Developmental consequences outcomes of late preterm birth

Katharine C Pike MRCPCH PhD[a,b,c] and Jane SA Lucas FRCPCH FRCP PhD[a,b]

[a]Clinical and Experimental Sciences Academic Unit, University of Southampton Faculty of Medicine, Tremona Road, Southampton SO16 6YD, UK.

[b]NIHR Southampton Respiratory Biomedical Research Unit, University of Southampton and University Hospital Southampton NHS Foundation Trust, Tremona Road, Southampton SO16 6YD, UK.

[c]University College London, Institute of Child Health, 30 Guilford Street London WC1N 1EH, UK.

Corresponding author: Dr Katharine Pike, Mailpoint 803, University of Southampton Faculty of Medicine, Tremona Road, Southampton SO16 6YD, UK

katypike@soton.ac.uk Phone: +44(0)23 81 206160 Fax: +44 (0)2380 878847

jlucas1@soton.ac.uk

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.

Future research directions:

The potential for catch-up lung growth in late preterm infants is not fully understood and requires careful study in animal models as well as prospective clinical studies. Interventions based upon maximising and protecting lung growth should also be evaluated. Useful areas for further exploration include, timing of obstetric intervention, effects of nutrition and growth upon respiratory development and benefits associated with RSV prophylaxis.

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Abstract

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.

1 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 respiratory later 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]

2 Mechanisms

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

Figure 1 mechanisms contributing to poor respiratory outcomes following late preterm birth
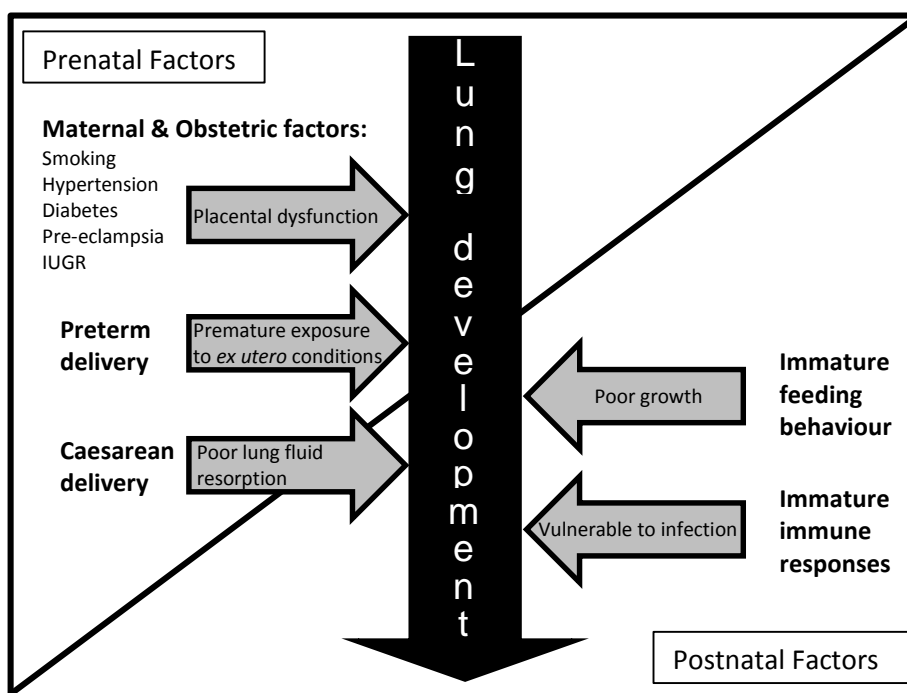
2.1 Consequences of prematurity

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]

2.2 Early life factors

2.2.1 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]

2.2.2 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]

2.2.3 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]

3 Respiratory morbidity

3.1 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]

3.2 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]

During infancy late preterm infants have rates of hospital admission for RSV infection (57 per 1000) exceeding those of term infants (30 per 1000), and approaching those of earlier preterm infants (66-70 per 1000).[38] Late preterm infants are vulnerable to severe symptoms since infection early in the course of immune maturation is associated with greater inflammatory responses and sloughing of dead cells,[39] this is then compounded by having relatively smaller airways than term infants.

Retrospective studies suggest late prematurity increases the risk of both childhood wheeze and asthma.[2, 40-44] A records-based survey of 7925 children from 31 medical practices demonstrated significant associations between late preterm birth and corticosteroid use (OR 1.68, 95% CI 1.20-2.29) and persistent asthma by 18 months (OR 1.68, 95% CI 1.01-2.80).[42] Recently, a large prospective cohort found 988 children born at 32-36 weeks' gestation to experience more wheeze and nocturnal cough at school age and also to receive more inhaled steroids than 573 term-born children.[44] Not all studies have been in agreement, however, particularly at older ages. Data from 537 late preterm and 5650 term-born children in the Third National Health and Nutrition Examination Survey, for example, failed to demonstrate a significant increase in doctor-diagnosed asthma in children aged 2-83 months.[45]

3.3 Adulthood
There are few studies and no prospective data describing long-term outcomes. One study of over six thousand young adults (25-53 years) found no association between late preterm birth and asthma medication use.[46] However, this study relied upon retrospective data and,

since pregnancy dating by ultrasound scanning was not routine 25-35 years ago, gestational dating was limited to estimation based upon last menstrual period data.

Table 1 Studies comparing long-term outcomes in individuals born late preterm with those in individuals born at term

	Study design	Late preterm	Term	Outcomes: late preterm vs term
Bird *et al* 2010[36] US	State wide insurance claims case control Matched according to propensity score Births 2001-2005, excluded multiple births and those with congenital anomalies	5188 infants 34 0/7-36 6/7 weeks	15303 infants 37 0/7-42 6/7 weeks	Additional first year health costs Outpatient $108, 95%CI $58-$158 Inpatient $597, 95% CI $528-$666 Total $734, 95% CI $630-$829 Rehospitalisation within first year OR 1.11, 95% CI 1.01-1.23
Harju *et al* 2014[41] Finland	Retrospective single centre case control Births 1989-2008	2355 individuals 33 0/7-36 6/7 weeks	22804 individuals 39 0/7-40 6/7 weeks	Asthma at any time OR 1.7, 95% CI 1.4-2.0
Boyle *et al* 2012[2] UK	Secondary analysis of birth cohort data Births 2000-2002	1107 children 34 0/7-36 6/7 weeks	12540 children 39 0/7-41 6/7 weeks	Wheeze or asthma at 3 years OR 1.3, 95% CI 1.0-1.5 Wheeze or asthma at 5 years OR 1.5, 95% CI 1.2-1.8 Asthma medication at 5 years OR 2.2, 95% CI 1.6-3.1
Berard *et al* 2012[40] Canada	Health record based health economic analysis Births 1997-2000	2051 children 33 0/7-36 6/7 weeks	33682 children 37 0/7	Health costs first 2 years of life CR 1.99, 95% CI 1.90-2.09 Health costs third year of life CR 1.46, 95% CI 1.39-1.54 Conditions in first 3 years Bronchitis/bronchiolitis OR 1.64, 95% CI 1.13-2. Asthma OR 1.2, 95% CI 1.11-3.30 Pneumonia 1.17, 95% CI 1.05-1.30 Other upper respiratory condition OR 1.16, 95% CI 1.06-1.28 Other respiratory condition OR 1.23, 95% CI 1.09-1.38
Crump *et al* 2011[47] Sweden	National registry data Births 1973-1979, excluded multiple births	22590 adults 34 0/7-36 6/7 weeks	626723 adults 37 0/7-42 6/7 weeks	Mortality 1-5 years and 18-36 years but not 6-12 or 13-17 years inversely related to gestation Mortality 18-36 years HR 1.31, 95% CI 1.13-1.50
Goyal *et al* 2011[42] US	Retrospective multi-centre cohort study from electronic records Births 2007, excluded those with congenital anomalies	582 infants 34 0/7-36 6/7 weeks	5540 infants 39 0/7-42 6/7 weeks	Within first 18 months Asthma OR 1.26, 95% CI 0.92-1.73 Persistent asthma OR 1.68, 95% CI 1.01-2.80 Corticosteroid use OR 1.66, 95% CI 1.20-2.29 Acute respiratory visits IRR 1.44, 95% CI 1.24-1.67
Vrijlandt *et al* 2013[48] Netherlands	Prospective multi-centre cohort with term controls	988 children 32 0/7-35 6/7 weeks	573 children 38 0/7-41 6/7 weeks	Respiratory symptoms in first year 22% vs 13%, p<0.001 Cough/wheeze during a cold age 4 years % vs 3% p<0.001 Cough/wheeze without a cold age 4 years 23% vs 15% p<0.001 Use of inhaled steroids age 4 years 9% vs 6% p=0.036 Asthma age 5 years 10% vs 6% p=0.022
Abe *et al* 2010[45] US	Nationally representative cross-sectional survey, excluded multiple births	537 children 34 0/7-36 6/7 weeks	5650 children 37 0/6-41 6/7 weeks	Aged 2-83 months at time of survey Asthma HR 1.3, 95% CI 0.8-2.0
Crump *et al* 2011[46] Sweden	National registry data Births 1973-1979	21918 adults 33 0/7-36 6/7 weeks	579359 adults 37 0/7-42 6/7	Assessed at age 25-35 years Extreme preterm birth associated with increased prescription of asthma medications but late preterm birth was not OR 0.97, 95% CI 0.9-1.04
Escobar *et al* 2010[43] US	Registry based prospective cohort Births 1996-2002	4288 children 34 0/7-36 6/7 weeks	50092 children 38 0/7-40 6/7 weeks	Recurrent wheeze third year of life OR 1.23, 95% CI 1.07-1.41

Original English language articles investigating late preterm infants with a clear comparison group identified from PubMed, MEDLINE, Embase, and Cochrane trials databases (July 2010-October 2014) search terms "34 weeks" or "35 weeks" or "36 weeks" and "late preterm" or "near term" and "complications" or "morbidity" or "outcome" including references identified in original articles or reviews identified by the above search. Abbreviations: IRR incidence risk ratio, HR hazard ratio, CR cost ratio, OR odds ratio, CI confidence interval.

4 Respiratory physiology

Studies evaluating the effects of prematurity independent from those of neonatal respiratory disease or its treatments have largely recruited late preterm infants since these infants generally require less intervention than those born at earlier gestations. Reduced expiratory flows at a year of age were reported in a study of 24 healthy preterm infants born at 29-36 weeks' gestation. [49] (Table 2) This study used the rapid thoracoadominal compression technique to measure maximal forced expiratory flow at functional residual capacity (V'_{maxFRC}), 3 weeks and one year after birth. V'_{maxFRC} at 3 weeks was not significantly different from predicted values based upon age, length and gender: this may, however, reflect overestimation of V'_{maxFRC} since physiological elevation of FRC is employed at this age to protects lung volume given the flexibility of the chest wall. A later study used the raised volume thoracoabdominal compression technique to measure timed forced expiratory flows independent of a volume landmark. Reduced forced expiratory flows were found at 8 weeks of age in 62 preterm infants (gestations 27-37 weeks) compared with 27 infants born at term;[50] forced expiratory flows were also reduced in the late preterm infants at one year of corrected gestational age.[51] More recently, passive respiratory mechanics and tidal breathing parameters were compared in 31 healthy 33-36 week infants at term-equivalent age and 31 term infants within 72 hours of birth. The late preterm infants had decreased respiratory compliance, decreased tidal ratio and increased respiratory resistance.[52]

No study has prospectively assessed respiratory physiology in late preterm individuals beyond infancy but cross-sectional studies suggest that forced expiratory flows remain reduced through childhood and into adolescence. In an early study, spirometry and lung volume measurements at 8-15 years were compared between 34 children born preterm (34-36 weeks) and 34 term-born siblings.[53] No between group differences in spirometry were identified, although both the mean residual volume and residual volume as a proportion of total lung capacity in the preterm group were significantly higher than those of the sibling controls. More recently, however, data from the Avon Longitudinal Study of Adults and Children demonstrate that in children born 33-34 weeks' gestation spirometry indices are reduced at 8-9 years of age and that measures of FEV_1/FVC and $FEF_{25-75\%}$ remain reduced at age 14-17 years compared to term controls.[54] Little is known about physiological measures other than spirometry in late preterm infants; children born extremely preterm, however, have been demonstrated to have normal levels exhaled nitric oxide at school age but evidence of airway obstruction, ventilation inhomogeneity, gas trapping and airway hyperresponsiveness,[55]

Table 3 Studies comparing respiratory physiology in individuals born late preterm to that in individuals born at term

	Measures and technique	Preterm	Comparator	Outcome difference between term and preterm values
McEvoy et al 2011[51] US	Respiratory compliance measured by single breath occlusion Ratio of time to peak expiratory flow to expiratory time measured from flow volume loops FRC from nitrogen washout	31 infants mean SD gestation 34.1 1.0 weeks Without clinical respiratory disease Tested at term corrected age	31 infants Matched for sex and race Tested within 72 hours of delivery	Crs 1.14 vs 1.32 ml/cm H_2O/kg p<0.02 TPTEF:TE 0.308 vs 0.423 cm H_2O/ml/s p<0.01 Rrs 0.064 vs 0.043 cm H_2O/ml/s p<0.01 No difference in RR or FRC
Friedrich et al 2006[50] Brazil	Forced expiratory flows measured by the raised volume rapid thoracoabdominal compression technique	62 infants Mean, SD gestation 33.4, 2.11 Less than 48 hour supplemental oxygen therapy Tested in first 12 weeks of life	27 term infants without respiratory disease tested age 0-3 years	Adjusting for length, age and sex FEF_{50} -92 ml/s (22%) p=0.013 $FEF_{25-75\%}$ -73 ml/s (20%) p=0.024 $FEV_{0.5}$ -19 m (13%) p=0.036
Hoo et al 2002[49] UK	Forced expiratory flows measured by the rapid thoracoabdominal compression technique	24 infants Mean 33.2 SD 2.2 weeks with no respiratory support tested at 3 weeks after birth and at a corrected age of one year	Sex-specific prediction equation z-scores for term infants	At 3 weeks mean V'_{maxFRC} z-score -0.06 SD 0.92 At 1 year mean V'_{maxFRC} z-score -2.0 SD 0.94 Mean, 95% CI 2nd-1st test z-scores -1.94, -2.27 to -1.60
Friedrich et al 2007[52] Brazil	Forced expiratory flows measured by the raised volume rapid thoracoabdominal compression technique	26 infants Mean, range gestation 32.7, 30-34 weeks Less than 48 hour supplemental oxygen therapy Tested at one year of age	24 term infants without respiratory disease tested age 0-3 years	FEF_{50} -85 ml/s p=0.078 $FEF_{25-75\%}$ -97 ml/s p=0.027 $FEV_{0.5}$ -16 ml p=0.348
Todisco et al 1993[53] Italy	Bronchial reactivity to methacholine and lung volumes	34 infants Mean 34.9 weeks	34 sibling controls Mean 39.5 weeks	RV 1.09 ± 0.3 litres late preterm vs 0.84 ± 0.1 litres term <0.01 RV/TLC 28 ± 6% late preterm vs 22 ± 2% term<0.01 No difference in bronchial reactivity (11.8% late preterm vs 5.9% term hyperreactive)
Kotecha et al 2012[56] UK	Spirometry	Children born 33 0/7-34 6/7 weeks 79 tested 8-9 years 49 tested 14-17 years	Children born 37 0/7-43 6/7 weeks 6144 tested 8-9 years 4105 tested 14-17 years	8-9 years FEV_1 -0.485, 95% CI -0.724 to -0.246 Also lower FVC, $FEF_{25-75\%}$, FEV_1/FVC, $FEF_{25-75\%}$/FVC 14-17 years $FEF_{25-75\%}$ -0.289, 95% CI -0.577 to -0.001 FEV_1/FVC -0.379, 95% CI -0.666 to -0.092 No significant deficit at gestation 35 0/7 − 36 6/7 weeks

Original English language articles identified from PubMed, MEDLINE, Embase, and Cochrane trials databases (July 2010-October 2014) search terms "34 weeks" or "35 weeks" or "36 weeks" and "late preterm" or "near term" and "complications" or "morbidity" or "outcome" including references identified in original articles or reviews identified by the above search.

Abbreviations: T_{PTEF} time to peak expiratory flow, T_E expiratory time, Crs respiratory system compliance, Rrs respiratory system compliance, FEF_{50} $FEF_{25-75\%}$ forced expiratory flow at 50% and between 25 and 75% of the forced vital capacity, $FEV_{0.5}$ forced expiratory volume in first 0.5 seconds of expiration, V'_{maxFRC} maximal flow at functional residual capacity, RV residual volume, TLC total lung capacity, Forced expiratory volume in the first second of expiration, CI confidence interval.

5 Interventions

5.1 Protecting prenatal lung development

5.1.1 Obstetric interventions

Preterm delivery may be spontaneous or indicated in response to adverse maternal or fetal conditions. Spontaneous premature deliveries continue to outnumber those attributable to obstetric indications, particularly after 34 weeks of gestation where spontaneous deliveries account for 80% of births;[57] nevertheless, prematurity due to obstetric intervention is increasing.[58] Whilst this increase has been associated with a decrease in stillbirths and likely reflects higher rates of maternal or fetal indications for intervention [59], given the adverse impact of prematurity upon respiratory development, the relative risks and benefits of iatrogenic pregnancy interruption should be carefully considered. For example, a recent clinical trial found no increased in neonatal sepsis after expectant compared with interventional management of preterm premature rupture of membranes,[60] however, pregnancy interruption at 34 weeks' when compared to interruption at 36 weeks' gestation is associated with increased risk of RDS (RR 8.6; 95% CI 2.7-27.5).[61]

5.1.2 Antenatal corticosteroids

Antenatal corticosteroid administration has been proposed to increase lung fluid clearance[62] and might potentially benefit late preterm infants. Despite this, tocolysis and antenatal steroid administration have not traditionally been considered indicated beyond 34 weeks of pregnancy. Observational data[63] and a small case controlled study of lung function following antenatal steroid administration[64] suggest this treatment may reduce neonatal morbidity after late preterm birth. Clinical trials, however, have not shown consistent benefit at later gestations.[65, 66] These studies might have been underpowered to demonstrate reduced RDS given possible heterogeneity, perhaps with greater benefit in those born by elective caesarean section, for example, and the low absolute incidence of RDS.

5.2 Protecting postnatal lung development

5.2.1 Growth and nutrition

There is evidence that growth restriction during the final weeks of term pregnancies is associated with poorer lung function: for example, small size at birth and rapid postnatal 'catch-up' weight gain have been shown to be associated with reduced infant lung function.[67] Since late preterm infants commence *ex utero* life during the phase of development equivalent to the last weeks of a term pregnancy, nutritional support during early postnatal life might help to prevent growth restriction and adverse effects upon respiratory development. Certainly, in early preterm infants bronchopulmonary dysplasia occurs most frequently in those with poor somatic growth.[68] Potential nutritional interventions to support respiratory development during the early life include appropriate

breastfeeding support,[69] acknowledging the immaturity of feeding behaviour in late preterm infants[70] and its impact upon lactation,[26] and supplementation where necessary.[7] Beyond infancy, the optimal pattern of growth for respiratory health is unclear. Whilst there is evidence that asthma risk is increased in teenagers who were born small for gestational age but later become obese,[71] no studies have specifically considered the impact of nutrition and growth upon respiratory outcomes in late preterm infants who, as a group, appear to be at increased risk of both early growth restriction[4, 7] and later obesity.[2]

5.2.2 RSV prophylaxis

Late preterm infants do not generally receive RSV prophylaxis, despite findings from the IMpact clinical trial demonstrating benefit to infants born up to and including 35 weeks gestation[72]. It has been suggested that vaccination programmes could be extended to less premature infants, particularly if those most at risk could be identified. The Italian FLIP study (Factors Leading to RSV-related Infection and hospitalisation among Premature infants) produced a model of seven variables predicting RSV-related hospitalisation in infants born at 33–35 weeks' gestation: predictors were gender, birth weight, birth within 10 weeks of start of season, breastfeeding for less than 2 months, siblings older than 2 years, and family history of atopy or wheeze.[73] Interestingly, given that considerable data exist supporting an association between parental smoking and lower respiratory tract infection, smoking was not included amongst these risk factors. Children from smoking households without RSV prophylaxis have, however, been found in a meta-analysis of FLIP-study and other data to be at 2.53 (95% CI 1.27-4.94) times greater risk of RSV hospitalisation compared to children living in non-smoking households.[74] Smoking was found to be correlated with a number of other risk factors for RSV hospitalisation, potentially explaining why it was not included in the FLIP model. In infants receiving RSV prophylaxis the risk of RSV hospitalisation did not differ significantly in smoking and non-smoking households. Taken together these findings suggest parents of late term infants should be supported in smoking cessation and that a risk factor-based approach might identify infants likely to benefit most from vaccination.

Integrated healthcare data from 71,102 children born in Northern California at 32 weeks of gestation or later found the risk of recurrent wheeze to be elevated in those with a previous RSV infection compared with those without.[43] Evidence is emerging that this association might reflect a causal relationship. If susceptibility to RSV places preterm infants at greater risk of altered immune or lung development, RSV infection should be regarded as an important cause of subsequent wheezing in this population. Indeed, non-randomised trials of measures to reduce RSV infection in preterm infants have demonstrated that prevention of

infection might reduce the number of days of symptomatic wheeze in the first year of life, although this protection appears possibly limited to non-atopic infants.[76]

6 Conclusion

Babies born late preterm are at increased risk of respiratory morbidity. Late preterm delivery interrupts normal lung development and is associated with obstetric complications and neonatal morbidities which compound the adverse developmental consequences of preterm birth. Infants born late preterm have poorer lung function from birth than infants born at term. Relative lung function deficits persist through infancy and late preterm birth appears to be associated with an increased risk of wheeze in childhood. The challenge now is to identify those individuals most at risk and to develop interventions which minimise the consequences of impaired lung development and where possible promote normal development of the respiratory system.

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