Seminars in Fetal and Neonatal Medicine 24 (2019) 48–53

Contents lists available at ScienceDirect

Seminars in Fetal and Neonatal Medicine

journal homepage: www.elsevier.com/locate/siny

Early childhood health and morbidity, including respiratory function in late preterm and early term births

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ARTICLE INFO

Keywords:
Late preterm birth
Early term birth
Health outcomes
Respiratory morbidity

ABSTRACT

Late preterm (LP) and early term (ET) infants have generally been considered in the same way as their healthy full term (FT) counterparts. It is only in the last decade that an increased risk of later poor health in children born LP has been recognised; evidence for health outcomes following ET birth is still emerging. However, reports are largely consistent in highlighting an increased risk, which lessens approaching FT but is measurable and persists into adolescence and beyond. The most thoroughly explored area to date is respiratory morbidity. This article reviews the body of available evidence for effects of LP birth on pulmonary function and ongoing morbidity, and other areas where an increased risk of health problems has been identified in this population. Implications for delivery of health care are considered and areas for further research are highlighted.

1. Introduction

Historically, most research relating to childhood health following preterm birth has been focused on the outcomes of extremely preterm (23^{+0} to 27^{+6} weeks of gestation) and very preterm (28^{+0} to 31^{+6} weeks) infants [1–3]. These infants require specialist neonatal services and admission to neonatal units and are most likely to suffer adverse long-term health problems as a result of their preterm birth. Late preterm (LP; 34^{+0} and 36^{+6} weeks) infants and early term (ET; 37^{+0} to 38^{+6} weeks) infants have been considered at low risk due to their larger size and perceived maturity, and have generally been managed in similar postnatal settings to their well full-term (FT; 39^{+0} to 41^{+6} weeks) counterparts. However, in the last decade, LP babies have been shown to have greater morbidity and mortality than previously thought, when compared with FT infants [4–8]. More recently, it is increasingly acknowledged that there is a gradient of risk across the full gestational age (GA) spectrum and, although the evidence base is smaller and risks less well delineated, it appears that health of children born ET is also worse [9–12]. Births at LP and ET gestation make up approximately one-third of all live births [13]. Although most do well, health consequences are now being identified and constitute a significant burden on health care resources for children and adolescents because of the large numbers of infants. The effects of LP and ET birth on early childhood health and morbidity will be reviewed here.

2. Early mortality

Death during infancy and childhood in the LP and ET population is uncommon. However, there is a body of evidence demonstrating that rates of mortality are higher compared with those born at FT. Crump et al. analyzed a Swedish cohort born between 1973 and 1979 [14]. They showed that LP infants had an increased risk of mortality in early childhood (1–5 years; adjusted hazard ratio (aHR) 1.53; 95% confidence interval (CI): 1.18–2.00; $P = 0.001$) and young adulthood (18–36 years) (aHR: 1.31; 95% CI: 1.13–1.5; $P < 0.001$), when compared with their term-born counterparts. This same study, however, showed no association between GA and mortality during late childhood and adolescence. A further study in the same cohort showed ET infants also had increased mortality in the post-neonatal period (28–364 days) aHR: 1.66; 95% CI: 1.44–1.92) and early childhood (1–5 years: aHR: 1.29; 95% CI: 1.10–1.51) when compared with FT infants born at 39–42 weeks of gestation [15]. An Australian study of mortality rates in children of different gestations at birth showed that LP and ET carried an increased risk of neonatal mortality when compared with FT birth but that there was insufficient evidence to link GA to mortality beyond the first year of life [16]. These findings were echoed by a French study showing a significant difference in infant mortality (34 weeks (aRR: 1.8) vs 39 weeks (aRR: 1.0)) [17]. However, Tomashek et al. found that LP infants had a three-fold higher rate of mortality when compared with term infants [7]. Reddy et al. also showed that ET infants had

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https://doi.org/10.1016/j.siny.2018.10.007

higher neonatal and infant mortality rates when compared with those born at FT [18]. King et al. found that the most common cause of post-neonatal death for LP and ET infants was congenital abnormalities, followed by sudden infant death syndrome (SIDS) and accidents. Infant mortality in LP singletons was higher than in LP twins, but this association was reversed in twins > 37 weeks gestation [19].

3. Neonatal morbidity in LP and ET infants

Whereas the majority of LP and ET infants will not experience significant neonatal complications, studies have consistently shown that they have increased morbidity when compared with FT birth [11,20–29]. This is illustrated by a study indicating that LP and ET infants were at increased risk for neonatal intensive care unit triage and admission (LP aRR: 6.14; 95% CI: 5.63, 6.71; ET aRR: 1.54; 95% CI: 1.41, 1.68) and neonatal respiratory morbidity (LP aRR: 6.16; 95% CI: 5.39, 7.03; ET aRR: 1.46; 95% CI: 1.29, 1.65) [22]. A Massachusetts population-based study compared outcomes of LP infants with term infants and showed that LPs were seven times more likely to have newborn morbidity than term infants. The newborn morbidity rate doubled for each gestational week prior to 38 weeks, and was increased when maternal risk factors were taken into account [30]. The commonest reason for neonatal unit admission in this population was respiratory morbidity, which includes respiratory distress syndrome, transient tachypnoea of the newborn, and respiratory infections. This may be related to their prematurity and associated lung immaturity, or to the mode of delivery. During birth hospitalization, LP and ET babies were more likely to have the following complications: hypothermia, hypoglycemia, respiratory distress, jaundice treated with phototherapy, feeding difficulties, and to require investigation for suspected infection [8,21,31–33]. There is, however, a paucity of knowledge about whether, or to what extent, early history and type and/or severity of neonatal illness influence later health outcomes.

4. Hospitalization in infancy and childhood

Late preterm and ET infants have been shown to have more hospital readmissions when compared with FT infants [34]. During the first weeks of life, jaundice, poor feeding, dehydration, and infection have been found to be the most common reasons for readmission. A population-based study by Iacobelli et al. reported that the most common causes of post-neonatal hospitalization were infection (bronchiolitis, gastroenteritis, ear, nose and throat disease), accidents and surgery, with LP infants accounting for 35.9% of these admissions [17]. Analysis of data from the UK Millennium Cohort Study [15] showed that 2.9% of children born LP and 1.2% of those born at ET gestation had three or more hospital admissions in the first nine months of life, compared with 0.6% of term infants. These proportions increased to 4.9%, 3.9% in LP and ET respectively vs 2.8% (term infants) at five years of age [9]. Subsequently, a recent meta-analysis by Isayama et al. compared health services use in LP and term (37–41 weeks) infants [35]. This demonstrated a higher likelihood of admissions for all causes in infants and children born LP that decreased with increasing age but remained significant up to 18 years of age (OR (95% CI): first year: 1.44 (1.13–1.47); 1–6 years: 1.39 (1.32–1.47); 5–12 years: 1.32 (1.29–1.35); 12–18 years: 1.09 (1.04–1.12)). Reasons included respiratory disease, infections, and neurological or psychiatric problems.

5. Childhood respiratory morbidity

Several large population-based studies have highlighted the growing recognition that these population subgroups have a greater incidence of respiratory morbidity than previously recognised, in the neonatal period and beyond [21,24,35–43]. The most prevalent of these morbidities are respiratory infections, respiratory syncytial virus (RSV) bronchiolitis, infant wheezing and asthma. Paranjothy et al. in a large Welsh population-based study of children born between 1998 and 2008, showed that risk of emergency admissions for respiratory problems decreased with every week of gestation, extending up to 40 weeks [44].

5.1. Lung development and pulmonary function

The third trimester of pregnancy represents a rapid stage of lung growth, characterized by transition from the terminal sac period to the alveolar period of development [45]. In the late saccular phase, numbers of bronchi are increasing, saccules start to form alveoli, and surfactant production occurs [46]. The alveolar stage of lung development starts at 36 weeks gestation to term, and continues into childhood. It has been suggested that interruptions to these processes are likely to lead to reduced gas exchange, reduced surfactant production, delayed reabsorption of fluid at birth and to increased susceptibility of the lungs to infection and other disease processes [47]. This may manifest as respiratory distress syndrome or transient tachypnoea of the newborn in the neonatal period, and later as ongoing impaired lung function and respiratory vulnerability. Although lung function in extremely preterm survivors has been explored, few studies to date have been designed to fully consider the long-term effects on childhood pulmonary function in these more mature infants.

Kotecha et al. used spirometry data – forced expiratory volume (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25–75% of FVC ($FEF_{25–75}$) – from those participants in the large UK Avon Longitudinal Study of Parents and Children (ALSPAC) who engaged with respiratory follow-up at 8–9 years and 14–17 years of age, to study lung function in children born at 33–34 weeks and 35–36 weeks compared with those born at 37 weeks of gestation or more [48]. FEV_1/FVC and $FEF_{25–75}$/FVC were also calculated as markers of airway obstruction and dysanapsis. Children born at 33–34 weeks of gestation had spirometry measures that were all significantly lower than those of their term-born peers at 8–9 years, with the effect size being similar to that seen in children born very preterm. By 14–17 years, FEV_1 and FVC had improved to similar levels as those in term-born adolescents, but differences in FEV_1/FVC and $FEF_{25–75}$/FVC remained significant. Measurements in the 35–36-week group were not different from those in the term-born children at either point in time. A second study reporting data from the ALSPAC cohort compared lung function in children born at ET gestation, compared with those born at FT [49]. Caesarean delivery was significantly more common in the ET group. In both studies, it was noted that non-attenders for spirometry follow-up were more likely to be of a lower social class and to have mothers who smoked. At 8–9 years, whereas standardized spirometry measures were within the normal range, they were lower in the ET group, compared with the FT group. Measures between the two groups were similar at age 14–17 years.

Thunqvist et al. looked at the impact on lung function over time in moderate to LP birth (32–36 weeks of gestation) using data from a large prospective Swedish cohort study, but they did not report on LP infants alone [50]. They compared lung function in this group with that in children born at 37–41 weeks of gestation and identified a gender difference at 8 years of age, with a lower FEV_1 in girls than boys after adjustment for height, age, and maternal smoking in pregnancy. They found no evidence of 'catch-up' over time and at 16 years of age a reduction in FEV_1 was seen in both boys and girls in the moderate to LP group compared with the term control children. It is not possible to ascertain to what extent the results are influenced by inclusion of children born more preterm, at 32–33 weeks of gestation.

Cardiorespiratory fitness in young adults born at ET gestation has been explored, using data from the Northern Ireland Young Hearts Project [51]. This included 110 early, 533 FT and 148 late term (41–42 weeks of gestation) individuals from singleton pregnancies. Cardiorespiratory fitness was classified as either normal or poor, in line with established age and sex-specific reference standards. The results

demonstrated a 14% reduction in relative risk of poor cardiorespiratory fitness for each week of increasing gestation at birth. ET individuals consistently had a 57% higher risk of poor cardiorespiratory fitness during adolescence and young adulthood than those born at ≥39 weeks of gestation (RR: 1.57; 95% CI: 1.14–2.16). Adjustments for potential confounding factors did not significantly change these results.

All of the studies described above reported a large loss to follow-up, and conclusions based on results from the proportion who attended for assessment. In the ALSPAC cohort this was just under 50% at 8–9 years and fewer than one-third at 14–17 years [48,49]; in the Swedish cohort, only 34% of the cohort had spirometry at both time-points [50]. The Irish study had significant drop-out between assessments in adolescence and young adulthood, and those who attended had a healthier profile than those who did not [51]. Given this, and the observation in the ALSPAC cohort of lower socio-economic status and increased exposure to maternal smoking in children who failed to attend, it may be that these studies are underestimating the impact of early birth on later lung function.

A prospective study used impulse oscillometry to explore lung function in 90 children aged 3 and 7 years who were born LP without a diagnosis of asthma or other diseases known to affect lung function. Results were compared with a group of healthy, term-born controls. Increased distal airways resistance was observed in the LP group, indicating greater peripheral airway obstruction when compared with healthy term-born controls [52]. This finding was not related to neonatal respiratory disease, but was associated with hospitalization for chest infections and with a history of passive smoking.

5.2. RSV bronchiolitis

Several studies in LP infants have shown increased rates of RSV bronchiolitis hospitalization during the first year of life [35]. However, most studies have included babies of lower GA in addition to a subset of the LP population. However, compared with term-born infants, those born LP appear to have higher rates of complications, such as longer hospital stays and increased risk of intensive care admissions [53]. Helfrich et al. studied infants aged < 2 years in a large retrospective cohort study of which 25,890 (4.3%) were healthy LP (33–36 weeks) infants [54]. Of 7597 children admitted with RSV infection, 8.5% were LP and these infants were more likely to be admitted to hospital and to require respiratory support during the course of their illness than term-born infants. They concluded that LP birth is an independent risk factor for severe RSV infection. A recent Spanish study focused on infants born at 34–36 weeks of gestation, showing significantly higher rates of admission for RSV infection in this group when compared with the term infants (15.2% compared with 10.3%; $P < 0.001$) [55]. RSV immune-prophylaxis has been proven to reduce RSV-related hospitalization by 55% [56] and is routinely administered to high risk infants, but it has yet to be determined whether its use in LP infants would be cost-effective. Further research is needed to identify those within this subgroup who are at higher risk of significant morbidity from RSV and who may benefit from targeted prophylaxis.

5.3. Wheeze and asthma

It is a widely reported association that very preterm neonates with chronic lung disease have a higher incidence of asthma later in life. Children born preterm have been noted to secrete more cytokines, chemokines, growth factors and immunomodulatory mediators in nasopharyngeal aspirates done at 1 year when compared with children born at term, suggesting that they were more responsive to pro-inflammatory stimuli, as seen in asthma [57].

Although a study published in 2010 by Abe showed no association between LP birth and asthma [58], several studies have since indicated otherwise, finding increased risk of wheezing illness and asthma in the LP population. Boyle et al. demonstrated increased parent-reported

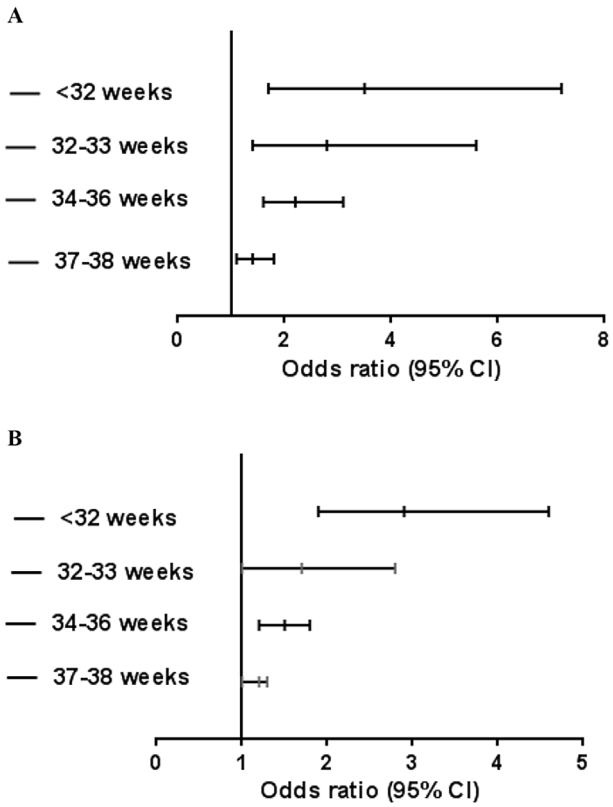

Fig. 1. Asthma and wheeze at 5 years of age reported by parents of children recruited to the UK Millennium Cohort Study [9]. (A) Reported wheeze and asthma at 5 years of age. (B) Reported use of asthma medication at 5 years of age. Reference group born at 39–41 weeks. Adjusted for: child's age at interview, sex and ethnicity, maternal age at birth, marital status, education, occupation, firstborn, breastfeeding, smoking, and alcohol consumption. CI, confidence interval.

wheezing and use of asthma medication at three and five years of age in LP and ET children participating in the UK Millennium Cohort Study, although the highest risk was seen in very preterm infants (Fig. 1).

Voge et al. in 2017, reported higher rates of asthma in LP infants when compared with the term population, but concluded that late prematurity was not an independent risk factor for the development of asthma [59]. A Canadian population-based study of all live-born children between 34 and 36 weeks gestation compared with FT children showed that the LP population had a significantly higher adjusted odds (aOR 1.33; 95% CI: 1.18–1.47) of asthma at school age compared with the population born at FT [60].

The need for asthma medication and hospitalization in children up to the age of 7 years was evaluated using data from the Finnish national registry [61]. LP children had an increased hospitalization rate for asthma when compared with term children (7.3% vs 4.8%). This study assessed a population of 1,183,012 children born over a 17-year period, and added that male sex, maternal smoking, maternal diabetes and ventilator therapy predicted the use of asthma medication use in the LP population. It also showed that hospitalization rates in this population for atopic dermatitis increased with increasing gestation age (term (5.2%) vs LP (4.7%)). A population-based study of Chinese children in Hong Kong also reported that LP children had a higher risk of hospitalization for asthma and other disorders than children born at FT but did not support an increased risk of hospitalisation for asthma for children born following ET birth [62]. A survey of children under the age of 5 years showed that ET children reported higher rates of wheezing under the age of 5 years when compared with FT children (48% vs 39%), and this was despite being stratified by mode of delivery and family history of atopy [63]. This survey also showed that ET

children had twice the odds of inhaler medication use (OR: 2.0; 95% CI: 1.4–2.9). A Swedish registry study confirmed an increased risk of asthma in both LP and ET individuals aged between 6 and 19 years by examining corticosteroid use, but noted that the effect lessened with increasing age. The increased risk in ET individuals was 10%, but this small increase accounted for nearly 2% of the total number of cases, because of the large numbers born at this gestation [64].

5.4. Other respiratory disorders

Tickell et al. looked specifically at electively induced ET delivery and noted an increased risk of hospitalization before the age of 5 years for lower respiratory disorders [42]. This persisted even after exclusion of infants with perinatal complications [42]. Walfisch et al. conducted a population-based prospective cohort analysis of all singleton deliveries in a single tertiary centre over a 12-year period [65]. They showed that there was a higher rate of hospitalisation for respiratory conditions in the first 18 years of life for ET children when compared with those born at FT and late term. A study in the same cohort also demonstrated a risk of obstructive sleep apnoea with increasing GA, with those born even at 37–38 weeks of gestation having an increased risk of obstructive sleep apnoea (aHR: 1.3; 95% CI: 1.2–1.5) when compared with late and post-term births [66].

6. Behavioural and psychiatric diagnoses

Several studies have shown that those born prematurely, particularly those born extremely and very premature, have increased risk of behavioural problems, inattention, hyperactivity and internalizing behaviour. Behavioural problems have also been reported in the LP and ET groups. Lindstrom et al. noted that children who were born LP had a 30% risk of developing neuropsychiatric and behavioural disorders when compared with those born FT [67]. The same study also noted that ET children were more likely (OR:1.1) to be prescribed medication for attention deficit/hyperactivity disorder medication. Conversely, Stene-Larsen et al. demonstrated an increased risk of LP and ET girls having emotional problems at 36 months, but did not find an increased risk of behavioural problems in this cohort [68]. Polic et al. did a comparison of children who were born LP and those who were born FT. This study added that the LP children who were admitted to a neonatal intensive care unit (NICU) after birth had more emotional and behavioural problems, and lower quality of life, when compared with LP children who were not admitted to NICU. This comparison also held when they were compared with children who were born at term who were admitted to NICU [69].

7. Growth and weight gain

Emerging evidence suggests that LP and ET infants may be more susceptible to developing childhood obesity when compared with term-born infants. A population-based study in the UK showed that children born LP had the highest proportion of obesity at 3 and 5 years [9]. An American study showed that extremely rapid weight gain seen between 4 and 24 months led to a high risk of being overweight/obese in children born LP (OR: 3.6, 95% CI: 1.8–7.5) or ET (OR: 3.3; 95% CI: 1.9–5.5) [70].

A further study by Levy demonstrated that children born ET were more overweight and obese (0–18 years of age, OR: 1.26; 95% CI: 1.02–1.56) and had a higher risk of type 1 diabetes (5–18 years of age, OR: 1.5; 95% CI: 1.08–2.09) when compared with those born FT [71]. These findings have significant implications for health surveillance in childhood, due to the increasing incidence of childhood obesity globally, and bring forth the question of whether the growth of these patients needs to be monitored more closely from an earlier age [72].

8. Implications for health care provision

Although the majority of LP and ET infants are well following birth, for those who require specialist input either in a neonatal unit, or in the normal postnatal ward setting, respiratory and nutritional support are not infrequently needed, and treatments for common early morbidities are common [21]. The large number of these infants means that there is a need for provision of a substantial amount of specialist services, incurring significantly higher costs [73,74].

Mounting evidence from multiple geographical settings suggests that, although effects associated with birth close to FT are small and may be attenuated with increasing age, these effects nevertheless remain measurable throughout childhood, adolescence and early adulthood. Potential ongoing adverse effects into later adulthood and old age have not yet been explored, but it is plausible that problems may persist. In view of the large number of infants born at this gestation, this presents a considerable burden to ongoing primary and secondary health care, education and public health services. For individuals, health impairment, in particularly of a respiratory nature, may impact on realization of school and occupational potential.

Currently, infants born LP and ET who have not had major neonatal morbidities are not offered routine detailed follow-up, and even for those who have required mechanical ventilation, ongoing monitoring is minimal. This may lead to late diagnosis and intervention. Many adult respiratory physicians do not consider the adverse effects of prematurity, even those associated with birth at more preterm GAs, which has implications for transfer of care to adult services [75]. It has been suggested that closer routine surveillance during childhood may be warranted in these groups, but the financial implication of this would be large; within current health care provision models, health care personnel would be insufficient. However, within this large population it is unlikely that whole population surveillance would be cost-effective or even necessary. Few studies have so far attempted to investigate in more detail individual factors that may place subgroups at higher risk of later morbidity. Such factors might include genetic factors, maternal morbidity during pregnancy, reason for early delivery, variation in early care or nutrition, and socio-economic or environmental factors [21,30,76–79]. Now that ongoing morbidities have been defined, further work is needed to elucidate whether there are modifiable factors with respect to pre-pregnancy, antenatal, neonatal, or childhood care that might improve outcomes. Interventional trials focused on obstetric, neonatal or paediatric care in these groups are very sparse and are warranted. With clarification of the factors contributing to adverse health outcomes would come the ability to target care and interventions to those at highest risk, but currently available evidence does not yet allow this.

9. Conclusions

Increasing numbers of reports from multiple developed countries consistently indicate an ongoing adverse effect of LP and ET birth on childhood health, which may persist into adulthood [35]. The impact of birth at these gestations in less developed areas, where it constitutes an even higher proportion of the newborn population, is likely to be even greater [80]. The area of greatest impact seems to be respiratory morbidity, which is known to be common and persists at least up to the age of 18 years [35]. However, in some areas, results of research are conflicting or sparse. The time is ripe for long-term follow-up studies, prospective studies, and interventional trials of therapies in these understudied populations. Only when there is a greater understanding of the influences at play in LP and ET birth will clinicians be able to direct care to those at greatest risk and to optimise ongoing health outcomes for this large and important population.

Conflicts of interest

None declared.

Funding sources

None.

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