

A Comparison of Neurodevelopmental Outcomes of Late Preterm Infants With Healthy Full-Term Infants at Imam Khomeini Hospital, 2019-2020

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Abstract

Objective: There is evidence that multiple insults during 34 to 36 6/7 weeks' gestation critical phase of neuronal and glial maturation in these infants cause white and gray matter injury. While all of this underscores the potential vulnerability of the late preterm infant (LPI) to neuronal brain injury and poor developmental and long-term outcome, detail is lacking on the precise domains that are affected. This study aimed to compare neurodevelopment and social-emotional development between late preterm infants and term-born control infants at age 18 months.

Materials and methods: We studied 122 infants at corrected age of 18 months using ASQ III in a historical cohort study including 68 late preterm infants in two groups of 34 intervened (infants with regular developmental visits and appropriate active rehabilitation and follow up) and not intervened infants (infants with just one visit at Growth and Development Clinic without any intervention and follow up by parents) who were born in Imam Khomeini Hospital complex, Medical University of Tehran, Iran during 2017-2018 and 54 full term infants as control group. Data from the first visit of the Growth and Development Clinic at birth were collected using a self-made validated questionnaire according to the Gesell development assessment tool in three fields, including gross motor, fine motor, and social domains.

Results: LPIs had poorer motor and social-emotional competence compared with controls at birth ($P < 0.001$). They also performed more poorly than controls in the fine motor domain of development at 18 months ($P = 0.030$). In comparison among the three groups, significant differences were observed in the gross motor ($P = 0.005$), fine motor ($P = 0.030$), and communication ($P = 0.020$) domains. After using logistic regression models, neurodevelopment in all domains at birth and 18 months of age was independent of late preterm birth but related to underlying morbidity and duration of Neonatal Intensive Care Unit (NICU) admission.

Conclusion: Late preterm birth is not effective on neurodevelopment alone, but a history of co-morbidity or NICU admission at birth is an effective factor. Early diagnosis and intervention can improve the neurodevelopmental outcome of late preterm infants.

Keywords: Late Preterm; Neurodevelopment

Introduction

Births between 34 and 36 6/7 weeks' gestation (referred to as late preterm births) account for a

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significant proportion of preterm births in North America and elsewhere. These infants are larger than usual premature infants, and they are generally passed off as mature infants, but they often manifest signs of physiologic immaturity or delayed transition in the neonatal period. Several studies have documented the high incidence of neonatal complications leading to neonatal intensive care unit (NICU) admissions in these infants. They have a higher incidence of transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS) (1), persistent pulmonary hypertension of the newborn (PPHN) (2), respiratory failure (3), jaundice, temperature regulation problems, hypoglycemia (4), and feeding difficulties than term infants (5).

Late preterm infants (LPI) included nearly 71% of the US total preterm births in 2011(6, 7). Nearly three out of four preterm births occur at late preterm gestational ages, and there has been a steady increase over the past couple of decades (7).

Despite advances in obstetric and neonatal medicine over the last two decades, late preterm infants are primarily responsible for the entire increase in the preterm birth rate (8).

The World Health Organisation (WHO) has acknowledged that whilst reducing mortality for newborns is the priority there is also a need to prioritise improving health, psychosocial well-being and the learning potential of children, particularly in the early years of life (9).

Concern about higher morbidity in late preterm infants has led to numerous publications with largely the same conclusions: Late preterm infants are more prone to problems related to delayed transition and overall immaturity, and they should be treated differently from their more mature term counterparts (10-14).

At 34 weeks' gestation, brain weight is only 65% of a 40-week term infant, and cerebral volume is 53% of a 40-week infant (4, 15). The brain of a late preterm infant is still immature and continues to grow until 2 years of age, when it reaches 80% of adult brain volume. The cerebral cortex is still smooth compared with that of a term infant because the gyri and sulci are not fully formed on the cerebral cortex, and myelination and interneuronal connectivity are still incomplete in these infants. There is evidence that multiple insults during this critical phase of neuronal and glial maturation in these infants cause white and gray matter injury, particularly in the thalamic region and the periventricular white matter.

All of this underscores the potential vulnerability of the late preterm infant to neuronal brain injury and poor developmental and long-term outcome (16).

Recent studies reported that LPIs are also at risk of long-term developmental problems, including deficits in neurocognitive/motor domains and behavioral problems. A review article described conflicting results about the impact of late-preterm birth on cognitive functioning, while LPI appeared to develop deficits of school performance and psychiatric disorders in young age and adulthood (17, 18). A population-based cohort study found that, in late and moderate preterm infants, cognitive impairments were the most common adverse outcome, followed by neuromotor/sensory outcome and neurodevelopmental disability (19). A recent review analyzing neurodevelopmental outcomes of preterm children reported several results about long-term issues regarding LPI; in fact, this population is characterized by lower cognitive performances and increased risk of special education services support, borderline clinical internalizing and attention problems, and higher risk of psychiatric disorder diagnosis in adulthood (20).

Since no study has been done in our society related to the neurodevelopmental outcome of late preterm infants and regarding the importance of evaluation of this high-risk group, it's crucial to do such a study to arrange our care and follow-up for this high-risk group according to the results.

Materials and methods

Population: We studied 122 infants at corrected age of 18 months in a historical cohort study including 68 late preterm infants in two groups of 34 intervened (infants with regular developmental visits and appropriate active early parent-based interventions and follow up) and not intervened infants (infants with just one visit at Growth and Development Clinic without any intervention and follow up by parents) who were born in Imam Khomeini Hospital complex, Medical University of Tehran, Iran during 2017-2018 and 54 full term infants as control group. We excluded infants with underlying CNS, metabolic, and neuromuscular disorders, congenital anomalies, moderate and severe birth asphyxia, neonatal seizure, meningitis, intra-uterine infections, IVH grade III and IV, and hydrocephalus.

Early parent-based intervention was performed as follows:

In the Follow-up Clinic of high-risk newborns (in Imam Khomeini Hospitals Complexes), parents were trained for simple instructions, such as performing some practice to improve their infant's sensory and motor skills. Child care-givers were asked to stimulate the hearing sense of their infants by whispering, singing, and playing music. By using some colorful papers, tissue, and toys, eye sight were stimulated. Gentle, symmetric skin massage and skin stimulation 3 times daily, 45 minutes daily, Kangaroo Mother Care, 5 minutes daily hydrotherapy (water game), and use of mentally targeted games 10 minutes, 2 times daily were also trained to mothers during one year investigator-led study. Mothers also received some training packages composed of books, music, and game CDs in each session.

This study was approved by the local ethics committee of Tehran University of Medical Sciences (1398.291). All children were recruited after obtaining written informed consent from their parents; in addition, no invasive intervention was used in this study.

General assessment

The data were collected according to maternal age and gravid, risk factors for pregnancy such as utero-placental disorders, maternal or fetal diseases, mode of delivery (emergent or elective cesarean section or vaginal delivery) and demographic features of the newborn (sex, gestational age, birth weight), APGAR score, perinatal complications (respiratory complications, jaundice, Necrotizing Entero-Colitis, admission and duration of hospital stay in the neonatal intensive care unit), feeding and care.

Neurodevelopmental assessment

Neurodevelopment status was evaluated by Data from the first visit of the Growth and Development Clinic at birth. We also collected data using a self-made validated questionnaire according to the WHO Milestones Chart in three fields, including gross motor, fine motor, and social domain, and the Age & Stage Questionnaire (ASQ III) by an expert clinician in two visits. The ASQ questionnaire is composed of five domains (communication, gross motor, fine motor, problem solving, and socioemotional domain) and 6 questions for each domain, with a score of 0-6. The ASQ questionnaire has been translated into Farsi and validated for Iranian children by the Child Bureau of the Iranian Health Ministry. Conclusions were stated as normal or abnormal according to cut off point (-2 SD) for each domain written in the guideline.

(We were to use Bayley Scales of Infant Development III, but due to the pandemic of SARS-Covid 19, none of the families accepted to come to the clinic, so we had to use ASQ instead)

Statistical analysis: All data were saved and analyzed using the SPSS software (version 23.0), and according to the objectives of the study, descriptive statistics were demonstrated as absolute and relative frequency for qualitative variables and mean and standard deviation for quantitative variables. Analytical statistics were obtained using chi-square test, T-test, Mann-Whitney, or Kruskal-Wallis test (when data distribution was not normal according to Kolmogorov Smirnov test), and logistic regression test to omit the effect of interfering and confounding factors. The prevalence of neurodevelopmental delay in the described fields, according to abnormal ASQ scores based on age-related cut-off tables, was recorded and analyzed. P. value <0.05 was considered statistically significant in all tests. The power of the study was 80%.

Results

The sample of the study included 122 infants who were studied in three groups:

1. 34 LPIs with intervention (active rehabilitation), 19 males and 15 females;
2. 34 non-intervention LPIs, 13 males and 21 females
3. A control group of 54 full-term babies aged 18 months.

Socio-demographic features of LPI and full-term infants are described in Table 1.

Maternal Mean age at the time of delivery was 30.5 ± 5.1 and 32.5 ± 5.1 years for the first and second group. Compared with mothers of control infants, mothers of LPIs had higher rates of disorders.

LPIs had higher rates of neonatal morbidity and NICU admission compared with controls. There was also the same difference between the intervention and non-intervention groups of late preterm infants.

Compared with controls, the late preterm infants were more likely to be IUGR at birth.

First visit and 18-month outcomes are summarized in tables 2-4.

There was evidence that LPIs had poorer motor and social-emotional competence compared with controls at birth (Table 2).

They also performed more poorly than controls in the fine motor domain of development at 18 months (Table 3).

Table 1: Socio-demographic characteristics of late preterm and term infants

Demographic data	No intervention N=34	Intervention (N=34)	Control (N=54)	P value
Gestational age,mean(SD),wk	34.53(0.788)	34.68(0.843)	38.9(0.820)	0.001
Male birth, No.(%)	13(38.2)	19(55.9)	22(40.7)	0.279
Cesarean delivery, No.(%)	32(94)	32(94)	42(77.7)	0.264
Birth weight,mean(SD),g	2177(408)	2179(504)	2954(612)	0.001
Apgar score at 1 minmedian (IQR)	8(2-9)	7.50(2-9)	9(8-9)	0.820
Maternal age,mean(SD),y	32.5(5.1)	30.5(5.1)	34.5(5.4)	0.120
Maternal underlying disorder, No.(%)	13(38.2)	13(38.2)	0	0.001
Neonatal underlying disorder, No./total No.(%)	23/34(67.6)	26/34(76.5)	0	0.001
Neonatal Intensive Care Requirement, No. (%)	11(32.4)	8(23.5)	0	0.001
Intrauterine growth restriction, No.(%)	3(8.8)	4(11)	0	0.001
Breast milk feeding, No.(%)	15(44)	21(61.8)	36(66.7)	0.137
Day care attendance, No.(%)	2(6)	1(2.9)	5(9.2)	0.076

In comparison among the three groups, there was a difference in gross motor, fine motor, and communication domains (Table 4).

Since there were confounding variables such as NICU admission at birth, resuscitation, IUGR. we used logistic regression models to determine other factors which might influence neurodevelopment besides late preterm birth.

The result showed neurodevelopment in all domains at birth and 18 months of age is independent of late preterm birth, but is related to underlying morbidity and duration of NICU admission in some domains:

Duration of NICU admission influences gross motor ($P=0.007$, $OR=1.132$), fine motor ($P=0.022$, $OR=1.077$), and social domains ($P=0.018$, $OR=1.070$) at birth. At the age of 18 months, none of them was an influencer except for resuscitation at birth, which can influence the social domain. ($P=0.028$, $OR=1.210$) (Tables 5, 6)

Discussion

This study didn't confirm that late preterm birth is associated with an increased risk of developmental

problems compared with term birth, but in the presence of associated morbidity or hospital admission at birth, it may cause developmental delay.

Using direct, subjective, standardized assessments, late preterm children at 1.5 years corrected age performed more poorly in communication and motor domains (both gross and fine motor) compared with term-born controls. These findings were similar to Cheong et al's outcomes (21). In a cohort study from South Carolina, late preterm infants were at increased risk of developmental delay in speech and communication domains compared with term infants (22).

In a study from Norway about Communication impairments in early term and late preterm children, they found higher communication impairment at both 18 and 36 months (23). A Spanish and Canadian study demonstrated a higher risk of communication impairment in complicated late preterm infants with a history of NICU admission according to ASQ III (24, 25). These early signs of challenge may be precursors for some of the school-age behavioral and learning problems described in late preterm children (21).

Table 2: First visit developmental data between the three groups

		Intervention	No intervention	Term	Total	P value
Gross motor	Normal	9	20	54	83	0.001
		26%	59%	100%	68%	
	Abnormal	25	14	0	39	
		74%	41%	0%	32%	
Fine motor	Normal	13	16	54	86	0.001
		38%	56%	100%	70%	
	Abnormal	21	15	0	36	
		62%	44%	0%	30%	
Social	Normal	14	23	54	101	0.001
		71%	68%	100%	83%	
	Abnormal	10	11	0	21	
		29%	32%	0%	17%	

Table 3: The 18-month developmental outcomes between the two groups

		Late preterm	Term	Total	P value
Communication	Normal	63	50	113	0.854
		92%	93%	93%	
	Abnormal	5	4	9	
		8%	7%	7%	
Gross motor	Normal	56	49	105	0.152
		83%	91%	86%	
	Abnormal	12	5	17	
		17%	9%	14%	
Fine motor	Normal	53	51	104	0.030
		78%	95%	85%	
	Abnormal	15	3	18	
		22%	5%	15%	
Problem solving	Normal	58	51	109	0.077
		85%	94%	89%	
	Abnormal	10	3	13	
		15%	6%	11%	
Social	Normal	54	46	100	0.218
		79%	85%	82%	
	Abnormal	14	8	22	
		21%	15%	18%	

In a large study by Woythaler et al on 1200 late preterm and 6300 term infants, LPIs had lower Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores compared with term infants at the age of 2 years (26).

Also in Cheong's study, moderate and LPI had a nine times increased risk of motor impairment at 2 years of age compared with term infants, although it may be because moderate preterm infants entered the study (21).

Table 4: The 18-month developmental outcomes between three groups

		Intervention	No intervention	Term	Total	P value
Communication	Normal	33	30	50	113	0.020
		97%	88%	93%	93%	
	Abnormal	1	4	4	9	
		3%	12%	7%	7%	
Gross motor	Normal	30	26	49	105	0.005
		88%	77%	91%	86%	
	Abnormal	4	8	5	17	
		12%	23%	9%	14%	
Fine motor	Normal	30	23	51	104	0.030
		88%	68%	95%	85%	
	Abnormal	4	11	2	18	
		12%	32%	5%	15%	
Problem solving	Normal	28	20	51	109	0.107
		83%	89%	94%	89%	
	Abnormal	6	4	3	13	
		17%	11%	6%	11%	
Social	Normal	28	26	46	100	0.305
		82%	77%	85%	82%	
	Abnormal	6	8	8	22	
		18%	23%	15%	18%	

Table 5: Logistic Regression (first visit)

Logistic Regression	Gross motor first			Fine motor first			Social first		
	B	P value	OR	B	P value	OR	B	P value	OR
Resuscitation	0.024	0.971	0.977	0.085	0.888	1.089	0.600	0.355	0.549
IUGR	0.409	0.507	0.664	0.476	0.416	0.621	0.186	0.771	1.204
IVH	0.395	0.662	1.485	11.714	0.132	0.180	0.680	0.455	0.507
Near. Term	20.804	0.997	0.000	120.649	0.997	0.000	19.413	0.997	0.000
NICU.day	0.124	0.007	1.132	0.074	0.022	1.077	0.068	0.018	1.070

Similar to a Swedish nationwide cohort study of more than one million children born at 32-41 weeks by Mitha and his colleagues, who found those born moderately preterm (32-33 weeks) or late preterm (34-36 weeks) showed higher risks of any long term neurodevelopmental outcome, such as motor, cognitive, and visual impairment, than children born full term (39-40 weeks) and these risks were highest at the earliest gestational age (from 32 weeks), and gradually decreased as gestational age increased, with higher risks also at early term (37-38 weeks) than at full term, they also found out among children born preterm, those born small for gestational age, especially in the <3rd centile, showed higher risks of long-term neurodevelopmental impairment than those born preterm with normal birth weight for gestational age (27).

A study by Ryan et al shows that Moderate to Late Preterm (MLP) infants are vulnerable to suboptimal neurodevelopment. There were no significant differences in scores found in Subscale B (Language and Communication) between MLP infants and term control infants. However, when controlled for sex, a significant difference was evident between the groups (28).

But in Santos et al's study on late preterm infants' motor development until term age at Sao Paulo, 29 late preterm newborn infants were evaluated by the TIMP (Test of Motor Infant Performance) at birth and every two weeks until term-corrected age. There were no significant differences in the motor evaluations between term infants at birth and LPI at the equivalent age, and the LPI presented a gradual progression of motor development until the term-corrected age, but differences with term infants at birth were not detected (29).

On the other hand, a study by Coletti et al showed LPI's scores in cognitive, language, and motor domains were within normal limits at one year corrected age (30). According to Neurodevelopmental outcome of late preterm infants in Johannesburg, South Africa, a study by Ramdin et al at age of 9-12 months and 15-18 months, the

neurodevelopmental outcomes of late preterm infants were similar to those of control term infants (31).

When we compared all LPI (intervention and non-intervention group) with the full term (control) group, the difference was only seen in the fine motor domain, and it was due to better outcomes of the intervention group when added to the non-intervention ones.

A main reason for the difference between the outcomes of intervention and non-intervention groups is that the latter group of infants appeared normal to parents after discharge at birth, so they didn't feel any need to do follow up visits at growth and development clinic, conversely the first group did the visits and developmental interventions (due to their underlying problems) so their results finally turned out within normal range.

We used corrected age for our assessments, so it might affect normal test scores in some domains, as Romeo et al. found that LPIs had significantly lower scores than full-term infants on the Bayley Scales of Infant Development II when using chronological age. However, when correcting age for prematurity, LPI had similar Mental Developmental Index scores to FTI at 12 and 18 months of age (32). It's important to assess these infants according to their chronological age so that we can identify developmental delay (if present) earlier and start proper interventions.

After using logistic regression models, we found out that the only effective factor is the history of NICU admission at birth and having comorbidities, as Kinney et al (33) and Bhutta et al (34) mentioned in their studies. Also, the Spanish and Canadian study found a higher risk of developmental impairment in complicated late preterm infants with a history of NICU admission compared with the uncomplicated group and healthy full-term infants (24, 25).

Other researchers showed poorer results in some neurodevelopmental domains for the complicated group as well (35, 36). In contrast, some groups reported no difference between the complicated and uncomplicated groups (37).

Table 6: Logistic Regression (18 months)

Logistic Regression 18 months	Gross motor			Fine motor			Problem solving			Communication			Social		
	B	P value	OR	B	P value	OR	B	P value	OR	B	P value	OR	B	P value	OR
NICU.day	0.032	0.331	1.033	0.017	0.668	1.017	0.002	0.964	0.998	0.069	0.088	1.072	0.031	0.454	1.031
Resuscitation	0.141	0.856	1.151	1.679	0.058	0.187	1.267	0.131	0.282	0.923	0.389	0.397	2.500	0.028	1.210
IUGR	0.330	0.645	0.719	1.323	0.244	3.755	0.101	0.912	0.904	0.666	0.570	1.946	1.188	0.324	3.282
IVH	0.242	0.837	1.273	0.385	0.767	1.469	0.886	0.412	0.412	0.589	0.674	0.555	0.017	0.990	1.017
Group	0.257	0.506	0.773	0.041	0.930	0.960	0.099	0.844	1.105	0.723	0.220	2.060	0.863	0.160	2.371
Constant	40.247	0.999	0.000	42.732	0.999	0.000	6.355	0.082	575.116	42.260	0.999	0.000	43.308	0.999	0.000

An Irish study found equal testing scores for cognitive, language, and motor abilities between LPI that required intensive care and those that did not in a homogeneous population without full-term controls (38).

Since the late preterm period involves considerable growth and maturation of the brain and increases in brain volume, whole-brain weight, and gyral and sulcal development are substantial in this period of late gestation (16), and larger volumes of total brain tissue, white matter, and cerebellum were associated with better cognitive, language, and motor scores at 2 years' corrected age (39). Any changes during this period of brain development can lead to developmental delay in these children (17). It seems that in our study, the results are partially influenced by our sample, who were recruited from a tertiary hospital and included a greater proportion of sicker LPI who were admitted to the NICU than in the general population.

The test scores of the intervention group improved after receiving rehabilitations and they had significant improvement in all domains, showing the importance of early diagnosis and early intervention (parent-based intervention) on better neurodevelopmental outcomes.

Conclusion

According to this study, late preterm birth is not effective on neurodevelopment alone, but a history of co-morbidity or NICU admission at birth is an effective factor. Early diagnosis and intervention can improve the neurodevelopmental outcome of late preterm infants. To identify the most effective interventions for their prognosis, larger cohort studies with a greater population are recommended. According to the high prevalence of late preterm deliveries, it is important to provide developmental follow-up and early parent-based intervention to this group and identify risk factors to target those at highest risk of developmental problems. Further research directions into potentially modifiable factors, markers of poor outcome, and the spectrum of deficits at school age and older children have the potential to greatly improve the long-term care for this large group of children.

This is a study on limited number of late preterm infants born at Imam Khomainsi Hospital Complex of Tehran, which is a referral center for high-risk pregnancies all around the country, and the results

may not be extensible to all of the late preterm infants. Besides, we planned to use the Bayley scale according to previous studies, but the COVID-19 pandemic made it impossible for us.

Conflict of Interests

Authors declare no conflict of interests.

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