

# Long-term health of babies born close to term

Preterm birth is defined as birth before 37 weeks of gestation and until recently, 'full term' has been used to refer to birth at or beyond 37 weeks of gestation. However, it has become clear in recent years that these definitions may require further thought and so preterm birth has been subject to reclassification and term birth to redefinition. So how and why has this challenge to established thinking come about?

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### Key points

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1. Births at 32-36 weeks of gestation represent around three quarters of all preterm births.
2. Long-term health outcomes for this group of babies are worse than for those born at full term.
3. Increased morbidity in this very large group is likely to have a substantial impact at the population level.
4. Further research is needed to identify groups at greatest risk of poor outcomes.

Historically, interest in both short- and long-term health outcomes associated with prematurity has been centred on very preterm infants, ie those born at <32 weeks of gestation. This comes as no surprise – these babies, the smallest and least mature, experience the greatest severity of illness following birth and are those most likely to have poorer long-term outcomes<sup>1-4</sup>.

Outcomes for this group are now well documented and universally acknowledged. Much less established are outcomes for babies born beyond 32 weeks of gestation. In contrast to the highest risk babies, routine data are not collected for these babies in many countries, including the UK. Most research studies have reported data from the USA and have been retrospective in nature, although a number of recent and ongoing studies are now looking at these infants prospectively and in more detail. The majority of these reports have focused on neuro-developmental and cognitive outcomes, with fewer relating to the long-term general health of this group. To date, most studies have drawn similar conclusions namely, that both neuro-developmental and health – in particular respiratory health – outcomes for more mature preterm babies are not as good as previously believed. Full discussion of all aspects of neurodevelopment is beyond the scope of this article, therefore the aim is to summarise the currently available evidence for long-term health outcomes of babies born at, or close to, term and to describe the rationale for recent changes in terminology to describe this group.

## Mortality in childhood and adulthood

Interest in babies born close to term was initially sparked by reports of increased mortality during the neonatal period in infants born at 34-36 weeks of gestation and this has been reported consistently by a number of researchers<sup>5-8</sup>. However, until recently there have been no published data addressing the relationship between gestational age at birth and later mortality. A national cohort study in Sweden of 674,820 singletons, born between 1973 and 1979, recently reported a gradient of increasing mortality with decreasing gestation<sup>9</sup>. The study included 22,590 infants born between 34 and 36 weeks of gestation. Birth at 34-36 weeks of gestation was associated with increased mortality in early childhood (one to five years) and young adulthood (18 to 36 years) compared to those born at 37-42 weeks gestation. Although congenital anomalies were often seen in this group, these did not fully explain the increased mortality. The same researchers have now also highlighted, in this cohort, an independent association between birth at 37-38 weeks of gestation and increased mortality in infancy, early childhood and young adulthood compared with those born at 39-42 weeks of gestation<sup>10</sup>. Death in early adulthood appeared to be strongly associated with congenital anomalies, diabetes and other endocrine disorders.

## Respiratory morbidity

Respiratory morbidities, including

transient tachypnoea of the newborn, respiratory distress syndrome and respiratory infections are among the most common problems in neonates born at 34–36 weeks of gestation<sup>11</sup>. This is thought to be related to functional immaturity of the lung structure at this stage of gestation, associated with delayed intrapulmonary fluid absorption, surfactant insufficiency, and inefficient gas exchange<sup>12</sup>.

The relationship between birth at 34–36 weeks of gestation and risk of later respiratory morbidity has been investigated in only a very small number of studies, but from some of these there is evidence that an increased susceptibility may continue throughout infancy and childhood. Some suggest that preterm birth itself, regardless of respiratory status in the neonatal period, may have adverse effects on lung growth and development leading to a reduction in pulmonary function<sup>13</sup>.

In 1993, Todisco et al compared respiratory function at eight to 15 years of age in a small group of children born at 34–36 weeks, who did not have significant respiratory problems in the neonatal period, with a control group born at term<sup>14</sup>. Although asymptomatic at the time of testing, some of these children showed statistically significant abnormalities of lung function and preterm infants with impaired lung function were more likely to have mothers who smoked.

More recently, there was a follow-up study of children participating in the Avon Longitudinal Study of Parents and Children (ALSPAC;  $n=14,049$ ). Spirometry was performed in these children at eight to nine ( $n=6705$ ) and/or 14–17 ( $n=4508$ ) years of age<sup>15</sup>. This study included 691 children who had been born between 33 and 36 weeks of gestation. The researchers demonstrated decreased lung function at school age in children born at 33–34 weeks of gestation. There was some improvement by the age of 14–17 years, but not all differences had resolved with time. Children born at 35–36 weeks of gestation had values similar to those of children born at  $\geq 37$  weeks. However, there was a very large loss to follow-up from this study, with non-attenders more likely to be from families of lower socioeconomic status and in which maternal smoking was more prevalent. This introduces the possibility that the study results might provide an under-representation of the true differences between the groups.

Asthma is a major cause of respiratory

morbidity in children but studies that have looked at the association between birth at 34–36 weeks of gestation and asthma in early childhood have produced conflicting results. A retrospective study of 71,102 children born at  $\geq 32$  weeks of gestation demonstrated that birth at 34–36 weeks, compared with birth at 38–40 weeks of gestation, was associated with increased risk of recurrent wheeze in the third year of life (adjusted OR 1.23; 95% CI 1.07–1.41)<sup>16</sup>. In another retrospective cohort study including 582 infants born at 34–36 weeks and 1,083 born at 37–38 weeks, it was shown that the preterm group, at 18 months of age, were more likely to have been given a diagnosis of persistent asthma, to have greater use of inhaled corticosteroids and to have had greater numbers of acute respiratory healthcare visits compared to infants born at 39–42 weeks of gestation<sup>17</sup>. In this cohort, those born at 37–38 weeks of gestation were also more likely to have a diagnosis of asthma and use inhaled corticosteroids than those infants born at 39–41 weeks. Another group studied inhaled corticosteroid use in six to 19 year olds and found an increased use of medication in those born at 35–36 weeks of gestation in comparison with those who were born at more mature gestations<sup>18</sup> (adjusted OR 1.24; 95% CI 1.19–1.30).

The Millennium Cohort Study (MCS) is a UK nationally representative longitudinal cohort study of more than 18,000 infants born between 2000 and 2002<sup>19</sup>. Infants who were alive and living in the UK at the age of nine months were recruited. Follow-up of this large cohort involved interviews with parents at the time of recruitment to the study and again when their children were three and five years of age. In the MCS cohort, there was an increased incidence of asthma and wheeze at three and five years in children who were born at 34–36 weeks (adjusted OR 1.5; 95% CI 1.2–1.8). This finding was supported by the fact that medications for asthma were the most prominent medications used by the children at five years, with their use being more common both in those born at 34–36 weeks (adjusted OR 2.2; 95% CI 1.6–3.1) and 37–38 weeks (adjusted OR 1.4; 95% CI 1.1–1.8) of gestation<sup>20</sup>. In contrast, a study in 2010 found no statistically significant association between birth at 34–36 weeks and the risk of developing asthma in childhood<sup>21</sup>. It is currently not known whether mechanisms of later respiratory

disease in children born at 32–36 weeks of gestation are similar or different to those of very preterm infants, nor how much of the burden of disease is correctly attributed to asthma in this group.

## Hospitalisation during infancy and childhood

A number of studies have shown increased rates of hospital readmission, during the weeks following discharge from neonatal care, among preterm infants born at 34–36 weeks compared with those born at  $\geq 37$  weeks of gestation<sup>22,23</sup>. Jaundice is the most common reason for hospital readmission in the first month of life<sup>22,24,25</sup>, with infection<sup>25</sup>, feeding difficulties and dehydration<sup>26</sup> also frequently seen. Breastfeeding has been associated with such problems, although it is failure to successfully establish adequate breastfeeding, rather than breastfeeding *per se* that is likely to be the important risk factor for difficulties in the early period after discharge<sup>24,27</sup>.

Fewer studies have addressed the need for hospital admission beyond the neonatal period. In the USA, it was found that infants born at 34–36 weeks of gestation were more likely than more mature infants to require at least one hospital admission within the first six months of life<sup>26</sup>. Costs related to health care were higher for this group of infants than term-born infants with the greater portion of this financial cost being related to hospital inpatient care episodes<sup>28</sup>. Infants born at 34–36 weeks of gestation were almost twice as likely to have required inpatient hospital care during the first year of life regardless of the timing of their discharge from neonatal care. As part of the MCS, parents were asked about their children's hospital admissions, excluding those related to trauma or accidents<sup>19</sup>. As might be expected, the most immature infants ( $< 32$  weeks) were most likely to need multiple hospital admissions. However, compared with infants born at 39–41 weeks of gestation, the odds of having three or more admissions before the age of nine months were higher for infants born at 34–36 weeks (adjusted OR 1.9; 95% CI 1.3–2.7)<sup>20</sup>. Unexpectedly, infants born at 37–38 weeks of gestation were also at greater risk of requiring hospital admission than those born just two or three weeks later (adjusted OR 1.4; 95% CI 1.1–1.8). The most common reasons for hospital admission were respiratory and gastrointestinal

problems. Chest infections, wheezing, gastro-intestinal infections and gastro-oesophageal reflux (GOR) were the most common conditions reported by parents as having led to hospitalisation. The odds of being admitted to hospital three or more times between nine months and five years of age were also higher in babies born at 34–36 weeks and at 37–38 weeks (adjusted OR 1.9; 95% CI 1.3–2.7 and 1.4; 95% CI 1.1–1.8 respectively) suggesting that this risk may persist<sup>20</sup>.

### Long-standing illness and disability

A large longitudinal study of all births in Norway between 1967 and 1983 showed that those born at 34–36 weeks had an increased risk of major disabilities that included epilepsy and visual and hearing impairments<sup>29</sup>. As adults, they were more likely to experience disability affecting their work capacity. The more recent MCS asked parents about long-standing illness, disability or infirmity, that had been diagnosed by a health professional and was of more than three months' duration<sup>20</sup>. This showed that long-standing illness at three and five years of age was more common in children born at 34–36 weeks than in more mature infants and that their illness was more likely to limit their activities<sup>20</sup>. Parents of the children born at 34–36 weeks and 37–38 weeks of gestation were more likely to report their child's health as being poor than those whose children had been born at 39–41 weeks. A study to determine the risk for cerebral palsy among 1,682,441 infants born between 1967 and 2001 at 37 weeks of gestation and above showed an increased risk of cerebral palsy in infants born at 37 and 38 weeks of gestation compared with those born at 40 weeks<sup>30</sup>. The risk in infants born at 37–38 weeks appeared also to be increased and similar to the risk in those born post term but the mechanisms for this remain unclear.

### Impact on classification of gestational age

While their morbidities are usually less severe, and their neonatal hospital stay shorter than those of their more immature counterparts, it is clear that longer-term outcomes for babies born at 34–36 weeks are worse than those for babies born after 37 or more weeks of gestation<sup>26,31–33</sup>. This realisation on the part of clinicians and researchers has led to calls for a reclassification of preterm birth in

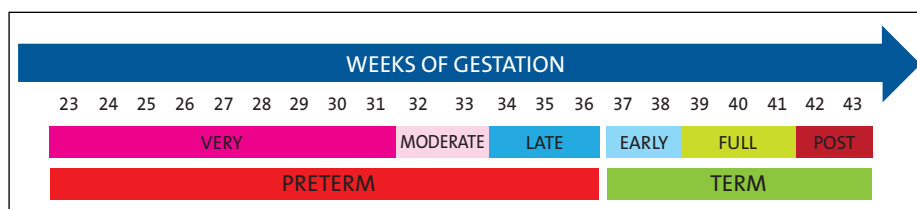


FIGURE 1 Classification of preterm and term birth.

recognition of this finding. A March of Dimes workshop in 2005 addressed issues around optimising care for babies born close to term<sup>34</sup>. The conclusion of this workshop was that previously used terminology, such as 'near-term', 'marginally preterm', 'mildly preterm' and 'borderline preterm' did not adequately reflect the physiological immaturity associated with birth at 34–36 weeks of gestation, and recommended that these babies should be classed as 'late preterm'. While this term is now widely used in published literature, there has been more limited agreement with respect to birth between 32 and 33 weeks of gestation – probably the most commonly used terminology now to describe this group is 'moderate preterm'. These babies have been less well studied, but their outcomes appear to lie between those of the very preterm and late preterm groups (FIGURE 1). This evidence of a gradient of risk in the preterm population, has now led researchers to consider babies that are born at 37 or more weeks of gestation and to investigate whether such a relationship between gestation at birth and long-term outcome exists within the most mature group. In general, babies born beyond 34 weeks of gestation are rarely subject to long-term clinical follow-up. Evidence about longer-term health of infants born late preterm is strengthening, but for those born at 37 weeks or more it remains extremely limited. However, the expression 'early term' has now been adopted by many to denote birth at 37–38 weeks of gestation, with 'full term' reserved for babies born at 39–41 weeks of gestation. This reflects emerging evidence that the gradient of risk probably extends right up to the higher end of the gestational age spectrum.

### What contributes to health outcome of late preterm and early term infants?

Although still limited, much of the available information about late preterm and early term gestations points to worse outcomes in these groups than in

individuals born at full term. However, we have as yet an even more limited understanding of the factors leading to birth at 34–38 weeks of gestation and those influencing long-term health in infants, children and adults. Crucial influences may be at play even before pregnancy starts, but factors relating to occurrences during pregnancy, the perinatal or neonatal period or perhaps later in childhood may also be important in determining risk. To what extent is the long-term health of these babies due to their preterm birth *per se*? There has not yet been enough detailed work in this area to allow us to answer this question. However, whereas outcomes following very preterm birth may, at least in part, be attributable simply to the effects of immaturity, it seems less likely that immaturity is the main factor influencing the health of those born close to term.

Other factors must be considered; likely to be among the most important are events that lead to the early delivery of the baby. Infants with congenital anomalies and multiple births commonly deliver following spontaneous onset of labour at late preterm or early term gestations, but a large number of births occur as a result of obstetric intervention. Concerns during pregnancy about the health of either the mother or fetus often lead to medically indicated deliveries during this period of gestation. Decisions made by obstetricians with respect to medical indications for delivery, timing of delivery and mode of delivery may therefore influence outcomes for the babies. The potential benefits associated with a longer period of gestation must be weighed against the risks of fetal demise *in utero*. Evidence to guide obstetric practice is limited for a number of the common complications of pregnancy, such as preterm premature rupture of the membranes, oligohydramnios, gestational hypertension and poor fetal growth and so the optimal timing of delivery remains unclear and requires further study<sup>35</sup>.

Neonatal care may also influence outcomes. There has been little research addressing the influence of the place and

type of neonatal care, discharge policies and duration of postnatal hospitalisation, but these will vary between centres. In addition, environmental and family factors following discharge, such as type of home, parental education, socioeconomic status and family lifestyle are other factors that may potentially affect longer-term health outcomes in these infants. Many of these are inextricably linked and their relative contributions to long-term infant and child health outcomes still need further exploration.

## What are the implications for provision of health care?

There has been, in recent years, a steady increase in the numbers of babies being born at late preterm gestations<sup>36</sup>. However, this now seems to have reached a plateau and may even be declining. This suggests that strategies for reducing avoidable births at these gestations may be having some success. Despite this, late preterm births represent around 70% of all preterm births (approximately 30,000 births per year in the UK) and UK births at early term gestation number almost 120,000 per year<sup>37</sup>. Emerging evidence about health outcomes appears to be mirroring previous data that have been reported for neuro-developmental<sup>38-43</sup> and educational<sup>44-46</sup> outcomes in these children although contemporary and prospective data remain limited. Poor health in large numbers of infants and children is likely to have a substantial impact on primary care, public health services and hospital services. Most preterm infants born at 34 weeks and above do not receive follow-up after discharge from neonatal care unless they have had a particularly difficult neonatal course. There is therefore no routine surveillance for their healthcare or developmental needs. Now that these children are increasingly being highlighted as a group at greater risk than has previously been appreciated, it will be important to ensure that their ongoing healthcare needs are being adequately met, though formal follow-up may not be appropriate or feasible in such a large group.

## Summary

It is becoming clear that it is no longer appropriate to view term and preterm birth as a dichotomy, as there appears to be a spectrum of risk that is at its greatest in the most preterm, but that still exerts an

effect at the more mature gestations, even close to full term. While the absolute effects and differences between groups of babies may in themselves be small, it is vital to remember that the impact on healthcare services of the more mature babies will be substantial at the population level, because of the sheer number of babies that are born at late preterm or early term gestations. Further research in this area is required to identify those at greatest risk of poor health outcomes in order to allow appropriate and targeted follow-up in these children.

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