Impact of neonatal morbidity on the risk of developmental delay in late preterm infants

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\section*{Abstract}

\textbf{Keywords:} Late preterm \\
Neonatal morbidity \\
Ages and stages questionnaires \\
Follow-up \\
Preschoolers \\
Developmental delay

\textbf{Background:} Late preterm infants (LPI) have a higher risk of developmental delay (DD) than term-born infants. The association of perinatal complications with specific morbidity is not clear.

\textbf{Aim:} (1) To compare the risk of DD at 4 years of age between LPI who have presence or absence of any morbidity associated with the prematurity at birth, called complicated (cLPI) or uncomplicated (uLPI), and term-born infants, (2) to determine maternal and perinatal factors associated with risk of DD, and (3) to analyze, in LPI, the association between perinatal morbidity and risk of DD.

\textbf{Methods:} A retrospective cohort study including 163 LPI – 47 cLPI and 116 uLPI – and 158 term-born infants (Terms) was conducted. Parents completed the Ages & Stages Questionnaires\textsuperscript{®} 3rd Spanish version (ASQ3). Risk of DD was defined as the presence of any ASQ3 domain scoring below the mean minus 2 SD. Association between risk of DD and maternal and perinatal factors was analysed using a multivariate logistic model. Incidence of risk of DD was analysed according to specific morbidity.

\textbf{Results:} Compared to Terms, cLPI have a higher risk of DD in the communication domain. Respiratory pathology was associated with a higher risk in the communication domain. Caesarean delivery was the only maternal perinatal risk factor for DD, especially in gross motor domain.

\textbf{Conclusions:} At the age of 4 years cLPI, especially those with respiratory morbidity, had a higher risk of communication delay. Caesarean delivery was the only perinatal risk factor associated with risk of DD.

\section{Introduction}

Prematurity, defined as birth before 37 weeks of gestation, represents the greatest risk of morbidity and mortality in newborn infants, where late preterm infants (LPI), born between week 34 0/7 and 36 6/7, represent the majority of this population [1,2]. In developed countries, the rate of prematurity is around 9.6\% [3], with LPI representing 70–80\% of all premature births. After a progressive increase of LPI in the two past decades, it appears now to be decreasing [3–5].

The National Institute of Child Health and Human Development (NICHD) issued a consensus document in 2005 on optimizing care in LPI in an attempt to improve outcomes in the short and long term and to decrease the consumption of resources by this population [1]. Complications in LPI are associated with higher costs than newborn infants with a lower gestational age (GA), due to the significant number of births in this stage of gestation [6,7]. An increased risk of perinatal morbidity has been demonstrated in LPI, with respiratory morbidity the most prevalent [8–13].

McGowan JE et al., in a review that included 10 studies evaluating LPI between 1 and 7 years of age, found that in all the age groups between 3 and 7 years, the LPI showed worse academic results and increased difficulties in school activities, revealing itself to be a population at risk of adverse neurological development and learning difficulties up to the age of 7 years, compared with term-born children [14].

In several articles, these LPI with perinatal morbidity are called ‘complicated’ (cLPI); they show greater risk of developmental difficulties in some studies [15,16] whereas this has not been demonstrated in others [17–18]. Regarding perinatal history, respiratory morbidity, hypoglycaemia, multiple gestations, and being small for gestational age have been related significantly with neurodevelopmental disorders in the LPI population [11,19,20]. In a previous study we found a greater prevalence of risk of developmental delay (DD) in LPI compared to term-born infants at the age of 4 years based on the overall performance of ASQ3, but we did not analysed those LPI with or without perinatal morbidity nor did we organized the analysis by domains [21]. For the

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current study we recruited a larger sample of children with the objectives of: (1) to compare the risk of DD at 4 years of age between LPI who have presence or absence of any morbidity associated with the prematurity at birth, called complicated (cLPI) or uncomplicated (uLPI), and term-born infants, (2) to determine maternal and perinatal factors associated with risk of DD, and (3) to analyze in LPI, the association between perinatal morbidity and risk of DD.

2. Methods

2.1. Population

A retrospective cohort study was carried out including 163 LPI (GA of 340/7 to 366/7 weeks) and 158 term-born infants (GA of 370/7 to 416/7 weeks) born in a private hospital of a healthcare insurance company with a Neonatal Intensive Care Unit, from 1 January to 31 December 2009 and 2011. The LPI were classified as complicated (cLPI) when they had any morbidity associated with the prematurity, such as clinical instability, respiratory problems, hyperbilirubinaemia requiring phototherapy, or hypoglycaemia. They were classified as uncomplicated late preterm infants (uLPI) when they did not require admission or were admitted without pathology, considering that all infants ≤ 35 weeks of GA are systematically admitted by protocol in the neonatal unit.

Inclusion criteria were: (1) For the study group, LPI born in the period whose parents were located and, after phone contact, agreed to participate by completing an informed consent form and the Ages and Stages Questionnaires® third edition in Spanish (ASQ3) at the age of 4 years. (2) For the control group, we selected a sample of children born in the hospital at GA of term matched by date of birth with LPI. We included only apparently healthy term-born infants (terms) without a history of complications in the neonatal period who were followed up by paediatricians belonging to our insurer group. Those contacted who agreed to take part in the study were included. Excluded were children with malformation syndromes or with known genetic or metabolic diseases and, in the terms group, those who needed to be admitted to hospital in the neonatal period. Fig. 1 presents the population studied.

The LPI in the study were 57.6% of the total LPI born in this period. Table 1 shows the characteristics of the LPI recruited and of those not included, with no statistically significant differences found with those

2.2. Measures

The following variables were recorded, as obtained from the clinical record of each newborn infant: birth weight, intrauterine growth restriction (IUGR = weight < 3% according to GA), GA evaluated according to obstetric data of last menstrual period and ultrasound scan control, twinning, form of delivery completion – vaginal or caesarean section – administration of antenatal corticosteroids (2 doses of beta-methasone between 7 and 1 days before delivery), and admission to the neonatal unit (NU). The latter case involved the recording of incidents of respiratory pathology (respiratory distress, transient tachypnea, meconium aspiration syndrome, persistent pulmonary hypertension), hyperbilirubinaemia requiring phototherapy, and hypoglycaemia (< 40 mg/dL first 48 h). Considered separately was admission to the NU due to a respiratory pathology requiring respiratory assistance

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**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>LPI not included (n = 120)</th>
<th>LPI recruited (n = 163)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (w), M (SD)</td>
<td>35.6 (0.6)</td>
<td>35.4 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>62 (51.7)</td>
<td>96 (58.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Birth weight (g), M (SD)</td>
<td>2533 (368)</td>
<td>2465 (420)</td>
<td>NS</td>
</tr>
<tr>
<td>Caesarean section, n (%)</td>
<td>79 (65.8)</td>
<td>100 (61.3)</td>
<td>NS</td>
</tr>
<tr>
<td>IUGR, n (%)</td>
<td>5 (4.2)</td>
<td>11 (6.7)</td>
<td>NS</td>
</tr>
<tr>
<td>Twins, n (%)</td>
<td>59 (49.2)</td>
<td>64 (39.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Neonatal morbidity (cLPI), n (%)</td>
<td>28 (23.3)</td>
<td>47 (28.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

LPI: late preterm infants; M: mean; SD: standard deviation; IUGR: Intrauterine growth restricted; cLPI: complicated late preterm infants; NS: not significant.

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