Impact of Neonatal Intensive Care on Late Preterm Infants: Developmental Outcomes at 3 Years

WHAT’S KNOWN ON THIS SUBJECT: Children born late preterm (34–36 weeks’ gestation) are at increased risk of adverse early childhood outcomes compared with term-born children. The impact of the neonatal experience on longer-term outcomes of these infants has not yet been well considered.

WHAT THIS STUDY ADDS: This study provides information regarding the development of late preterm infants at 3 years. Late preterm infants who received neonatal intensive or high-dependency care had similar developmental outcomes to children born late preterm who did not receive this care.

abstract

BACKGROUND: Late preterm infants (LPIs) (34–36 weeks’ gestation) account for up to 75% of preterm births and constitute a significant proportion of all neonatal admissions. This study assessed the impact of neonatal intensive or high-dependency care (IC) on developmental outcomes of LPIs at 3 years of age.

METHODS: This cohort study included 225 children born late preterm in Northern Ireland during 2006. Children born late preterm who received IC were compared with children born late preterm who did not receive IC. Cognitive, motor, and language skills were assessed by using the Bayley Scales of Infant and Toddler Development, Third Edition. Growth was assessed by using anthropometric measures of height and weight.

RESULTS: LPIs who received IC were more often less mature (34 weeks’ gestation), with lower birth weight (<2500 g) and Apgar scores (<7 at 5 minutes) compared with the control group. They were more often born by cesarean delivery and more likely to have received resuscitation at birth. At 3 years of age, children born late preterm who received IC demonstrated similar cognitive, motor, and language skills compared with children in the control group. Measurements of growth also did not differ significantly between groups.

CONCLUSIONS: Despite having increased maternal, perinatal, and neonatal risk factors, there were no significant differences in early childhood development between LPIs who received IC and those who did not. LPIs do not receive routine follow-up after IC and this study provides useful and reassuring data for parents and clinicians on the long-term outcome of this infant group. Pediatrics 2012;130:1–8
Late preterm infants (LPIs; born at 34+0–36+6 weeks’ gestation) account for up to 75% of all preterm births, with a reported 25% increase in late preterm births from 1990 to 2006. LPIs have unique and particular concerns in the neonatal period with an increased risk of morbidity and mortality in comparison with term infants, and these infants account for 20% to 25% of all neonatal admissions.

Although most research to date pertaining to outcomes beyond the neonatal period has focused on infants born extremely premature (<28 weeks’ gestation) or at very low birth weights (<1500 g), there has been an increasing focus on the longer-term outcomes of LPIs in recent years. These studies have suggested that, in comparison with term infants, those born at late preterm gestations are at increased risk of adverse early neonatal factors or admission status. Not all LPIs require neonatal intensive or high-dependency care (IC) and yet, to date, a control group of infants born within the same gestational age range has not been used in study designs, and thus the impact of IC admission on longer-term outcomes has not been fully explored. The aim of this study was to assess early childhood development at 3 years (including cognition, language, motor skills, and growth) of children born late preterm who received IC in comparison with LPIs who did not receive IC to further understand the outcomes among this large and significant group of neonatal graduates.

METHODS

Study Population

All children born in Northern Ireland (NI) at 34 weeks + 0 days to 36 weeks + 6 days of gestational age, between January 1 and December 31, 2006, were eligible to take part in the study. Gestational age was determined by the best obstetric estimate, based on fetal ultrasound, at ~20 weeks in most cases. The study group was composed of children who were born late preterm and had received any episode of neonatal IC as defined by the British Association of Perinatal Medicine (Table 1). These children were identified from the Neonatal Intensive Care Outcomes Research and Evaluation (NICORE) database, which contains anonymous data on infants who are admitted to all 7 NICUs across NI. The control group was composed of children born within the same gestational age range but who did not receive any IC or who received special care (SC) only for ≤3 days. These children were identified from labor ward records. Exclusion criteria included children who received SC only for >3 days and those with recognized congenital syndromes/infections. Ethical approval was sought and granted from the Office for Research Ethics Committees NI (application number: 08/NIR02/116).

Recruitment

Recruitment and data collection took place simultaneously from March 2008 to March 2009, when the children were 3 years of age. A trace of eligible children was conducted to ensure that parents/guardians with a child who died in infancy were not contacted. Parents/guardians of eligible children were sent an invitation letter and 2 reminder letters if necessary, from the neonatal consultant at their hospital of birth; a handwritten flyer was included and a thank-you gift voucher was offered to participants. Figure 1 summarizes the eligibility and recruitment of children to the study. Written consent was attained from parents/guardians before the assessment of children. At the outset of the study there were concerns relating to the imbalance in gestational age among LPIs admitted to IC and those not requiring IC, with a higher proportion of infants of 36 weeks’ gestation among...
the non-IC group. To address this concern surrounding gestational age bias and following statistical advice, all eligible children born at 34 and 35 weeks’ gestation who were identified for the control group were invited to take part in the study, whereas only a random sample of eligible control children born at 36 weeks were invited to take part (Fig 1).

**Outcome Measures**

**Developmental Outcomes: Cognition, Language, and Motor Skills**

The primary outcomes of cognition, language, and motor development were assessed by using the Bayley Scales of Infant and Toddler Development, Third Edition.19 Each developmental domain was assessed by using a specific subtest for cognition, language, and motor skills. Each subtest provides a raw score, which is the sum of the number of points scored; composite scores are derived from these raw scores to facilitate standardized comparison among children. Both the language and motor subtests have more than 1 scale; language skills included expressive and receptive communication and the motor assessment included fine and gross motor skills.

**Growth**

Anthropometric measurement of height and weight was assessed as a secondary outcome measure. Height was assessed by using the SECA Leicester Portable Height Measure (Birmingham, UK) and weight was assessed by using SECA Flat Analog Scales (Birmingham, UK), graded to 0.5 kg.

**Additional Measures**

Maternal, perinatal, and infant data were collected from maternal medical records and from data contained on the NICORE database, after the attainment of written maternal consent. In addition, descriptive sociodemographic information was collected by using a parent report questionnaire designed specifically for the study. To assess sociodemographic status of children, deprivation quintiles were calculated by using the NI Multiple Deprivation Measure.20 This spatial measure of deprivation based on geographical postcodes comprises 7 domains of deprivation, including income, employment, health, education, proximity to services, living environment, and crime; these are then combined to allow assessment of deprivation by quintiles.

**Statistical Analysis**

A sample size calculation stipulated 120 children per group to detect a 4-point difference in mental and psychomotor outcomes on the Bayley Scales of Infant Development,21 assuming an \( \alpha \) level of 0.05, a power of 80%, and an SD of 11 points. Statistical analyses were undertaken by using SPSS 18.0 statistical software (SPSS Inc, Chicago, IL). All tests were 2-tailed and the level of significance was set to an \( \alpha \) of 0.05. Descriptive characteristics of infants in the study and control groups were compared by using the \( \chi^2 \) test. Means and SDs were used to compare the continuous data from primary outcome variables (cognition, language [expressive and receptive], and motor [gross and fine]). The independent \( t \) test was then used to compare means between the study and control groups. Further exploration of primary outcome data
involved a subgroup analysis of the mean scores based on gestational weeks to reveal, if any, the impact of gestational age on the scores attained.

Additional subgroup analysis was undertaken with the exclusion of infants who received SC only for ≤3 days from the control group to clarify whether the inclusion of SC-only infants in the control group was influential to variation in mean scores between the study and control groups. Height and weight were also compared between the groups by using means and SDs; the independent t test was used to compare the means.

RESULTS

Of all eligible children born late preterm who were invited to take part in the study (n = 494), 240 (48.6%) were recruited. In total, 225 children (94%) were assessed and completed the study (Fig 1). Of these children recruited, 103 children had received IC and were included in the study group. The control group was composed of 122 children, including those who did not require any neonatal care (n = 99) and those who required SC only for ≤3 days (n = 23).

Descriptive Characteristics of Children by Group

Perinatal, maternal, and infant characteristics in the study and control groups are presented in Table 2. Most children in both groups were born to mothers who were classified as “white” (94.2% in the study group and 98.4% in the control group). This is indicative of the NI population. Only 5 children were born to mothers from other ethnic minorities; all of these children were in the study group, leading to a significant difference between the groups.

Within the control group, a greater proportion of children were born to mothers who were <24 years old (11.5%) and >35 years old (37.7%), when compared

TABLE 2 Maternal Characteristics, Perinatal Factors, and Infant Characteristics by Group

<table>
<thead>
<tr>
<th>Infant Group</th>
<th>Study; n = 103 (Col. %)</th>
<th>Control; n = 122 (Col. %)</th>
<th>χ²</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant gender</td>
<td>Male 53 (51.5)</td>
<td>58 (47.5)</td>
<td>0.34</td>
<td>.558</td>
</tr>
<tr>
<td></td>
<td>Female 50 (48.5)</td>
<td>64 (52.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestation, wk</td>
<td>34 42 (40.8)</td>
<td>18 (14.8)</td>
<td>22.11</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
with mothers in the study group (7.8% and 22.3%, respectively). Despite this, most mothers in both the study and control groups were aged between 25 and 34 years. Indicators of sociodemographic status and health behaviors, including marital status (living alone or living with a partner), smoking status, and deprivation level (based on postcode) did not vary significantly between the groups. Mothers of study children were significantly more likely to have an additional health-related risk factor (which included anemia, hypertensive illness, infection, asthma, neoplasia, mental health illness, placental problems [eg, intrauterine growth retardation, oligohydramnios, polyhydramnios], antepartum hemorrhage, and preterm labor) recorded in their maternal medical records, compared with mothers of control children. Maternal Rhesus-negative status was also significantly increased in the study group. Children in the study group were significantly more often born by cesarean delivery (69.9%) than those in the control group (32.8%) \((P \leq .001)\). The rationale for cesarean delivery, whether emergency or elective, did not vary significantly between the groups. In comparison with 16% of children in the control group, \(~45\%\) of children in the study group required resuscitation at birth (including facial oxygen, positive pressure, cardiopulmonary resuscitation) \((P \leq .001)\). Other perinatal risk factors did not vary significantly between the groups.

There was significant variation in the gestational age of children within each group \((P \leq .001)\), with 41% of study children born at 34 weeks’ gestation compared with 15% of control children. Significantly more study children were low birth weight \((P = .003)\). Approximately 18% of children in both groups were of twin gestation. The mean age at assessment did not vary significantly between the 2 groups \((P = .94)\), with study children assessed at the mean age of 39.06 \((\pm 0.75)\) months and control children at 39.07 \((\pm 0.85)\) months.

### Developmental Assessment: Cognition, Language, and Motor Skills

The results of the primary outcomes are presented in Table 3. For all 3 domains of development measured at 3 years, there were no statistically significant differences in the mean score between the study children who received IC and control children who did not, although study children scored slightly lower in overall cognition, expressive language, and both the gross and fine motor scales of the Bayley Scales of Infant and Toddler Development, Third Edition, and slightly higher in receptive language compared with control children (Table 3). Additionally, subgroup analysis by gestational age in weeks revealed no variation between age groups on any of the scales, and subgroup analysis with the exclusion of SC-only infants from the control group did not affect the findings between the groups (data not shown).

### Growth

The mean height and weight of LPIs in the study group who received IC did not vary significantly from those LPIs in the control group who did not receive IC (Table 3).

### DISCUSSION

The overall aim of this study was to consider the longer-term outcomes of the substantial population of LPIs who...
receive IC. The inclusion of a comparison group of LPIs who did not receive IC facilitated a unique exploration of the impact of receiving IC, with its associated morbidity and risks, among this group. Findings suggest that, despite increased maternal and perinatal risk factors, LPIs in this study who received IC did not perform differently in terms of cognitive, language, and motor abilities and growth, compared with their peers born within the same gestational age range who did not receive IC.

The longer-term follow-up of children after late preterm birth has increased over recent years, and although there remains a limited evidence base for the longer-term outcomes of these infants, LPIs are increasingly regarded as being at increased risk of adverse outcomes, including neurodevelopmental disabilities, poorer educational ability, early intervention requirements, and medical disabilities in comparison with term-born children, up to 7 years of age.14,22–24 The neonatal admission status of LPIs and their subsequent early childhood development has not been well considered. However, 3 studies that specifically assessed development among LPIs reported as having received IC, all detailed negative outcomes with visuospatial and verbal fluency deficits reported at 3 years, compared with term-born children22,23; moderate cognitive impairment at 5 years, among ∼19% of admitted LPIs (at 34 weeks) (no comparison group)26; and an equal requirement for early intervention (at age 1 year) in comparison with very preterm children (<32 weeks) after adjustment for neonatal comorbidities.15 A further recent study by Baron et al27 also compared LPIs with term-born children, with a subgroup analysis of 2 small groups of infants, those defined as “complicated” LPIs, requiring IC admission (n = 90) and “uncomplicated” LPIs, not requiring IC admission (n = 23). Mean assessment scores were significantly lower for complicated LPIs compared with term-born children and uncomplicated LPIs did not differ significantly from children in the term group. In the current study, comparison of maternal, perinatal, and infant characteristics in the study and control groups revealed that among study children (who received IC), there was increased incidence of maternal health-related risk factors, increased cesarean delivery, and more children who required resuscitation. Additionally, a larger number of study children were less mature (born at 34 weeks’ gestation). Despite this, similar developmental outcomes were found at 3 years of age among LPIs irrespective of requirement for IC.

It is important to consider methodological factors that may have affected the findings. Of the parents of LPIs invited to take part in the current study, a sufficient number were recruited to meet the requirements set within the sample size calculation. Descriptive characteristics of those who did and did not respond to the study invitation were compared for eligible study infants by using data from the NICORE database (data not shown). This analysis revealed that fewer young mothers, more smokers, and single parents chose not to take part in the study. Mothers in higher deprivation areas were also marginally less likely to take part. Previous research has reported the difficulties of including hard-to-reach groups and the importance of the influence this may have on the interpretation of study findings.28 Despite this, however, comparison of the sociodemographic characteristics of children who were recruited to the study were largely similar between the study and control groups.

The subtlety of variation between the scores of LPIs who received IC and those who did not may suggest that the assessment tool used may not have been sufficiently sensitive to the subtle variations displayed by children in this study. The assessment of developmental delay among children without major disability is extremely complex and caution has been recommended in measuring outcomes after prematurity, as assessment tools may underestimate or fail to detect developmental concerns among preterm children.29 It may also be the case that children born at late preterm gestations do not exhibit delay that can be detected by using developmental assessments at the age of 3 years. Children may not present concerns until later, when an accumulation of factors results in the presentation of behaviors or delay of detectable significance.30 A consistent finding across many follow-up studies is that cognitive deficits become more apparent as age increases.31–33 However, it is also important to acknowledge that by the age of 3 years, LPIs who initially received IC may have caught-up with their nonadmitted counterparts, resulting in similar scores between the groups.

Although a number of methodological factors have been highlighted as potentially influential, the findings from this study are reassuring for parents of LPIs who have had increased perinatal risk factors and received IC, suggesting that these early adverse outcomes may not be detrimental in comparison with their late preterm peers who did not receive IC. Within NI, LPIs are not routinely followed after receiving neonatal care. This is in accordance with UK guidelines that suggest follow-up of infants of <32 weeks’ gestation or a birth weight of 1500 g.34 Other infants are followed only if there are additional indicators, such as biological risks, family circumstances, or having had particular interventions in the neonatal period. These guidelines are similar to those in the United States.35 There remains a global dearth of clinical
guidelines relating specifically to the longer-term follow-up of LPIs; however, this study provides useful and reassuring data in relation to the longer-term outcomes of this group for clinicians involved in the follow-up care of children who have received IC.

It is acknowledged that the addition of a term-born control group would have enhanced the study; however, a number of studies have previously assessed development in LPIs in comparison with term-born controls. The aim of this study was to provide additional information relating to outcomes for LPIs. In particular, it has included a large sample of recently born LPIs from a well-defined geographical population.

Few previous studies of LPIs have conducted prospective infant assessments, rather using data collected and stored for other purposes (e.g., medical and educational registries). Additionally, other studies have used surrogate measures of development, such as special education requirements or teacher reports of academic achievement. The current study involved prospective data collection, by using a standardized assessment tool, to assess LPIs at 3 years of age. McCain et al identified the preschool period as a pivotal time of development and learning. Although the assessment of infants at age 3 years is not without complexity, it is an important developmental phase, before the influence of formal education, which has been neglected before this study.

A major strength of this study is the comparison of LPIs who received IC with a control group of infants of the same gestational age who did not receive IC. It has facilitated exploration of the impact of IC, with its associated neonatal morbidity, on the early childhood development of LPIs. Boyle and Boyle recently suggested that the consequences associated with the place of postnatal care of LPIs warrants further research. Findings from this study provide useful data in response to these concerns.

CONCLUSIONS

Children born late preterm are a large and eclectic group, with varied etiologies surrounding their early birth and wide-ranging morbidities in the neonatal period, both of which, aside from preterm birth itself, may be influential in their longer-term outcomes. The current study has explored the heterogeneity of LPIs in terms of their requirement for IC and revealed that despite having increased maternal, perinatal, and neonatal risk factors, there were no significant differences in early childhood development between LPIs who received IC and those who did not. LPIs are not routinely followed after receiving IC, and this study provides useful and reassuring data on the longer-term outcome of this group of infants for both clinicians and parents alike; however, it is recognized that adverse outcomes may present later in childhood. In light of this, further research to follow-up on this important late preterm population of infants throughout the school years is recommended.

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