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Review

Respiratory consequences of late preterm birth

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EDUCATIONAL AIMS

- To review the evidence for respiratory morbidity, in particular long-term adverse outcomes, associated with late preterm birth.
- To consider the mechanisms by which late preterm birth impacts upon respiratory development.
- To recognise interventions which might protect respiratory development and improve outcomes for this patient group.

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SUMMARY

In developed countries most preterm births occur between 34 and 37 weeks' gestation. Deliveries during this 'late preterm' period are increasing and, since even mild prematurity is now recognised to be associated with adverse health outcomes, this presents healthcare challenges. Respiratory problems associated with late preterm birth include neonatal respiratory distress, severe RSV infection and childhood wheezing. Late preterm birth prematurely interrupts *in utero* lung development and is associated with maternal and early life factors which adversely affect the developing respiratory system. This review considers 1) mechanisms underlying the association between late preterm birth and impaired respiratory development, 2) respiratory morbidity associated with late preterm birth, particularly long-term outcomes, and 3) interventions which might protect respiratory development by addressing risk factors affecting the late preterm population, including maternal smoking, early life growth restriction and vulnerability to viral infection.

INTRODUCTION

Babies born between 34 and 37 weeks of gestation have, until recently, been considered sufficiently mature to be treated similarly to term infants. Whilst for many of these infants outcomes are good, it is now recognised that significant maturation occurs during the last weeks of gestation, placing late preterm infants at increased risk of adverse health outcomes in the neonatal period and beyond [1,2]. Late preterm delivery interrupts normal *in utero* respiratory development and relative immaturity is compounded by associated adverse perinatal factors. These include increased rates of caesarean delivery [3], and increased rates of intrauterine growth retardation[4] and associated maternal factors, including hypertensive disorders, diabetes and smoking [5,6]. Additionally, morbidities incurred during the early postnatal period, including neonatal respiratory distress [1], poor feeding and growth [7], and vulnerability to respiratory viruses [8] have lasting consequences for respiratory development. (Figure 1) This is significant since early life lung development is increasingly recognised as a determinant of later respiratory health [9]. Moreover, following temporal changes in maternal age, infertility treatments, multiple birth prevalence, and obstetric interventions [10,11], late preterm deliveries now account for the largest and most rapidly increasing proportion of preterm births [12–14].

MECHANISMS

Normal lung development proceeds from the embryonic period (day 26-52) through pseudoglandular (day 52-week 16), canalicular

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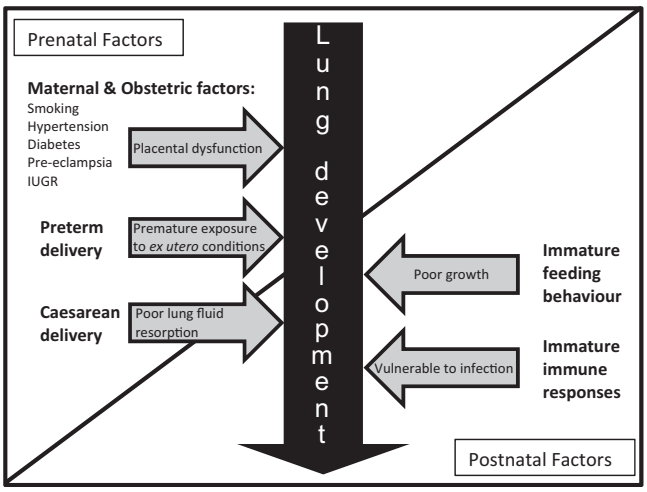

Figure 1. mechanisms contributing to poor respiratory outcomes following late preterm birth.

(17-26 weeks) and saccular periods (24-36 weeks to term) to the alveolar period; during which alveolar development commences at 36 weeks' gestation and continues into postnatal life [15,16]. Extreme preterm (< 28 weeks) and very preterm birth (28-32 weeks) occur, respectively, during the canalicular period; characterised by precapillary and bronchiole formation, and the saccular period; characterised by capillary proliferation, saccule formation and commencement of surfactant production. Late preterm birth occurs during the most rapid period of lung maturation, at the transition between saccular and alveolar periods [17].

Consequences of prematurity

Histologic studies suggest preterm birth is associated with structural changes in the lung, including increased bronchial muscle, collagen and elastin [18]. Premature exposure to high oxygen tension and other aspects of the *ex utero* environment likely contributes to these effects [19]. The maturational processes affected by late preterm birth are those occurring during the final weeks of pregnancy; a progressive decrease in air-space wall thickness and a simultaneous increase in air-space surface area [17]. These maturation processes are proposed to improve parenchymal elastance and airway-tethering. The functional consequences of late preterm birth have been hypothesised to include difficulty protecting functional residual capacity, and vulnerability to airway collapse and increased airway resistance [20]. After late preterm birth, lung fluid clearance is delayed since this is dependent upon developmentally regulated epithelial sodium (ENaC) channels [21].

Early life factors

Prenatal growth

Many of the complications associated with late preterm delivery increase the risk of placental insufficiency and *in utero* growth restriction. Epidemiological data suggest *in utero* growth restriction might be associated with persistently impaired respiratory development [22], although few studies have specifically followed up late preterm individuals. Due to difficulties associated with gestational age assessment, particularly in large population-based studies, distinguishing the effects of prematurity and growth restriction is challenging. For example, whilst a large meta-analysis of European birth-cohort data, concluded that gestational age at birth appears to largely explain the inverse relationship between birthweight and childhood asthma, the association found between rapid postnatal weight gain and later wheeze might reflect 'catch-up' growth in individuals with restricted growth misclassified for gestational age [23]. Although the contribution of *in utero* growth restriction to clinical outcomes remains contentious, mechanistic animal studies, nevertheless, suggest structural and functional changes in the lung follow restricted prenatal growth [24,25].

Postnatal growth

Late preterm infants are at risk of postnatal growth restriction due to the combined effects of increased nutritional demands associated with respiratory and other morbidities, and of developmental difficulties with feeding, particularly breastfeeding [26]. Weight gain in babies born late preterm falls below expected intrauterine norms [7] and poor growth often persists beyond the neonatal period [27]. Millennium study data demonstrate that the odds of being underweight at 3 and 5 years of age increase progressively with decreasing gestation, such that late preterm infants are at increased risk compared with term infants [2]. However, early growth restriction, particularly when followed by rapid catch-up growth, is increasingly recognised as a risk factor for obesity [28]. Within the Millennium study the late preterm group contained the highest proportion of children classified as obese [2].

Immunity

Premature birth interrupts maternal antibody transfer, and immune maturation does not occur until midway through the first year of life [29]. Late preterm infants are susceptible to lower respiratory tract infections as a consequence of immature humoral immunity. Additionally, adaptive cytotoxic T-lymphocyte responses are immature and viral clearance by innate immune responses is inefficient [8].

RESPIRATORY MORBIDITY

Neonatal

A 2011 systematic review and meta-analysis concluded that late preterm infants are more likely to need mechanical ventilation (RR 4.9; 95% CI, 2.8–8.6), and are at higher risk of neonatal respiratory morbidities, including respiratory distress syndrome (RDS) (RR 17.3; 95% CI, 9.8–30.6), transient tachypnoea of the newborn (RR 7.5, 95% CI 5.0–11.2), persistent pulmonary hypertension (RR 4.9, 95% CI 3.8–6.3), apnoea (RR 15.7, 95% CI 11.8–20.9), pneumothorax (RR 3.4, 95% CI 1.8–6.4) and pneumonia (RR 3.5, 95% CI 1.4–8.9) [1]. Respiratory complications appear to increase proportionately with increasing prematurity [30], although pregnancy complications, particularly those affecting placental function, might compound the effects of relative immaturity [31]. Recent studies comparing the neonatal outcomes of late preterm with term infants confirm late preterm infants to have higher rates of respiratory morbidity [32,33] and to be more likely to require respiratory support or surfactant therapy [34,35].

Infancy and childhood

Within the late preterm population relatively high rates of respiratory morbidity generate significant healthcare activity and costs in infancy and childhood [36]. (Table 1) A US study of children under 2 years of age requiring intensive care for a respiratory illness found that 30% were born prematurely and over a third of these were born late preterm. Median hospital stay was 2 days greater in late preterm infants and, even after adjusting for this, total hospital charges were approximately one and a half times those of term infants [37].