persistent impairment of pulmonary function[43]. Repeated measurements of the sheep in the 8 weeks following birth showed that, in comparison to controls, IUGR resulted in increased minute ventilation, decreased pulmonary diffusing capacity, decreased functional residual capacity and total lung capacity. Static lung compliance was reduced and chest wall compliance increased in IUGR lambs, but the reason for stiffer lungs was unclear and, of note, surfactant production appeared normal[43].

Adult rats demonstrate echocardiographic and histological evidence of pulmonary hypertension following in utero hypoxia-induced IUGR[44]. This model mimics the hypoxic causes of IUGR such as smoking or living at altitude, but may not equate to nutritional causes. Because of the differences between human and rat lung development, the effects of hypoxia at different stages of fetal development may differ between species.

Long term cardiorespiratory effects of IUGR in humans (heading level A)

Epidemiological evidence (heading level B)

Ecological studies conducted in the 1980s found that regions of the UK with a high rate of death due to coronary heart disease also had high infant mortality[45]; subsequent investigation identified infants with the highest rates of death during infancy were those with the lowest birth weights and surviving infants born at low birth weight went on to have the highest risk of cardiovascular disease in adulthood[46]. These findings were closely followed by the discovery that size at one year was a significant predictor of death in adulthood from respiratory causes suggesting that growth restriction early in life adversely impacts upon respiratory health[47]. Numerous epidemiological studies have been conducted with the aims of clarifying the long term respiratory consequences of IUGR. Although observational studies are unable to categorically identify individuals whose growth is restricted, in many cases low birth weight has been used somewhat imprecisely, as a crude proxy for IUGR. Impaired prenatal growth is increasingly believed to be associated with impaired respiratory function

and poor respiratory health not only immediately after birth but throughout childhood and into adulthood[48].

Consequences of IUGR for childhood and adult lung function (heading level C)

Observational studies show that within a group of term babies of normal average birth weight, forced expiratory flow decreases with decreasing birth weight[49] and that respiratory morbidity in early childhood is associated with lower infant lung function [50]. These findings suggest that an in utero environment less conducive to somatic growth also impairs lung development, with consequences for early respiratory health. Impairment is more pronounced in children who gain weight rapidly after birth[49, 51], hence rapid postnatal weight gain following low birth weight may indicate mismatch between pre- and postnatal nutrient supply and thus identify infants subjected to fetal growth restriction.

Impairments of lung function, specifically reduced expiratory flows[52, 53] and hyperreactive airways[54], are found beyond the period of infancy in children who were of low weight at birth. Early studies generally compared children selected for low absolute birth weight to controls of average birth weight[53], although some attempted to control for maturational effects by considering term infants separately from preterms[54] or using weight for gestation z-scores[52], and others attempted to identify growth restricted fetuses by assessing lung function in children born at significantly lighter birth weight than their co-twin[52]. More recent studies considered the issue of fetal growth restriction across the full range of birth weights. For example, a large study of more than 2000 children aged 5-11 years demonstrated that those born at lower weight adjusted using a regression method for gestational age had lower than expected values of FEV_1, regardless of whether they were born at term or preterm[55]. Persistently impaired lung function following fetal growth restriction is unsurprising given prospective cohort studies demonstrated lung function to 'track' in individuals followed up from infancy through childhood[56, 57] and into later life[57].

A large, early epidemiological study of British men aged 59-70 years demonstrated reduced FEV_1 standardised with respect to age and height in those born with lower birth weights compared to others in this cohort[47]. Similar results were found in a survey of men and women from southern India[58].

Although in many historical studies gestational age is uncertain, prematurity is unlikely to confound these results as survival following preterm birth was low at the time these individuals were born[58]. Moreover, studies in which the association between birth weight and lung function were adjusted for gestational age and maternal factors (including height, weight and parity) suggest that growth restriction is responsible for this effect[59]. More recently, birth weight was positively associated with both FVC and FEV_1 in a large prospective population-based cohort of men and women aged 31 years in Finland. These findings were independent of adult height, gestation, maternal smoking and respiratory disease[60]. Similarly, a recent meta-analysis of eight studies exploring the relationship between LBW and adult lung function reported an increase in FEV_1 of 48 mL per kilogram increase in birth weight after adjustments for age, smoking, and height[61]. However, although reduced lung function in adulthood following fetal growth restriction appears a reasonably robust finding, the extent to which 'catch-up' growth might compensate for the effects of intrauterine adversity is less clear. Whilst early infant lung function studies suggest poorer lung function is associated with rapid early growth[49, 62], other studies provide evidence of compensation for the effects of fetal growth restriction upon lung function measured later in life[60, 63, 64].

Consequences of IUGR for childhood and adult respiratory morbidity (heading level C)

Many investigators have sought an association between evidence of fetal growth restriction and childhood asthma or wheeze, given both the observed association between birth weight and forced expiratory flows and the prominence of airways obstruction in these respiratory disorders. Whilst acknowledging that low birth weight is not synonymous with IUGR and epidemiological techniques are limited in their ability to determine to what extent each individual has fulfilled their growth potential, birth weight is used by many as a proxy for fetal growth to assess long term respiratory morbidity: an association between an increased risk of childhood wheeze and lower birth weight[65, 66] has been found by some, however, others have found an association with higher birth weight[67], and some no relationship at all[54, 68-70]. Although a recent meta-analysis concluded that an increased risk of asthma in childhood or early adult life is associated with higher birth weight[71], the conclusions of individual studies differed considerably on this point. Some misclassification of outcome may have occurred in this analysis as wheeze outcomes measured at different ages were combined; this may not be valid

given that the prevalence of the various wheeze phenotypes varies with age[72]. Moreover, this meta-analysis included only those studies dichotomising birth weight as above average or average and did not consider the full range of birth weights.

The clinical symptoms recognised as asthma probably arise from a number of related syndromes rather than a single illness[72, 73]. Although there is considerable overlap between the different 'wheezing syndromes', the early life histories of those children whose symptoms are limited to early childhood may differ from those who suffer persistent wheeze, and in particular from those suffering wheeze in association with atopy. The health outcomes of infants demonstrating disproportionate growth support a role for restricted fetal growth in the development of an atopic predisposition or symptoms of atopic disease. For example, infants with larger head circumference at birth are at increased risk of elevated serum total IgE[67,74] and asthma in childhood[75] compared to children with smaller head circumferences. Disproportionate head growth may reflect prioritisation of the growth of the brain over that of immune tissue such as the thymus under conditions where the nutritional needs of the fetus cannot be met. These findings are not without controversy. The proposed association between disproportionate growth and atopic disease is an inconsistent finding of all epidemiological studies; some studies found atopy is associated with higher birth weight[76, 77] and length[67]. Moreover, there is evidence to contradict the proposal that larger head size is associated with decreased thymic volume[78].

Poor lung function in adulthood is a consistent independent predictor of all-cause mortality and deaths due to respiratory and cardiovascular disease[79, 80]. This suggests fetal growth restriction may have lasting clinical effects with important public health implications. Studies of young adult conscripts[81, 82] demonstrated an inverse relationship between asthma risk and birth weight and this conclusion was recently confirmed by follow-up of individuals from the 1970 British national birth cohort[83] and a large Swedish twin study[84]. Lower weight at birth and in early infancy is also associated with a higher standardised mortality from chronic obstructive pulmonary disease[47]. These findings have led to the proposal that impaired lung growth may lead to chronic airflow obstruction in late adult life through a failure to obtain maximal lung function potential as a young adult, even if the subsequent rate of decline with age is normal[85, 86].

There is also evidence that IUGR is associated with abnormal pulmonary vasculature. Pulmonary arterial branch stenosis is generally considered a transient phenomenon in neonates and young infants. It does however persist beyond a year in a minority of cases, and this persistence is related to IUGR but not prematurity[87]. IUGR, as measured by ponderal index for gestational age, is also associated with an increased incidence and severity of persistent pulmonary hypertension of the newborn[88].

In summary, <u>in vivo</u> models of IUGR support the epidemiological findings that fetuses subjected to impaired nutrition and oxygen have impaired morphological and functional features of lung and pulmonary vascular development. Importantly these changes persist or even develop with increasing age.

Conclusions (heading level A)

Epidemiological studies using low birth weight as a proxy for IUGR, demonstrate associations with reduced infant lung function and early respiratory morbidity, and also reveal that impaired lung function and respiratory disease persist into adulthood. IUGR can be caused by maternal, placental or fetal causes, and it is difficult in epidemiological studies to tease out the relative factors (such as tobacco exposure, infections or maternal vascular disease) and whether these are having a direct or indirect (affecting the nutrient supply) effect on lung development. Additionally, uncertainties about gestational age at birth confound many, but not all epidemiological studies and future studies should aim to separate maturation from IUGR by analysing gestational age and birth weight z-score rather than birth weight.

<u>In vivo</u> models of maternal nutrient restriction in later pregnancy have provided important insights into the structural and functional implications of IUGR. These studies show that impaired nutrient and oxygen availability to the fetus causes microscopic structural changes which are apparent not only soon after birth, but persist in mature lungs. Fetal nutrition was restricted during the alveolar phase of lung development in many studies. This coincides with the timing when placental insufficiency and

other causes of IUGR are most likely to occur. The impact of variations in the timing and severity of restriction still need further elucidation.

PRACTICE POINTS

- Compromise during pregnancy has life-long implications for respiratory health, morbidity and mortality in the off-spring.
- Prevention of fetal compromise through careful monitoring and intervention during pregnancy.
- Avoidance of preventable causes of IUGR, in particular education and assistance to avoid tobacco smoking in pregnancy.
- Future epidemiological analyses need to carefully separate contribution of gestation and intrauterine growth restriction by using birth weight Z score rather than birth weight as the indicator of intrauterine nutrition.

RESEARCH DIRECTIONS

- Development of effective methods to prevent mothers smoking in pregnancy.
- A greater understanding of the changes in lung development that are caused by IUGR may lead to further research to investigate ways of blocking the abnormal development or enhancing normal lung development.
- Evaluation of the long term effects of IUGR on surfactant production, innate immunity of the lung, mucins, and ciliary function, and function of the respiratory musculature.
- A better understanding of how different causes, timing and duration of IUGR impact on lung development.
- Improved detection of fetal compromise during pregnancy, and methods to intervene.
- Assessment of the effect of fetal lung maturational treatments (such as glucocorticoids) on the viability and long term cardiorespiratory outcomes of the IUGR infant.

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Figure 1 - Causes of Intrauterine Growth Restriction: Maternal, fetal, placental and environmental

(outside circle) factors that contribute to development of intrauterine growth restriction