Title: Outcomes of infants born near term

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ABSTRACT

Most research on outcomes of preterm birth has centered on babies born at <32 weeks gestation and at highest risk of mortality and serious morbidity. Recent years have seen a dramatic increase in studies focusing on late preterm infants (34-36 weeks gestation). Early epidemiological studies demonstrated increased risks of mortality and adverse neonatal outcomes in this group, prompting further investigations. These increased risks have been confirmed and more recent studies have also included babies born at 37-38 weeks, now defined as 'early term' births. It now seems that it is inappropriate to consider term and preterm as a dichotomy; gestational age rather represents a continuum in which risk and severity of adverse outcomes increase with decreasing gestational age, but where measurable effects can be detected even very close to full term. In this review, we summarise current evidence for the outcomes of infants born at late preterm and early term gestations.

Outcomes of Infants born near term

INTRODUCTION

Historically, a 'term' baby has been defined as one born after 37 weeks gestation. There is now growing interest in the outcomes for babies born 'near term', and it is becoming clear that gestational age represents a continuum from the least to the most mature rather than a dichotomy of 'term' and 'preterm' (Figure 1).

<< FIGURE 1>>

Nomenclature has previously been unclear, but births at 34-36 weeks gestation are now defined as 'late preterm' (LPT), those at 37-38 weeks as 'early term' (ET) and births at 39-41 weeks as 'full term' (FT)¹. We will use definitions shown in Table 1 to categorise timing of birth and focus on outcomes for LPT and ET babies. Due to their larger size and perceived maturity, these infants are often managed like their FT counterparts, but recent and emerging evidence suggests that this may not be appropriate.

<< TABLE 1 >>

Many deliveries before 39 weeks gestation follow spontaneous onset of labour but others result from induction of labour or elective caesarean section that may or may not be medically indicated. Professional bodies have discouraged non-indicated delivery before 39 weeks gestation²⁻⁴. However, with prolongation of pregnancies comes the risk of stillbirth. Nicholson et al studied stillbirth rates in the USA following the ACOG recommendation to delay delivery to 39 weeks, inferring a causal relationship between this recommendation and increased stillbirth rates from 1.103/1000 (2007-2009) to 1.177/1000 (2011-2013)⁵. Efforts to reduce stillbirths by early identification of

intrauterine growth restriction and timely delivery according to the perceived level of risk are likely to increase numbers of small LPT/ ET babies requiring neonatal care and with ongoing problems. At least half of twins and 90% of triplets are born before 37 weeks gestation⁶. The NICE guideline on multiple pregnancy advises elective delivery of uncomplicated monochorionic twin pregnancies from 36+0 weeks, dichorionic twins from 37+0 weeks and triplet pregnancies from 35+0 weeks, after a course of antenatal corticosteroids has been offered⁷. Therefore, the competing risks of continuing pregnancy with potential risk of stillbirth versus possible sequelae of early delivery must be carefully considered.

The Office for National Statistics, 2013 data for England and Wales showed LPT births accounted for approximately 36,000 and ET for 135,000 births (5% and 19% of all live births respectively)⁸. In this large group, economic and social consequences of even slight increases in developmental problems, and/or healthcare needs are probably greater than in the smaller more immature groups. Published data about outcomes for the highest risk babies are now extensive⁹, but what do we know about those born LPT and ET, and their later outcomes? In this review we aim to summarise currently available literature, focusing principally on long-term outcomes for this group of babies.

NEONATAL OUTCOMES

Most LPT and ET infants will not experience significant neonatal complications. Nevertheless, LPT infants and a proportion of ET infants are physiologically and metabolically immature; for such babies, neonatal complications and/or care may influence later outcomes. Rates of complications decrease with increasing gestational age, but compared with FT infants, both LPT and ET infants have a higher incidence of common and important neonatal problems including respiratory distress, hypoglycaemia, temperature instability, jaundice, infection, apnoea, and feeding difficulties, resulting in prolonged hospitalisation^{10, 11}. Whilst difficulties encountered in the neonatal period by LPT and ET infants may be relatively small on an individual basis, and many of the morbidities 'minor' in nature, the broader impact due to large numbers of babies in this group is substantial and important when considering costs of care and later outcomes. Brown et al suggested that additional factors such as placental ischaemia and other hypoxia exacerbated the effects of gestational age¹¹. This leads to the question of whether there may be a specific group of LPT/ET babies at particular risk of later morbidity related to their gestation and the potential to identify and target these babies for early intervention.

Breastfeeding

Studies have shown that LPT and ET infants struggle with feeding, especially breastfeeding. Data showed that high hospital support increased rates of exclusive breastfeeding in US hospitals, but even after adjustment, the rate of exclusive breast feeding in the LPT group was significantly lower than that in FT babies (39.8 vs. 62.3%, p = 0.002)¹². A Canadian Study of 92 364 infants demonstrated that the odds of breastfeeding at hospital discharge decreased with each week of gestation between 41 and 37 weeks¹³. Decreased likelihood of breastfeeding may be important with respect to later outcomes, given the known long-term health and neurodevelopmental benefits of breastmilk.

Neonatal respiratory morbidity

Respiratory morbidities are the most common neonatal problems for LPT and ET babies and may be related to either immaturity or mode of delivery. The RCOG recommends that all mothers having planned delivery before 38+6 weeks receive antenatal corticosteroids; steroids are not routinely given to women with spontaneous onset of labour beyond 34 weeks⁴. Studies of antenatal steroid administration at LPT gestations are few and results conflicting. Porto et al¹⁴ were unable to demonstrate benefit, but Gyamfi-Bannerman demonstrated that giving betamethasone to women at risk of LPT

delivery significantly decreased neonatal respiratory complications and the need for respiratory support in the first 72 hours after birth¹⁵. Although respiratory distress syndrome (RDS) is among the commonest neonatal problems in LPT infants¹⁶, the use of surfactant in this population is variable and has been poorly studied. It is uncertain whether, or how much, early respiratory morbidity is directly related to later respiratory problems.

OUTCOMES IN CHILDHOOD AND BEYOND

Hospitalisation in infancy and childhood

LPT and ET infants are more likely to be readmitted to hospital in the neonatal period with problems such as jaundice, feeding difficulties and sepsis; an increased risk of hospitalisation appears to persist through childhood. Oddie studied early discharge from neonatal care; readmission in the first month occurred in 6.3% of babies of 35-37 weeks' gestation compared with 3.4% and 2.4%, respectively, of those born 38-40 and >40 weeks¹⁷. Among children from the Millennium Cohort Study (MCS), those born preterm were significantly more likely to be admitted to hospital than those born at FT¹⁸. Although the greatest risk occurred in very preterm infants, the much larger numbers of LPT and ET children contributed more to the total burden of disease associated with prematurity. Population attributable fractions for having \geq 3 admissions to hospital between 9 months and 5 years were 4.7% for LPT and 7.2% for ET infants compared to 3.8% of those born at <32 weeks gestation¹⁸. The most common reasons for hospitalisation were respiratory disorders, gastrointestinal disorders, viral illness and fever. Parents of children born LPT and ET were more likely to report longstanding illness in their children (Figure 2). These studies provide evidence of greater childhood healthcare needs in the LPT and ET population and of a gradient of worsening health outcomes with decreasing gestational age at birth.

<< FIGURE 2 >>

Long-term respiratory morbidity

Respiratory morbidity has been a particular area of research in children born

LPT and ET^{16, 18-21}. Several studies have shown associations between birth a few weeks early and increased likelihood of childhood wheezing and respiratory admissions. A survey of children below five years of age found that 48% of ET children compared with 39% of FT children had presented with wheezing over the preceding 12 months (OR 1.5 95% CI 1.1-1.89)¹⁹; these results persisted after correction for mode of delivery and family history of atopy. The authors also showed an association between ET birth and increased inhaler and antibiotic use in children over 5 years of age. Compared with FT children of a similar age, ET children had up to 70% greater risk of respiratory symptoms and 50% greater inhaler use. Boyle reported similar findings up to five years of age¹⁸. Tickell looked specifically at ET children born following elective induction of delivery and showed increased risk of hospitalisation before 5 years for lower respiratory disorders (adj.OR 1.31; 95% CI 1.11-1.55) with this difference persisting after exclusion of 5% who had respiratory care on NICU²¹. However, a study of >8000 Chinese infants and children aged 9 days to 12 years did not support an increased risk of hospitalisation for asthma following ET birth²²; others have argued that observed associations may be accounted for by confounding factors²³.

An increased risk of respiratory syncytial virus (RSV) bronchiolitis has been observed in the LPT/ET population. A large cohort study looked at admissions with RSV infection and found that LPT infants accounted for 8.5% of RSV hospitalisations²⁴. The incidence density for RSV hospitalisation in LPT infants was higher than in FT children (12.1 vs 7.8 per 1000 person-years). LPT infants had longer hospital stays and required more respiratory support. Currently in the UK, administration of RSV prophylaxis is limited to high risk groups; recommendations do not include LPT infants.

Neurodevelopmental Outcomes

Historically, neonatal clinicians have not perceived neurodevelopmental impairment to be of significant concern in LPT and ET birth due to the low incidence of intracranial pathology in this more mature population compared with the very preterm group. Outcomes have been assumed to be similar to those of FT babies and so routine follow-up has not occurred. In addition, until recently, neurodevelopmental outcomes have been poorly studied in the LPT and ET groups. However, more recently studies have highlighted unexpectedly poor outcomes. It is thought that neurological impairment seen in these children may be due to different mechanisms²⁵. At 34 weeks the brain weighs 65% of the FT brain and at 38 weeks 90% and it is plausible that birth within this critical period might disrupt normal development²⁶.

Research has shown children born LPT are three times more likely than FT born children to be diagnosed with cerebral palsy²⁷. Finnish national data from 1,018,302 births showed an increased incidence of cerebral palsy in 7 year olds from 0.1% in children born FT to 0.6% in LPT children. Associated factors included resuscitation at birth, neonatal antibiotic treatment, one minute Apgar score of <7, and intracranial haemorrhage²⁸.

Johnson et al showed that children born MPT/LPT, compared with FT peers, were at double the risk of neurodevelopmental disability at 2 years corrected age but that this was almost entirely accounted for by cognitive impairment (6.3% v 2.4%; RR 2.09, 95% CI 1.19 to 3.64)²⁹. Male sex, socio-economic disadvantage and maternal pre-eclampsia were independent predictors of low cognitive scores.

A Norwegian Study investigated language delay and found an inverse linear relationship between gestational age and severity of difficulties³⁰. Mean language comprehension scores at 18 months for LPT children and ET children were 0.34-0.39 SD and 0.14-0.23 SD lower respectively than those born at FT; by 36 months these effects were less pronounced.

Some researchers have suggested that uncomplicated preterm birth does not in itself increase cognitive impairment. Baron and Romeo showed similar outcomes in LPT births as control FT infants; Romeo chose to assess outcome at corrected gestation age^{31, 32}. A study in Northern Ireland considered whether early neonatal course influenced long-term outcomes and found equal testing scores for cognitive, language and motor ability between children born LPT who required intensive care and those who did not, but did not include FT controls³³. Longer term follow-up at 15 years by Gurka did not find differences between LPT and FT infants in cognitive achievement, behavioural/emotional or social disability³⁴.

Educational Outcomes

By school entry many assume that subtle cognitive deficits will have disappeared and that LPT and ET children will have 'caught up', but this does not appear to be so. Mackay, in a large Scottish study, showed a strong relationship between special educational needs and gestational age, extending up to FT³⁵. Quigley et al showed poorer educational performance at five years in children recruited to the MCS, but found that LPT and ET birth exerted smaller effects than socio-demographic factors³⁶. Chan's metaanalysis also showed higher rates of SEN and poorer performance in general cognitive tests, with decreased likelihood of completing secondary and postsecondary education (RR 1.13 (1.11-1.15)³⁷. Analysis of data from the MCS corrected for month of birth when looking at educational outcomes and determined that, if the LPT and ET children had been born at FT, some would have been in another academic year³⁶. It may also be postulated that the health impact of LPT/ET birth leads to school absences and therefore impacts on educational achievement. There has been debate about whether delayed school entry is more appropriate for preterm-born children. Opinion is divided with respect to benefits and drawbacks of this approach, but it seems clear that those providing education should be aware of potential difficulties faced by preterm children in order to provide appropriate monitoring of academic performance and highlight need for support.

Behavioural and psychiatric diagnoses

In childhood, studies have shown that those born LPT and ET have increased risk of inattention, hyperactivity and internalising behaviour^{38, 39}. Several have reported on the prevalence of psychiatric disorders, particularly in LPT and MPT populations. Lindstrom found a 30% higher risk for organic and neuropsychiatric disorders compared with FT adults³⁸. Moster found a 30-40% higher risk for schizophrenia and 40-50% higher risk of developmental, behavioural and emotional disorders³⁹. Buchmayer et al, in a case control

study found that an observed increased risk of autistic spectrum disorders in MPT/LPT children was explained by complications that occurred during pregnancy and in the neonatal period⁴⁰.

<< FIGURE 3 >>

Adult Health Outcomes

Data for adult outcomes comes mainly from longitudinal cohort studies and due to the nature of the datasets, many reports on outcomes in adulthood are, of necessity, based on historical data. When considering very long term, adult outcomes, based on a small gestational interval such as the ET group, these may be affected by how the pregnancies, were initially dated. This was most commonly by date of last menstrual period and there may be some inaccuracies in using this method. There is also the interaction of gestational age and fetal growth; these factors have been investigated independently and, for example, the cardiovascular risk associated with growth restriction at birth is well known. In addition, changes in both antenatal and postnatal care have changed markedly in recent years, which may decrease the relevance for preterm deliveries today.

The Swedish National Cohort Study looked at 674 820 singleton births between 1973 and 1979 and published adult outcome data based on gestational age at birth for mortality asthma, hypertension, diabetes mellitus, and hypothyroidism^{41, 42}. They found that LPT birth was not associated with an increased risk of asthma, at least into young adulthood, but there was a modest increase in diabetes mellitis and hypertension associated with LPT birth, The Norwegian national register showed the risk of disability in adulthood (age 18-36 years) was increased by 26% for ET births compared with that in FT controls (n=431 656) adjusted RR 1.26 (1.17,1,36)⁴³. Rogvi et al has suggested that females born LPT are at increased of gestational diabetes and preeclampsia if they become pregnant⁴⁴. It seems increasingly likely that clinicians from many, if not all branches of adult medicine will encounter the health consequences of LPT/ET birth throughout the life course of these individuals and will need to be aware of the effects of the timing of

birth.

Mortality

The threat of death due to prematurity has historically been assumed to be confined mainly to those born at the lowest gestational ages, It is now clear that the risk of greater mortality persists across the whole range of gestational age up to FT. Data from England and Wales, 2013 (Figure 3) shows the percentage of infant deaths was 1% for babies born at 34 weeks gestation and fell for each week to 38 weeks gestation when the percentage of infant deaths was 0.1%⁴⁵. Crump et al showed that this increase in mortality continues into early adulthood⁴¹. Their data showed that the LPT young adults, aged 25 to 35 years, had increased mortality compared to FT born adults (HR 1.53; 95% CI 1.18-2.00 p=0.001). Importantly these findings were independent of birth weight.

SUMMARY

We have presented a summary of the widely available data for the outcomes of LPT and ET babies and the long term health and educational issues that they may experience due to their early delivery. These include an increased likelihood of problems during the neonatal period, but also an increased risk of long-term health, developmental and behavioural difficulties, the consequences of which may be lifelong. In contrast to the very preterm and extremely preterm infants, the absolute differences between the outcomes for these babies as they grow and those born at FT are often small, and this particularly applies to the ET group. However, the mounting evidence points to measurable differences and excess needs which, because of the substantial number of babies born before 39 weeks of gestation, are significant at a societal level and in terms of costs associated with ongoing health care, education and other support services. Knowledge about this previously under-studied population is increasing, but many questions still remain, and there is limited information about antenatal, perinatal and later factors that influence outcomes for this group of babies. There is a need to explore the possibility of targeted interventions that might be effective in reducing adverse outcomes and maximising the health, educational and occupational potential for a large group of individuals.

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JVG and EMB reviewed the literature included in this review paper. JVG drafted the manuscript. EMB revised the manuscript and both authors approved the final submission.

Table 1: Definitions of gestational age

Definition	Gestational age band
Extremely Preterm	≤ 27+6 weeks
Very Preterm	28+0 - 31+6 weeks
Moderately Preterm	32+0 - 33+6 weeks
Late Preterm	34+0 - 36+6 weeks
Early Term	37+0 - 38+6 weeks
Full Term	39+0 - 41+6 weeks
Post Term	≥ 42 weeks

Figure 1. Gestational age as a continuum

Figure 2. Hospital admissions and longstanding illness in children born at late preterm, early term and full term gestations (Boyle et al BMJ 2012)

Figure 3. Percentage of infant deaths and number of live births by week of gestation, 2013, England and Wales; Source: Office for National Statistics (reproduced with permission)