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

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ABSTRACT

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.
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.
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®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.
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.
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.

1. 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 $34^{0/7}$ to $36^{6/7}$ weeks) and 158 term-born infants (GA of $37^{0/7}$ to $41^{6/7}$ 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 LPI not included in the study.

Table 1
Description of the population of late preterm infants, comparing those recruited and those who were not included in the study.

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

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

Sample size calculation: assuming a prevalence of 5% of children to be at risk of DD in the term-born infants and 20% in the cLPI [21,22], a significance level of 5%, statistical power of 80%, and ratio of 3:1 term infants per case, a sample size of 42 cLPI and 125 term infants were requested.

The project was approved by the Hospital Teaching and Ethics Commission.

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 betamethasone 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

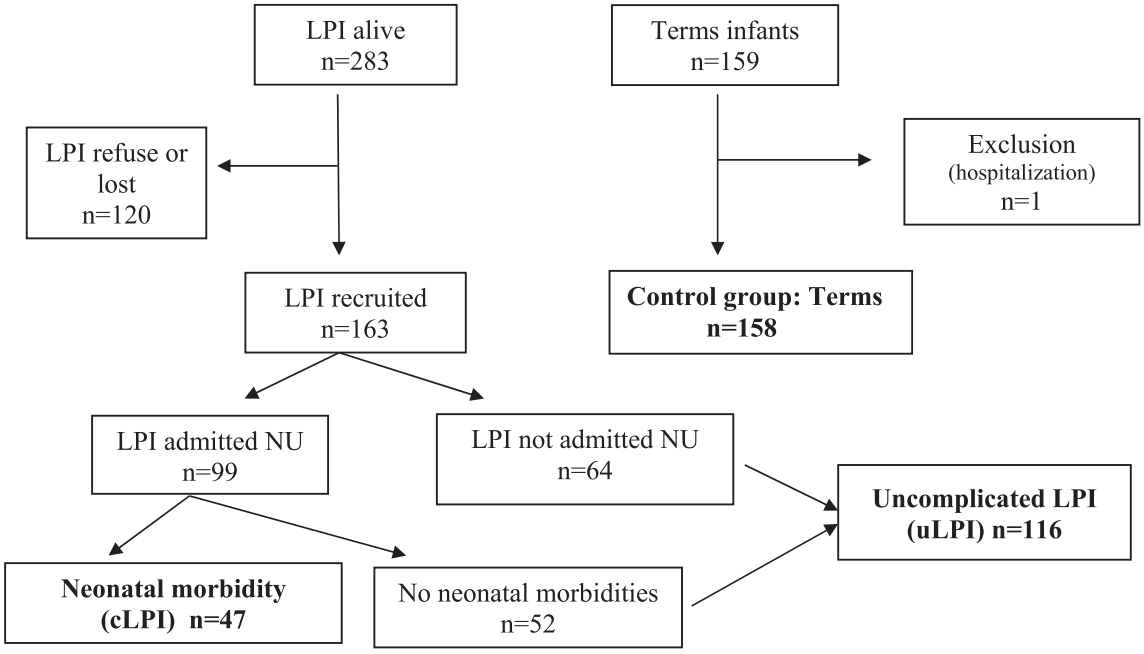

Fig. 1. Description of the studied population.
LPI: late preterm infants; Terms: term-born infants; NU: Neonatal Unit; cLPI: complicated LPI; uLPI: uncomplicated LPI.

(oxygen therapy, mechanical ventilation, or CPAP).

A survey was applied to parents asking for information on feeding by means of breast-feeding over one month of postnatal life, the mother's age at assessment time, and the education level of the parents. The socio-economic level of the participants was considered middle-high due to the social characteristics of the population analysed, assuming that this population could afford an expensive private healthcare center.

The evaluation instrument was the Ages & Stages Questionnaires®, third version in Spanish (ASQ3) [23]. The ASQ3 is a validated parent-completed developmental screening tool. Twenty-one questionnaires are available from 1 to 66 months of age. In this study the 4-year questionnaire was used and assessed at 48.3 ± 1 months. Parents answer 30 questions covering 5 domains of development, including communication, gross motor, fine motor, problem solving, and personal-social. Parents are instructed to try activities with their child to facilitate accurate assessment. A pass/fail score was assigned for each area of development. The ASQ3 has been validated in several countries for both term-born and preterm infants [24–27]. In Spain, ASQ was validated in a community sample of 12- to 36-month infants, showing adequate psychometric properties [28]. Infants were considered at risk of DD if they scored > 2SD below the mean of the sample in any ASQ3 domain (referral zone), and were considered with positive screen if at least one domain was in the referral zone. Parents were offered the option of completing the questionnaire by e-mail or with a home visit by a person other than a healthcare professional, who only carried the document and provided advice.

2.3. Statistical analyses

Frequencies and percentages were used to describe maternal and infant demographic characteristics and birth outcomes. Sample characteristics were compared using Student *t*-test to detect mean differences among LPI versus terms, and for mean comparison between cLPI and uLPI.

To assess the risk of DD of cLPI compared with uLPI and terms, a deficit risk analysis was performed in each of the developmental areas and for global risk of DD. Anova with Bonferroni correction was used to address multiple comparisons.

We also analyze the risk of DD using a multiple logistic regression model. Control variables included in the model were gender, twinning, the mother's education and age, delivery mechanism, and breast-feeding [22]. Given the high collinearity between maternal and paternal education and between maternal and paternal age, only maternal education and age were included in the multivariate analysis.

All tests were considered to be statistically significant if $p < 0.05$. The analyses were conducted with Statistical Package Stata.

3. Results

Those recruited were 163 LPI: 47 cLPI and 116 uLPI, and 158 terms. The biodemographic, perinatal, and social characteristics of the groups are presented in Table 2. The parents' ages, the rates of caesarean sections and twinning frequency were significantly higher in the LPI compared to the terms, while university education of the father and breast-feeding were lower in the LPI. There were no differences between the two groups in gender or the incidence of IUGR. Of the 163 LPI included in the study, 47 (28.8%) were considered cLPI as they were admitted to the NU at birth because of clinical instability or presented morbidity: 16 (9.8%) had hypoglycaemia, 25 (15.3%) hyperbilirubinaemia, 18 (11%) respiratory morbidity, 1 (0.6%) sepsis, and 2 (1.2%) apnoeas. Eleven (6.7%) of the LPI had 2 associated pathologies and only one infant had 3. Forty-one (25.2%) received antenatal corticosteroids and 94 (57.7%) were breast-fed. In Table 2, by comparing the cLPI with the uLPI, there were no statistically significant differences in the biodemographic, social, or perinatal variables, or in relation to breast-feeding. The cLPI were of lower GA and weight at birth than the uLPI, and a higher proportion of them received antenatal corticosteroids than did the uLPI.

As shown in Fig. 2, cLPI have a higher frequency of DD than uLPI and terms. These differences are significant in the communication domain, compared with uLPI (p 0.008) and with terms (p 0.006). We did not find differences between the uLPI and terms group. Uni- and multivariate analysis were done to compare the frequency of risk of DD in cLPI and uLPI compared to terms, by domains. See Table 3. In unadjusted analysis, cLPI obtained a lower performance in the communication domain compared to terms (uOR 6.15 [1.37–27.63], p 0.006) and in adjusted analysis this difference was found at the limit of significance (aOR 4.60 [0.91–23.16], p 0.06). In the adjusted analysis we found, in the limit of significance (aOR 11.32 [0.91–140.40], p 0.05) a higher risk of DD in the personal-social domain in cLPI compared to the terms.

To understand the perinatal factors associated with the risk of DD, multivariate analysis was performed, in which caesarean delivery was the only significant factor associated with the risk of positive screen ($p < 0.05$), which means at least one domain is > 2SD below the mean area score. In the analysis by domains, mother's age ≥ 35 years was a protective factor in gross motor domain ($p < 0.01$), and the method of delivery was a significant risk factor for risk of deficit in gross motor domain ($p < 0.05$).No other factors were found to be significant. See Table 4.

In the analysis of risk of DD in each domain, those LPI with respiratory pathology showed a risk of delay in the communication domain (22.22% versus 2.07%, chi square = 15.73, p = 0.000). Children with hypoglycaemia had higher DD frequencies in different domains but they did not reach statistical significance. See Table 5.

4. Discussion

In this study, the cLPI group had a higher frequency of risk of delay in the communication domain compared to uLPI and term-born infants, and in adjusted analysis, when comparing cLPI with term-born infants, we found a risk of delay in the personal-social domain that was at the limit of significance. However, in other studies, there are differences between groups of cLPI and uLPI in other domains [11,15,16]. Our results coincide with the study by Ballantyne M et al., which showed that LPI who require admission to neonatal intensive care have increased risk of DD measured with the ASQ3, especially in communication domain [22]. Baron IS et al. showed that the subgroup of LPI with neonatal complications have subtle cognitive deficits at 3.8 years old [16], while McGowan JE et al. found no differences in performance at 3 years of age between cLPI and uLPI [17,18]. Different studies use NU admission or the presence of perinatal morbidity in an equivalent way to determine whether there is a relationship with DD, and researchers obtain conflicting results [11,15–18,22]. The differences may be explained in part by the fact that the evaluation of the LPI are not done in the same way, and it is important to consider that the admission to a NU is not itself a criterion to consider a birth as complicated, given that the admission criteria of LPI in different neonatal units are not uniform. Only those hospitalized with significant perinatal morbidity should be considered as a cLPI.

Regarding the associated morbidity, Kerstjens JM et al. and Schonhaut L et al. performed an evaluation of the risk of DD in moderate and late preterm infants and only found an association with hypoglycaemia [19,20]. On review of specific morbidity, in our study children with hypoglycaemia had higher DD frequencies in different domains but these did not reach statistical significance. However, possible associations should be studied in greater depth in a larger sample. A higher risk of DD in the communication domain was found in the group of children who presented respiratory morbidity. In this line, Wachtel EV et al. showed that respiratory pathology, which predominated in their group of LPI, was associated with worse

Table 2
Analysis of biodemographics, social and perinatal variables comparing terms and late preterm infants, and comparing late preterm infants with and without complications.

	Total sample			LPI		
	Terms n = 158	LPI n = 163	p[a]	cLPI n = 47	uLPI n = 116	p[b]
Biodemographic and social variables						
Male gender, n (%)	91 (57.2)	96 (58.9)	NS	27 (57.4)	69 (59.5)	NS
Maternal age (y), M (SD)	37.1 (3.5)	38.2 (4.3)	0.006	38.0 (4.2)	38.4 (4.3)	NS
Paternal age (y), M (SD)	38.5 (5.0)	39.6 (5.2)	0.02	38.8 (4.3)	40.0(5.4)	NS
University mother, n (%)	134 (84.3)	126 (77.3)	NS	38 (80.9)	88 (75.9)	NS
University father, n (%)	131 (82.4)	110 (65)	< 0.001	32 (68.1)	78 (67.2)	NS
Perinatal variables						
Gestational age (w), M (SD)	39.3 (1.0)	35.4 (0.7)	< 0.001	35.0 (0.8)	35.6 (0.6)	< 0.001
Birth weight (g), M (SD)	3267 (419)	2465 (420)	< 0.001	2340 (434)	2516 (405)	0.007
Caesarean section, n (%)	69(43.4)	100 (61.3)	< 0.001	30 (63.8)	70 (60.3)	NS
Twins, n (%)	2 (1.3)	64 (39.3)	< 0.001	15 (31.9)	49 (42.2)	NS
Antenatal steroids, n (%)	0(0)	41 (25.2)	< 0.001	20 (42.6)	21 (18.1)	< 0.001
IUGR, n (%)	8 (5.1)	11 (6.7)	NS	3 (6.4)	8 (6.9)	NS
Other variables						
Breastfeeding, n (%)	113 (71.5)	94 (57.7)	0.05	23 (48.9)	71 (61.2)	NS

Terms: term-born; LPI: late preterm infants; cLPI: complicated late preterm infant; uLPI: uncomplicated late preterm infants; IUGR: intrauterine growth restricted; M: mean; SD: standard deviation; NS: not significant.

[a] Comparison of all children born late preterm infants with the born term.

[b] Comparison of late preterm infants depending on whether or not complications or neonatal morbidity.

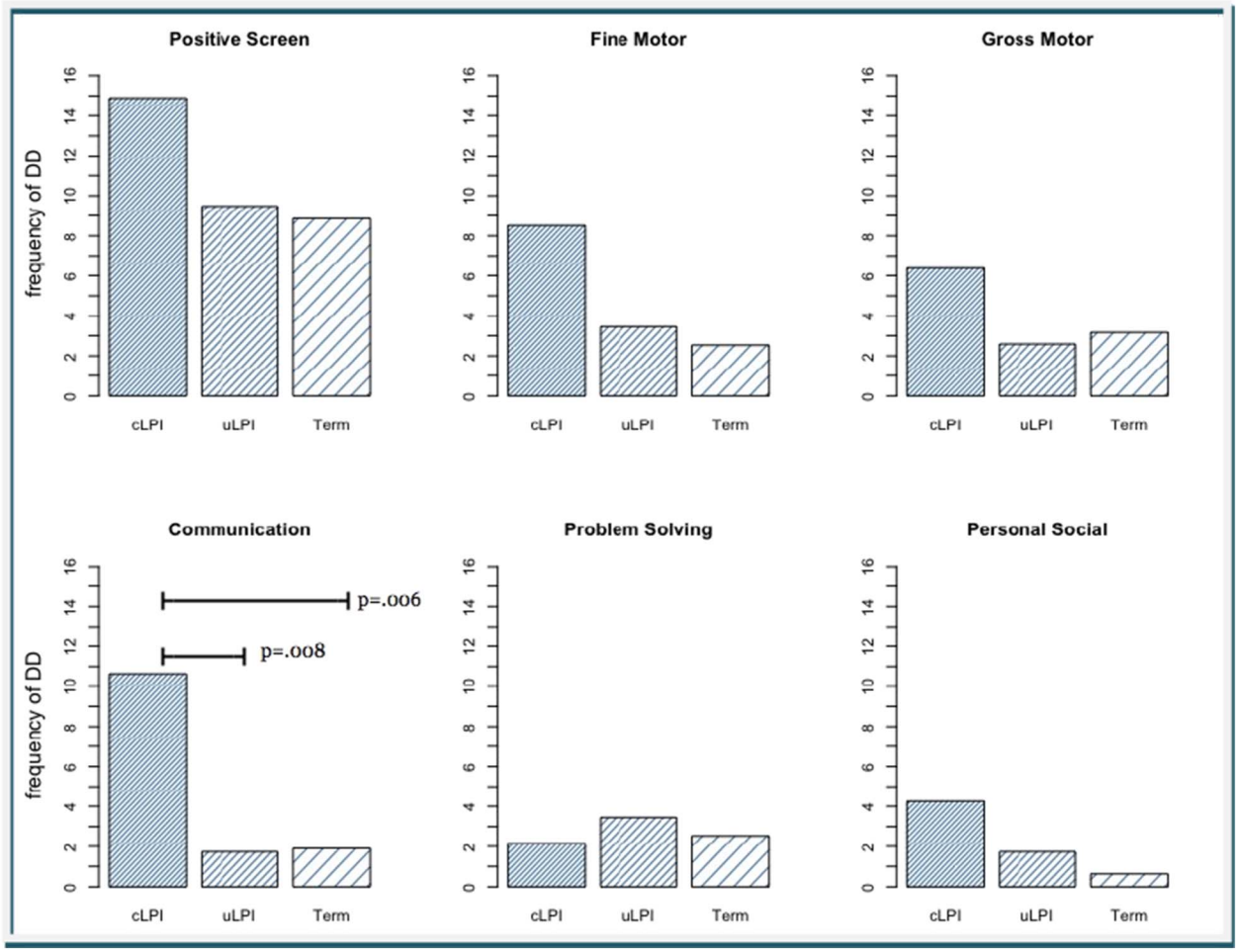

Fig. 2. Frequency of children with risk of developmental delay by domain and positive screen in ASQ3, comparation between complicated, uncomplicated late preterm infants and term-born infants.
Positive screen: any domain ASQ3 > 2 SD below the mean score; DD: developmental delay.

Table 3
Analysis of the risk of developmental delay in different ASQ3 domains by comparing late preterm infants with and without complications with term-born infants. Unadjusted and adjusted analysis.

		Unadjusted analysis uOR [95% CI]		Adjusted analysis aOR [95% CI][a]	
ASQ 3 domains	Referral zone, n (%)	uLPI n = 116	cLPI n = 47	uLPI n = 116	cLPI n = 47
Communication, n (%)	Terms 3 (1.90)	0.91	**6.15**	0.62	**4.60**
	uLPI 2 (1.72)	[0.15–5.53]	**[1.37–27.63]**	[0.08–4.64]	**[0.90–23.16]**
	cLPI 5 (10.64)	NS	**p 0.006**	NS	**p 0.06**
Gross motor, n (%)	Terms 5 (3.16)	0.81	2.09	0.57	2.44
	uLPI 3 (2.59)	[0.19–3.47]	[0.48–9.14]	[0.10–3.35]	[0.44–13.41]
	cLPI 3 (6.38)	NS	NS	NS	NS
Fine motor, n (%)	Terms 4 (2.53)	1.38	3.58	1.15	3.50
	uLPI 4 (3.45)	[0.33–5.63]	[0.85–15.14]	[0.23–5.57]	[0.75–16.39]
	cLPI 4 (8.51)	NS	NS	NS	NS
Problem solving, n (%)	Terms 4 (2.53)	1.38	0.83	1.16	0.74
	uLPI 4 (3.45)	[0.33–5.63]	[0.09–7.71]	[0.22–6.03]	[0.72–7.65]
	cLPI 1 (2.13)	NS	NS	NS	NS
Personal-social, n (%)	Terms 1 (0,63)	2.75	6.98	2.90	**11.32**
	uLPI 2 (1.72)	[0.25–30.98]	[0.60–80.77]	[0.22–37.62]	**[0.91–140.40]**
	cLPI 2 (4.26)	NS	NS	NS	**p 0.050**
Positive screen	Terms 14 (8,86)	1.07	1.80	0.89	1.58
	uLPI 11 (9.48)	[0.47–2.47]	[0.67–4.79]	[0.33–2.34]	[0.55–4.36]
	cLPI 7 (14.89)	NS	NS	NS	NS

ASQ3: Ages and Stages Questionnaire 3rd version; uOR: unadjusted odds ratio; aOR: adjusted odds ratio; 95%CI: 95% confidence interval; cLPI: complicated late preterm infants; uLPI: uncomplicated late preterm infants; Terms: term-born infants; Referral zone: > 2SD below the mean area score; Positive screen: at least one domain in referral zone.

[a] Logistic regression model to estimate the percentages of developmental delay risk adjusted for gender, twinning, the mother's education and age, delivery mechanism and breast-feeding.

development outcomes [11]. It has been suggested that respiratory morbidity could be responsible for neurodevelopmental impairment in the long term, with the main problems referred to being cerebral palsy and learning difficulties [10,12]. On this subject, Kugelman A and Colin A suggest that discontinuing gestation in the last 6 weeks disrupts normal fetal development in a critical period for cerebral and lung growth and development [29].

For this reason, the use of antenatal corticosteroids in pregnancies at risk of preterm delivery is recommended [30–32]. Although our study was not designed to evaluate the influence of antenatal corticosteroids in the LPI population, with a percentage of antenatal corticosteroid administration of 25%, no association was found between its administration and performance in the ASQ3.

On analysing possible factors associated with ASQ3 performance, we found that mother's age older than 35 years was a protective factor for gross motor development, whereas caesarean delivery was associated with a risk of DD, especially in gross motor domain. Current studies shown the difference between the gut microbiota among those born by caesarean and those by vaginal delivery is associated with deficits in neurodevelopment, diabetes, and obesity [33]. There is a need to perform more in-depth studies on the role of the microbiota in neurological disorders in relation to mode of delivery and the possible consequences of this in later life. Note the high incidence of caesarean delivery in LPI.

We are aware of the limitations of our study in terms of sample size and its retrospective nature, although memory bias was avoided by reviewing the hospitalisation records. Another limitation is the low prevalence of the different perinatal morbidities, which determines a low statistical power of the association analysis, i.e., increases the probability of error B, as prospective studies with larger sample size are needed. ASQ3 has not been validated for the 4-year evaluation in Spain, but considering the wide international experience in the use of this test, and the demonstration of its appropriate psychometric properties for evaluating children from other age groups in Spain, we considered it appropriate for use in our population. The positive aspect of our study is the highlighting of some perinatal morbidity's being associated with the

Table 4
Perinatal factors associated with the risk of deficit in ASQ3, adjusted analysis.

	Communication aOR [95%CI][b]	Gross motor aOR [95%CI][b]	Fine motor aOR [95%CI][b]	Problem solving aOR [95%CI][b]	Personal-social aOR [95%CI][b]	Positive screen[a] aOR [95%CI][b]
Demographic variables						
Male (vs female gender)	3.6 [0.71, 18.44]	0.43 [0.11, 1.70]	4.12 [0.85, 20.11]	2.58 [0.52, 6.03]	1.07 [0.16, 7.32]	1.12 [0.52, 4.56]
≥ 35 years (vs < 35 years mother age)	0.78 [0.14, 4.45]	**0.14 [0.04, 0.52]** **	0.34 [0.09, 1.24]	0.52 [0.12, 2.27]	0.34 [0.46, 2.53]	0.46 [0.20, 1.08]
University (vs Not university mother education)	1.08 [0.21, 5.72]	0.74 [0.17, 3.23]	0.451 [0.13, 1.61	1.19 [0.23, 6.01]	0.32 [0.49, 2.10]	0.89 [0.36, 2.21]
Birth outcomes						
Twinning (vs Single)	1.27 [0.23, 7.17]	0.81 [0.12, 0.40]	0.69 [0.12, 4.02]	1.19 [0.23, 6.01]	1 [omitted]	0.97 [0.33, 2.78]
Caesarea (vs vaginal method of delivery)	2.04 [0.44, 9.55]	**6.30 [1.16, 34.00]** *	1.68 [0.45, 6.22]	1.22 [0.29, 5.07]	4.66 [0.46, 47.40]	**2.46 [1.07, 5.66]** *
Other factors						
Not breast-feeding (vs breast-feeding)	2.00 [0.50, 7.98]	0.27 [0.05, 1.53]	1.53 [0.45, 5.22]	1.42 [0.36, 5.62]	0.29 [0.03, 3.35]	1.16 [0.54, 2.51]

[a] Positive screen:at least one domain ASQ3 in the referral zone (referral zone: > 2SD below the mean area score).

[b] Logistic regression model to estimate the percentages of developmental delay risk adjusted for gender, twinning, the mother's education and age, delivery mechanism and breast-feeding.

* $p < 0.05$.

** $p < 0.01$.

Table 5
Risk of developmental delay in late preterm infants by ASQ3 domains in relation to neonatal morbidity and antenatal steroids.

	ASQ3 domains											
	Communication		Gross Motor		Fine Motor		Problem solving		Personal-social		Positive screen[b]	
	Referral zone[a], n (%)	p	Referral zone[a], n (%)	p	Referral zone[a], n (%)	p	Referral zone[a], n (%)	p	Referral zone[a], n (%)	p	Referral zone[a], n (%)	p
Respiratory morbidity												
Yes (18)	**4 (22.22)**	**0.000**	1(5.56)	NS	2 (11.11)	NS	0 (0)	NS	1 (5.56)	NS	4 (22,22)	NS
No (145)	**3 (2.07)**		5 (3.45)		6 (14.14)		5 (3.45)		3 (2.07)		14 (9.66)	
Hypoglycaemia												
Yes (16)	1(6.25)	NS	1(4.00)	NS	2(12,50)	NS	1 (6.25)	NS	1 (6.25)	NS	2 (12.50)	NS
No (147)	6 (4.08)		5 (3.40)		6 (4.08)		4 (2.72)		4 (2.72)		16 (10.88)	
Hyperbilirubinaemia												
Yes (25)	1(4.00)	NS	1(4.00)	NS	2 (8.00)	NS	1 (4.00)	NS	1 (4.00)	NS	2 (8.00)	NS
No (138)	6(4.35)		5 (3.62)		6 (4.35)		4 (2.90)		3 (2.17)		16 (11.59)	
Antenatal steroids												
Yes (41)	1(2.44)	NS	3(7.32)	NS	1(2.44)	NS	0 (0)	NS	0 (0)	NS	3 (7.32)	NS
No (122)	6(4.92)		3 (2.46)		7 (5.74)		5(4.10)		4 (3.28)		15 (12.30)	

[a] Referral zone: > 2SD below the mean area score.
[b] Positive screen: any domain in the referral zone.

outcomes of these premature infants.

In conclusion, our study shows that at the age of 4 years, the cLPI have a higher risk of DD in the communication and personal-social domains compared with term infants and uLPI. The cLPI with respiratory pathology had a higher risk of deficit in the communication domain. Caesarean delivery was the only perinatal risk factor associated with risk of DD, especially in the gross motor domain.

Knowing which groups are at highest risk of developmental difficulties within the overall LPI group, such as those with neonatal morbidity, and especially respiratory morbidity and children born by caesarean delivery, makes it possible to develop monitoring programs targeted at the most vulnerable group.

Conflict of interest statement

All authors have no personal or financial conflicts of interest to disclose.

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