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The Late Preterm Infant

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Abstract

Late preterm birth refers to birth at 34 to 36 weeks of gestation, which can occur for many different maternal and fetal reasons. Infants born late preterm represent almost three quarters of all preterm births, yet they have been studied much less than their more immature counterparts born at the limits of viability. Whilst problems of late preterm infants are generally fewer and milder than those of the most immature infants, nevertheless they are at increased risk of adverse neonatal outcomes. Mortality rates are higher, and common morbidities in the neonatal period for late preterm infants include hypothermia, hypoglycaemia, difficulties in establishing oral feeding, jaundice and respiratory compromise. Long term health and neurodevelopmental problems, as well as educational difficulties are also known to occur, and effects of prematurity in this group may extend into adolescence and adulthood.

Currently neonatal care for late preterm infants is delivered in a variety of settings and management varies between centres. Care for these infants should be tailored to the needs of the individual infant and family, as far as possible and further research in this group is required to define optimum care pathways. A major importance of late preterm birth lies in the very large number of affected infants, which exerts a significant impact on provision of neonatal care, health care, and educational services.

The Late Preterm Infant

Introduction

The health outcomes of the late preterm infant is an area of growing interest and research amongst neonatologists and paediatricians. In the last few years, it has become clear that gestational age at birth cannot be simply divided into categories of extreme preterm, preterm and term; there is variability in the pathologies affecting babies at each week of gestation, up to and including between 37-42 weeks' gestation. Gestational age is now viewed as a continuum and categorised into extremely preterm (<27 weeks' gestation), very preterm (<32 weeks' gestation), moderately preterm (32-33 weeks' gestation), late preterm (34-36 weeks' gestation), early term (37-38 weeks' gestation), full term (39-41 weeks' gestation) and post term (>42 weeks gestation). Late preterm infants, defined as those born between 34 +0 and 36+6 weeks of gestation are the focus of discussion for this review. Babies born late preterm make up 5-6 % of all live births annually in the United Kingdom and more than 70% of all preterm births, and therefore their health care needs impact significantly upon paediatric healthcare service provision (Table 1).

<< Please insert Table 1>>

There has been a longstanding interest in those babies born at the lower extremes of gestational age (<27 weeks' gestation) but by comparison the late preterm group is relatively understudied as many of these babies will survive without significant disability and have outcomes within normal limits. Current neonatal research is building a body of evidence about this cohort of babies, with some risks identified for impaired educational, neurodevelopmental and respiratory outcomes which are consistent within the literature base. Indeed, the overall number of children with health problems is

much larger for children born at moderate/late preterm or early term gestation as compared to term counterparts.

Previous studies have identified that late preterm delivery is associated with significantly increased mortality and morbidity rates compared with those observed among infants born 37-42 weeks' gestation. However, interpretation of study results may be confounded by differences in birth weight criteria used and the varied reasons triggering preterm delivery. This review aims to identify some of the key themes in the available evidence for late preterm babies and consider how this may impact upon health outcomes for these babies now and in future life.

Background

Definition of 'late preterm' arose from a 'US National Institute of Child Health and Human Development workshop' in 2005, which changed the definition of this group of babies from 'near term' to late preterm in order to acknowledge the fact that more mature preterm infants experience increased morbidity and mortality that had been underestimated due to their more developed appearance and larger size.

The most common health problem in the late preterm group is respiratory morbidity, both in the neonatal period and in the long-term. Increased hospital admissions have been identified in the first 9 months of life with readmission rates in the first month following early neonatal discharge significantly more common in infants born at 35-37 weeks of gestation compared those born at 37 weeks or more. This has a considerable impact not only on health outcomes, but on quality of life for the child and family. Parents' assessments of child health correlate with these findings and this has been demonstrated in parental ratings of their children's health. The potential ongoing adverse

effects of late preterm delivery are wide and varied, encompassing the not only the child's physical health, but mental health as well as educational and social abilities. The long term impact of late preterm delivery, particularly regarding health and social outcomes in adolescence and adulthood, continues to be an area with limited evidence available, and should be an area for further exploration.

Reasons for late preterm delivery

Preterm labour is defined as contractions leading to cervical change prior to 37 weeks' gestation. Spontaneous preterm delivery is multi-factorial in its aetiology and is usually a result of infection, uterine over-distention (hence increased risk of preterm delivery in multiple pregnancy) or changes in the hypothalamic-pituitary-adrenal (HPA) axis.

Management of complications of pregnancy

There is considerable variability in practice of obstetricians internationally for women >34 weeks' gestation in preterm labour or without active labour but with prolonged preterm rupture of membranes (PPROM). Evidence from systematic reviews shows that, with the administration of broad spectrum antibiotics to mothers with PPRM, rates of neonatal infection and chorioamnionitis are significantly decreased up to 37 weeks' gestation and this is now usual accepted practice. Early delivery in PPRM is not thought to confer benefit over expectant management in reducing rates of neonatal sepsis, perinatal mortality, intrauterine deaths or neonatal deaths. Pregnancy induced hypertension can result in preterm delivery, particularly if severe. However, if delivery is augmented at 34-36 weeks gestation for management of mild gestational hypertension, there is increased neonatal morbidity without maternal benefit. Oligohydramnios can be a cause for concern for obstetricians, but it is thought that isolated

oligohydramnios (particularly identified later in pregnancy) is not related to adverse perinatal outcome. Pregnancy complications such as placenta praevia and accreta require regular monitoring in order to determine the optimal time for delivery. It is not known exactly what the optimal time of delivery for women with placenta praevia is, but it is thought to be appropriate to deliver women in the early term period. However, there is consensus to deliver women with placenta accreta at 34 weeks' gestation to optimise both maternal and neonatal outcomes.

Other maternal and fetal reasons

There are many other pregnancy related complications that might underpin late preterm delivery including maternal obesity, multiple pregnancy and intra-uterine growth restriction. Multiple births are more common in preterm populations as compared with term groups.

Impact of maternal choice

Patient participation in treatment options and shared decision making between patient and clinician is the gold standard of care where possible. When considering facilitating late preterm delivery of a pregnant woman, it is essential that the potential risks to the baby of early delivery are communicated and understood, where delivery is not inevitable.

It is clear that when considering late preterm infants as a sub-group of preterm infants, obstetric practices and maternal health issues will be significant contributing factors to neonatal outcomes. The risks attributable to prematurity associated with late preterm delivery must be balanced with maternal health concerns and risk of stillbirth and intra-uterine fetal death. Ongoing evaluation of

obstetric practices may help decrease rates of prematurity and its associated health care burden. However, it is likely now that the majority of elective late preterm deliveries are unavoidable.

Mortality in late preterm infants

Studies have identified significantly increased risks in both morbidity and mortality for the neonatal and infant periods in babies born late preterm, as compared to term. Early and late neonatal mortality have been shown to be, respectively, six and three times higher and infant mortality three times higher than that of term born infants. These differences persist even when infants with congenital anomalies are excluded.

Health issues following late preterm birth

Respiratory morbidity

Late preterm infants are at greater risk of early respiratory disorders compared to full term infants including respiratory distress syndrome, transient tachypnoea of the newborn and pneumonia. The physiological mechanisms that cause respiratory morbidity in the very preterm infants, including surfactant deficiency and immature lung structure, can also affect late preterm infants and lead to respiratory failure.

Following early increased risk of respiratory morbidity, there is evidence to suggest that late preterm babies may also experience an increased risk of RSV (respiratory syncytial virus) bronchiolitis and subsequent increased risk of wheezing and other respiratory complications as compared to term babies, for 12 months after the infection with RSV. A risk assessment tool for RSV infection has been

devised for use in babies born at 33-35 weeks of gestation as a result of research into RSV associated morbidity.

Currently, the UK has specific criteria in order to determine which babies should receive RSV infection immunisation with palivizumab (Synagis[®]) over the first winter following birth. Criteria for administration of palivizumab include babies with congenital heart disease, children under 2 years of age with severe combined immunodeficiency disease and preterm infants who have moderate or severe bronchopulmonary dysplasia requiring supplemental oxygen at >36 weeks completed gestation. These criteria were developed due to the significant cost implications associated with palivizumab use. However, as the evidence for late preterm-associated respiratory morbidity is increasing, the health economics of including this specific group of babies in a winter vaccination programme in the UK should perhaps be considered. Health economic assessments have suggested that it may be cost-effective to administer RSV vaccination to moderate-late preterm infants, if they are identified as being at high risk of RSV infection.

Despite evidence supporting increased respiratory morbidity in late preterm children, there is conflicting opinion about an association between late preterm birth and a subsequent diagnosis of asthma in childhood. Reduced spirometry measurements have been demonstrated in late childhood and teenage years in individuals born late preterm compared with those born at term.

Children born late preterm require increased treatment for respiratory symptoms, cough, wheeze and asthma compared to full term infants, and this has been consistently shown. Infants born late preterm will be exposed to the same population risk factors known to be linked to wheezing including (but not limited to) smoking during pregnancy, history of parental asthma and allergen

exposure in childhood. Factors most strongly associated with respiratory problems in mature preterm infants have been shown to be family history of asthma and identification of respiratory problems in the first year of life.

There are implications for adult respiratory care, and there is a growing awareness among respiratory physicians of the potential causative nature of preterm birth upon chest disease in adulthood. However, it is unlikely that the majority of respiratory specialists routinely ask about patients' early life factors, despite increasing evidence that preterm birth may be relevant for adults with persistent airway disease. The British Thoracic Society has recommended that respiratory physicians improve their awareness of early life events, in order to effectively manage their current and future patients that have been born preterm.

Hypothermia

Maintenance of normothermia following delivery is known to be a key standard of neonatal care for babies of all gestations. A significant proportion of late preterm infants require active management for hypothermia, such as care in a heated cot or incubator. Hypothermia in preterm infants is known to be associated with worse outcomes.

Hypoglycaemia

Infants born at 34-37 weeks' gestation are more likely to develop hypoglycaemia than are full term infants, and to require support with intravenous fluids. The adaptive responses of late preterm infants are not synonymous with those seen in term infants, likely due to the limited glycogen stores of babies born at <37 weeks gestation. The late preterm infant is consequently less likely to enact

ketogenic pathways in response to falling blood glucose levels, which may increase likelihood of long-term neurological sequelae of neonatal hypoglycaemia.

Hyperbilirubinaemia

Jaundice is common in late preterm neonates and has consistently been found to be the most common reason for readmission to hospital in the first month of life. This is likely, in many cases, to be due to the increased risk of difficulties in establishing breastfeeding in a late preterm baby, secondary to immature suck and swallow coordination, and a lower degree of wakefulness. Registries show that kernicterus is more frequently reported in late preterm than term born babies.

Growth

Growth in infancy and later childhood is accepted to be poor for infants born extremely preterm, but growth failure is not confined to this population. The cumulative protein and energy deficits of being born preterm may mean that postnatal catch up growth is also affected in the late preterm group irrespective of the presence of intra-uterine growth restriction.

Neurodevelopmental outcomes

Cognitive consequences of late preterm birth in later childhood have been less well studied than in very preterm infants. However, neurodevelopmental outcome is impaired in late preterm infants compared with term born infants, with cognitive impairment being the primary contributor to observed deficits. Research studies have identified lower cognitive performance for infants born late preterm when compared to their term counterparts, showing 2 to 3 times the risk of exhibiting an IQ score below 85. This threshold marks borderline intellectual functioning and could have implications

for quality of life and ability for future independent living for some children. In addition to the cognitive risk to intelligence, a diagnosis of cerebral palsy in children born late preterm is three times more likely than term children. Some studies have suggested additional links between late preterm birth and attention deficit/hyperactivity disorders, features of autistic spectrum disorders and reduced likelihood of completing childhood education.

Despite increasingly convincing evidence that late preterm children as a group demonstrate measurable cognitive and socioemotional problems, a high proportion show normal or above-average intellectual functioning. This reflects the complexities of interpreting psychometric data, due to multiple factors that contribute to psychological well-being. However, in many of the studies of late preterm children relating to cognitive function, children with severe impairments such as cerebral palsy are excluded and therefore may be disproportionately underrepresented when considering cognitive outcomes of late preterm infants. Many of the studies of cognitive function in late preterm infants are confounded by skewing of data. Some studies show a high proportion of babies born to affluent families or are not able to prove that worse neurodevelopmental outcome was solely related to late preterm birth, due to an identified association between socioeconomic factors and mental delay. The risk of very preterm birth with associated adverse outcome is known to be increased in deprived populations. Although fewer research studies of late preterm birth have addressed socioeconomic status in late preterm birth, it is likely that it is also a major contributing factor to outcome in this population.

Young adults that are born at late preterm gestation are also thought to be at increased risk of disability. It has also been suggested that late preterm birth may be a risk factor for cognitive impairment in old age, though more research in this area is required.

Neonatal care

There is, at present, no formal guidance in the United Kingdom for the neonatal management of infants born late preterm. Currently, they may be offered care in a number of settings, including neonatal units, transitional care, or normal postnatal wards and it is not known where care is optimally delivered. There is substantial variation in care between centres and the impact of this variation on outcomes is not known. A large number of late preterm infants never require admission to a neonatal unit for specialist care, but nevertheless they represent a significant burden in terms of postnatal reviews for relatively minor problems such as feeding difficulties. A balance exists between development of prematurity-associated problems and the benefits of avoiding separation of mother and baby.

Breast feeding in late preterm infants

Exclusive breastfeeding is recommended for all infants, but can be challenging for many mothers to successfully establish, especially for primigravida women. Breast feeding rates are low in late preterm babies, and particularly in late preterm multiple births, despite the fact that length of hospital stay, and therefore potential access to increased support, may be longer than in their term-born counterparts. However, with appropriate training of healthcare professionals and the provision of feeding support, breastfeeding rates at discharge from hospital may be improved. Mothers of late preterm infants should receive additional support in feeding establishment, whatever the chosen method, as infants of lower birthweight are likely to take longer to establish oral feeding successfully. This is particularly so for breastfed infants. Robust assessment of feeding in the late preterm baby is essential to reduce the risk of feeding related health complications including hypoglycaemia and jaundice.

Follow-up of late preterm infants

Currently late preterm infants are not routinely invited for hospital follow-up unless they have been required intensive care in the neonatal period. It has been suggested that closer post-discharge surveillance would be optimum in view of the recognised poorer health and developmental outcomes. However, costs of formal developmental follow-up in this group would probably be prohibitively high, making this approach unfeasible. In addition, it is likely that parents of well late preterm infants may feel that this was warranted. However, primary care professionals who are likely to bear the burden of early health care demands in this population may have only limited training about the impact of late preterm birth upon future childhood health.

Areas for future research consideration

The bulk of evidence for both early and late outcomes following late preterm birth has been generated by observational studies, and there are few, if any high quality randomised controlled trials looking at interventions and health outcomes for late preterm infants specifically. Such trials would allow many of the questions discussed here to be studied in a robust way and provide guidance to neonatologists in the context of likely long term mortality and morbidity outcomes. This could potentially lead to significant changes in the current management of this population of babies and the way in which expectant parents are counselled antenatally, and throughout their baby's neonatal course, about expected challenges and outcomes.

The potential implications on obstetric and neonatal services from this growing area of research is as yet unknown. It is known that extremely preterm birth leads to an increased risk of respiratory morbidity in childhood. However, it is not yet conclusively shown if late preterm birth leads to an increased risk of developing significant childhood respiratory disease, including RSV bronchiolitis,

viral induced wheeze and asthma in childhood. There is a building body of information that suggests there is a probable associated increase in respiratory morbidity with decreased gestational age, even at the late preterm gestations when compared to term counterparts.

Whilst previous research has focussed on the outcomes for the most vulnerable babies born at the extremes of gestational age, the annual birth rate of babies born late preterm is significantly higher and should remain an area of ongoing interest in order to accurately assess and aim to improve long term health outcomes for this cohort.

Given the information that is now available to neonatologists about the risk of complications associated with late preterm birth in both the short and long term, it may be worth considering correcting for gestational age for all babies born <37 weeks gestation. Current practices in the UK would not traditionally accommodate for late preterm delivery and only correct for gestational age for those babies born at <34 weeks gestation. However, if educational attainment is potentially adversely affected by late preterm delivery, should this be taken into account for schooling purposes? A dose-dependent relationship between educational problems and decreasing gestational age at birth and risk of having special educational needs has been shown. However, other studies have shown that otherwise healthy late preterm infants have no long term problems at school. There is a growing trend towards adjusting for prematurity for starting school for those born at extremely preterm gestations and perhaps in future this may be considered for all health and educational parameters for those born at any gestation <37 weeks, deemed to be in at increased risk of long term educational difficulties.

Conclusions

Although most evidence from studies in the late preterm population points to an increased risk of later problems, there should be further longitudinal research, preferably with randomised controlled trials of late preterm outcomes. This would help guide future interventions for this group of babies, tailored for their specific needs. It would also allow clearer breakdown of identified health issues according to gestational age, as much of the currently available evidence base considers moderately preterm and late preterm babies together. Consideration by week of gestation might identify different patterns or cut-off points to allow targeted intervention according to gestation at birth.

Further study would also help neonatologists to develop a risk stratification for determining if follow up is required and allow researchers and clinicians to determine whether it is late preterm delivery itself that impacts upon later health outcomes, or a composite of many other factors including parental education, socioeconomic status and individual neonatal units' care or discharge policies that has the greater impact.

More information about this sub-group of babies would also help with service planning and the production of universal guidelines to support management, hence limiting the current variability in care received for these babies. Given that there is a body of evidence supporting the centralisation of newborn services for the most at-risk babies born at the margins of viability, if late preterm infants have specific needs, then neonatal services will need to provide guidance and recommendations for their care as part of the service specification in a more detailed and robust way in the future. This may incur additional cost and must be balanced with the clinical relevance of any future health or social issues associated with late preterm delivery.

The current economic burden of the late preterm group to health services is substantial. The initial hospital stay is longer, number of prescriptions supplied in first 6 months is increased and proportion of infants using health care services between 12 and 24 months is increased. However, the provision of healthcare support staff to assist with relatively simple interventions, such as early implementation of good feeding support, and standardised neonatal care practices could help improve early and late outcomes, reduce future readmission in infancy and potentially reduce overall costs of care in this population.

Practice Points

- Late preterm infants (born at 34 to 36 weeks of gestation) are at increased risk for adverse neonatal and long term health and neurodevelopmental outcomes.
- Routine newborn care is of particular importance in late preterm infants, and should include avoidance of hypothermia and maintenance of normoglycaemia.
- Feeding support facilities should be tailored to the individual needs of the late preterm infant, with recognition that duration of time to successful oral feeding can be variable.
- Services should consider developing specific criteria for discharge following neonatal care, including liaison with outreach or community practitioners for the late preterm infant.

Conflict of interest statement

None declared

Funding sources

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Further reading

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Table 1. Live births by gestational age, England 2014 (Source: Office for National statistics)

Weeks of gestation	Number of live births	Gestational age group (% of preterm births)	Total births by gestational age group	% of all live births	% of all preterm births
23	323	Very preterm	7499	1.1	15.2
24	404				
25	453				
26	592				
27	666				
28	910				
29	892				
30	1413				
31	1846	Moderately preterm	6190	1.0	12.6
32	2581				
33	3609	Late preterm	35533	5.4	72.2
34	6495				
35	9539				
36	19499	Early term	133183	20.3	
37	44468				
38	88715	Full term	455570	69.3	
39	159499				
40	175614				
41	120457	Post term	19219	2.9	
≥ 42	19219				
Total	657194				

Excludes births at <23 weeks of gestation and births where gestational age was not stated