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Neurodevelopmental outcomes of the late preterm infant

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ABSTRACT

Late preterm infants (born at $34^{0/7}$–$36^{6/7}$ weeks gestation) have been found to have increased morbidity and mortality compared to full term infants. Research has also been done to explore longer-term neurodevelopmental outcomes. This review details neurodevelopmental outcomes from birth to adulthood for late preterm infants. Outcome studies indicate that they are at increased risk of developmental disability, school failure, behavior problems, social and medical disabilities, and death. Many questions still remain regarding late preterm infant neurodevelopmental outcomes and future research should be done into this topic. Given the high prevalence of late preterm births, even small differences in abilities, special education, and length of education may have broader consequences.

1. Introduction

In 2005, the National Institute of Child Health and Human Development renamed the group of infants with gestational ages $34^{0/7}$–$36^{6/7}$ weeks from "near term" to "late preterm" [1]. They felt that this designation would be helpful to convey the fact that these infants, although "close to term," have higher rates of morbidity and mortality than full term infants. Previously, physicians underestimated their risk for morbidity and mortality which led to less thorough evaluation, monitoring, and follow-up. At the same time these infants were re-labeled "late preterm," there was also a call for research into their short and long term outcomes.

Since 2005, more research has been done into the short and long term outcomes of late preterm infants (LPI) which confirmed that they act more like preterm infants with metabolic, neurologic, and physiologic immaturities, and are at higher risk for mortality as well as multiple morbidities. Research has also verified that preterm infants, including LPI, are at higher risk for having neurodevelopmental delays and problems than full term infants (FTI). Outcome studies of LPI indicate that they are at increased risk of developmental disability, school failure, behavior problems, social and medical disabilities, and death.

Although more research has been done, we have yet to settle several questions: Which LPI are at highest risk for neurodevelopmental struggles? Are there specific delays that are common in LPI or are they global? Do the observed delays demonstrate a lag in development that may resolve, or are they associated with life-long issues? Is there opportunity to proactively intervene leading to better outcomes?

2. Early developmental outcomes

Current published research on neurodevelopmental outcomes has examined infants and children across a broad range of ages. Some reports have focused on neurodevelopmental outcomes during the period between birth hospital discharge and school age (0–5 years). Often, they have compared results between LPI and FTI, including early developmental outcomes, rates of cerebral palsy and other neurologic diagnoses, speech and language issues, as well as rates of referral and usage of early intervention services.

2.1. Developmental outcomes

In a large nationally representative study of LPI and FTI born in 2001 using the Early Childhood Longitudinal Study Birth Cohort, Woythaler et al. [2] reported that LPI had significantly lower mean scores and scores < 70 on the Bayley Scales of Infant Development Short Form at 24 months of age. This was both in the derived Mental Developmental Index and Psychomotor Developmental Index. A score < 70 indicates severe developmental delay. In another developmental follow-up study using the Bayley Scales of Infant Development III, 198 LPI and 183 FTI were followed to 2 years corrected age. Compared to FTI, LPI performed worse in cognitive, language, and motor domains, with greatest disparity in the language domain. They also showed evidence of poorer social–emotional competence [3]. This study included infants who were born moderately preterm (32–33 weeks completed gestation), which may have contributed to the magnitude of differences reported between the groups. Romeo et al. found that LPI had significantly lower scores than FTI on the Bayley Scales of

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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 [4]. This raises the question as to whether we should correct LPI for prematurity for evaluation or whether using uncorrected age may identify infants who will show difficulties at school age.

2.2. Cerebral palsy

The incidence of early intervention in LPI compared to FTI has been explored in several studies as evidence of brain injury. Petrini et al. [5] used retrospective data using the Northern California Kaiser Permanente Medical Program inpatient and outpatient data, looking at the presence of diagnostic codes for early intervention, developmental delay/mental retardation and seizures in infants ≥30 weeks gestation. They found that as gestational age decreased, there was increased incidence of early intervention and of developmental delay/mental retardation. LPI were more than three times as likely as FTI to be diagnosed with early intervention. They were also more likely to be diagnosed with developmental delay/mental retardation.

In a very large cohort study in Finland of infants born from 1991 to 2008, LPI had an increased risk of early intervention compared to FTI by the age of 7 years. Factors predictive of an increased early intervention risk included resuscitation at birth, antibiotic treatment during the first hospitalization, 1 min Apgar score < 7, and intracranial hemorrhage [6].

2.3. Speech and language delay

Some analyses focused on speech/language issues of LPI. In a retrospective cohort study of data obtained from the South Carolina Medicaid claims and vital record databases from January 2000 to December 2003, LPI were found to have a greater risk for developmental speech and or language delay than FTI [7]. In a Norwegian study on the risk of communication impairments at 18 and 36 months, LPI had an increased proportion of communication impairments at both time-points [8].

2.4. Early intervention usage

Because LPI do not automatically qualify for early intervention, researchers have investigated early intervention enrollment as a proxy for developmental delay. In a study in New York City looking at a 1999–2001 cohort, the authors report that 21% of LPI were referred for early intervention program services compared with 12% of FTI [9]. In a Florida study, LPI with short hospital stays (< 72 h) had a 36% higher risk than FTI of participation in early intervention [10].

In a large state-wide cohort of Massachusetts-born infants, Shapiro-Mendoza et al. [11] found that earlier gestational age was associated with an increased prevalence of early intervention program service enrollment among singleton, neonatal survivors born $34^{0/7}$ through $41^{6/7}$ completed weeks gestation. Enrollment increased with each week of gestation before 41 completed weeks with approximately one-third of children born at 34 completed weeks gestation and one-fourth of children born at 35 completed weeks gestation enrolled into the Massachusetts early intervention program. Male children and those with mothers who were ≥40 years old, not high school graduates, and who were publicly insured had the highest prevalence of enrollment; Asian children had the lowest compared with other race-ethnicity groups.

Kalia et al. [12] used a retrospective cohort from New York, showing that 30% of LPI qualified for and received early intervention services. This rate was lower when compared to very preterm infants. However, after controlling for comorbidities of prematurity including Apgar score at 5 min, use of caffeine, diagnosis of bronchopulmonary dysplasia, respiratory distress syndrome, and length of stay, there was no significant difference in the likelihood of qualifying for services between LPI and very preterm infants. They concluded that it is the morbidities experienced in the newborn period that most profoundly impact the developing brain [12].

Many researchers have hypothesized that the worse neurodevelopmental outcomes of LPI may have to do with their more complicated medical courses compared to FTI. Many studies do not have hospital stay data to compare medical courses; however, some studies have looked at LPI with complicated (neonatal intensive care unit (NICU) admission) vs uncomplicated (no NICU admission) courses to try to answer this question. In one study performed in Spain, the complicated LPI group had a higher risk of delay in the communication domain compared to uncomplicated LPI and FTI using the Ages and Stages Questionnaire (ASQ)-3. Complicated LPI compared to FTI also had a risk of delay in the personal–social domain [13]. Another study similarly showed that LPI who require admission to the NICU have increased risk of developmental delay as measured with the ASQ-3, especially in the communication domain [14]. In other studies, LPI with specific morbidities have been identified as having increased risk for developmental delay including respiratory morbidities [15] and hypoglycemia [16]. Other researchers found worse outcomes in complicated vs uncomplicated LPI in other domains of neurodevelopment [17,18]. In comparison, some groups found no difference between complicated and uncomplicated LPI [19].

3. School-age outcomes

It is important to look at school performance when discussing neurodevelopmental outcomes, as it is an indicator of future academic achievement, employment prospects, socio-economic status, and adult health. There are many reports of LPI neurodevelopment during this time-period using multiple different measures including standardized testing, need for special education, as well as specific outcomes such as language and social outcomes.

In a study looking at Florida state records from early intervention and the public-school student database, researchers looked at school-age outcomes of LPI. All infants had a length of stay at ≤72 h categorizing them as “uncomplicated.” They looked at seven different school-age outcomes. Compared to FTI, risk for suspension in kindergarten was 19% higher. Disability in pre-kindergarten at 3 and 4 years of age, exceptional student education, and retention in kindergarten all carried a 10–13% increased risk [10].

In a nationally representative cohort of 5–6-year-olds born in 2001, Woythaler et al. found that LPI had significantly worse total school readiness, reading, math, and expressive language scores and higher odds of severe impairment, compared with FTI. When comparing school readiness to 24-month developmental testing, those who had significant developmental delay at 24 months had increased odds of being severely impaired at school age. However, the predictive validity of having a total school readiness score in the bottom 5% given a mental developmental index < 70 at 24 months was poor. In this cohort, late preterm children living in an impoverished household with primary language other than English, lower maternal education, and black maternal race were also at increased risk for total school readiness < 5% at kindergarten [20].

3.1. School testing results

Researchers have looked at compulsory school testing to compare outcomes between late preterm and FTI. In a nationally representative cohort, Chyi et al. [21] found that LPI scored lower in reading in kindergarten and first grade. They were less proficient in reading in kindergarten and first and fifth grades by teacher rating, and in math in kindergarten and first grade when compared with FTI. They also had increased needs for an individualized education plan and special education enrollment. This demonstrates that LPI have academic challenges that persist through elementary school.

Two reports from the UK investigated the Millennium Cohort Study of children born in 2000–2001. This cohort was followed at 9 months, 3, 5, and 7 years of age [22,23]. The first paper looked at outcomes of this cohort at 5 years of age or first school year in the UK [22]. The percentage of children not reaching a good level of overall achievement increased as gestational age decreased, with a 12% increase in late preterm children. They showed that being born premature had a smaller effect than the child's sex, age within the school year, and mother's level of education. However, they pointed out that gestational age is one more element that affects the risk profile of a child. At 7 years of age, late preterm children continued to have poorer academic performance compared to their full term peers with a 36% increased risk of achievement below expected level as measured by their standardized KS1 assessments [23]. Late preterm children also performed worse than full term children in reading and writing. These findings are similar to another study from the UK of KS1 performance, which found that moderate to late preterm children were less likely to be successful in achieving expected level of performance [24].

3.2. Special education needs

Multiple studies have examined the need for special education during school as a product of worse neurodevelopmental outcomes. Lipkind et al. [25] obtained linked birth and educational data for all singleton births born from 1994 to 1998 in New York City who had a third-grade standardized test score. Children delivered late preterm had a 30% higher adjusted odds of needing special education than those born full term. They also had lower adjusted math and English scores. MacKay et al. [26] examined Scottish school-age children, finding that late preterm children were at higher risk of needing special education. Gestation at delivery accounted for 10% of the adjusted population-attributable fraction of special education needs.

3.3. Intelligence quotient (IQ) scores

IQ scores are a known important predictor of future social, occupational, and health outcomes, which makes it a great predictor of neurodevelopmental outcomes. In a study looking at IQ scores at 6 years of age, Talge et al. [27] found that in comparison with FTI matched on sex- and gestational age-referenced birth-weight *z*-scores, LPI exhibited lower levels of cognitive performance and higher levels of behavioral problems. With respect to cognitive performance, LPI had two to three times the risk of exhibiting full-scale IQ and performance IQ scores < 85, a threshold that marks borderline intellectual functioning. These findings were independent of socio-economic factors and maternal IQ, which they interpreted as proxies for genetic and environmentally mediated influences on child cognitive functioning.

3.4. Language skills

A group of researchers used the prospective Bavarian Longitudinal Study to investigate language performance over time in preterm and FTI. Infants were broken down into very preterm, moderate–late preterm (32–36 weeks) and term [28]. They assessed language at 5 and 20 months, 4, 6, and 8 years of age. At three of the five ages, moderate–late preterm children scored lower than full term children (and better than very preterm children). This study's novel contribution to the literature was its analysis of the stability of individual differences in the language of preterm children. From very early in development, very preterm, moderate–late preterm, and term children's language abilities were stable. This is important because, by 20 months of corrected age, children who were performing poorly relative to their peers were likely to continue to perform poorly at later ages. This suggests that assessment of language around 2 years of age can be highly predictive of later abilities and may indicate the need for intervention.

3.5. Social/behavioral outcomes

The role of behavior and attention in school performance is important as children with behavior and attention issues can have worse school outcomes even if intelligence and functioning is within normal. It is also increasingly recognized that they are associated with later psychopathological conditions [29,30].

Research suggests that late preterm children have higher rates of attention-deficit hyperactivity disorder (ADHD) and problematic behaviors in teacher and parent rating scales [31]. Talge et al. [27] analyzed teachers' ratings of behavioral problems using the Children's Behavior Checklist. Children born late preterm had a higher risk for teacher-reported behavioral problems, most consistently observed in the attention and internalizing problem domains. Although teacher ratings were obtained at school age, internalizing problems in early childhood has been prospectively linked with risk for a variety of psychiatric disorders in adolescence and adulthood, particularly mood and anxiety disorders [32,33].

Attention problems in middle childhood have also been prospectively linked to a wide range of outcomes, notably ADHD, poor academic performance, and reduced likelihood of completing high school [34].

In a prospective cohort of Danish children, investigators looked at behavioral and emotional problems which were measured by the Child Behavior Checklist. Higher scores indicate worse outcomes. They found that children born at 32–35 weeks gestation (70% were 34 and 35 weeks gestation) had higher scores on all syndrome scales, including internalizing, externalizing, and total problems than term-born controls. They were also at higher risk for somatic complaints. This was especially true for girls [35].

Not all studies have found worse neurodevelopmental outcomes in LPI. Gurka et al. reported no differences between LPIs and FTIs in cognitive, achievement, behavioral/emotional, or social disability at 15 years of age [36]. One group from Northern Ireland found equal testing scores for cognitive, language, and motor abilities between LPIs that required intensive care and those that did not in a homogeneous population without full term controls [37]. Likewise, a US-based group found similar rates of learning disability and ADHD diagnoses in LPI and FTI in a white, middle-class community without ethnic and racial diversity [38].

4. Adolescent age and adulthood

There are few papers that follow LPI into adolescence and adulthood. Such studies come out of Scandinavia where the countries have National Health Registries. We should be careful when generalizing these results, however, because many of the participants were born as many as 50 years ago. Since then, neonatal care has improved considerably. Accordingly, it remains uncertain whether the same results would be observed among the current late preterm population if followed into the future.

Moster et al. [39] linked compulsory national registries in Norway of children born between 1967 and 1983. They followed them through 2003 in order to document medical disabilities and outcomes in adulthood. The relative risk of LPI was higher than FTI for: early intervention; mental retardation; disorders of psychological development; behavior, and emotion (by diagnosis); blindness, low vision, hearing loss, and epilepsy; and any medical disability severely affecting working capacity and receiving a disability pension. They found no difference in the rates of schizophrenia, autism spectrum disorder, school attainment, low job-related income, or unemployment. They also found no difference in social attainment such as being married or divorced, criminality, or receiving a sentence for a committed crime.

Eide et al. [40] reported on a large Norwegian cohort of 18–19-year-old boys without significant disabilities entering military service. Late preterm boys had an increased odds for lower IQ compared to full term

boys. After adjusting for social confounders and adult body size, the odds for low adult intelligence scores for late preterm vs full term 19-year-olds remained significant. In a large Swedish cohort of 18–19-year-old men also going into military service, the mean cognitive test scores decreased in a stepwise manner with gestational age [41]. Socio-economic status was a significant modifier. Socio-economic status decreased the effects of gestational age by 26–33% after adjustment. It is still important to note that even with adjustment for socio-economic status, there are still long term effects of gestational age at birth.

Multiple papers have been published looking at the long term outcomes of LPI using the Arvo Ylppo Longitudinal Study in Finland. Participants in this study were born in 1985–1986. The first looked at growth after late preterm birth and whether it predicts neurocognitive functioning, academic performance, or mental health [42]. For every 1 SD faster weight and head growth from birth to 5 months, and head growth from 5 to 20 months, participants had higher IQ, executive functioning score, and grade point average, and lower odds of special education, after adjusting for sex, gestational age, follow-up age, and parental education. Faster head growth from 20 to 56 months was associated with fewer internalizing problems but was not associated with neurocognitive or school outcomes. Otherwise there were no consistent associations with mental health outcomes. This suggests that faster growth during a critical early period after birth is associated with better adult neurocognitive functioning. Another paper using this longitudinal study [43] looked at mental disorders in 25-year-olds born late preterm. They found that both LPI and FTI were at similar risk for any common mental disorder, mood, anxiety, and substance use disorders, and comorbidity of these disorders. The latest paper published using this cohort studied whether late preterm birth was associated with neurocognitive deficit at age 25 years and whether small-for-gestational-age birth worsened outcomes [44]. They found similar scores between LPI and FTI on full-scale and verbal IQ after adjustments except for those born small for gestational age. They concluded that late preterm birth may not increase the risk of poor neurocognitive functioning in adulthood; however, the double burden of being born late preterm and small for gestational age seems to increase this risk [44].

4.1. Potential causes of worse neurodevelopmental outcomes

The overwhelming evidence suggests that LPI have short and long term neurodevelopmental, social, and psychological challenges. The underlying mechanisms leading to poor outcomes of children born late preterm, as compared with children born full term, are likely multifactorial; however, there are at least two possibilities as to why this happens. First, the impaired outcomes seen in LPI could represent some infants with overt brain injuries among a group with normal potential. Second, LPI could have a decrease in the means of normally distributed scores so that they represent a different population than FTI. Unfortunately, the underlying neuroanatomical cause for this aberrant achievement and development in LPI is not yet fully understood.

The major neuropathologic cause of brain damage in premature infants has been coined “the encephalopathy of prematurity” [45]. The condition involves combined gray and white matter lesions resulting from the effects of injuries acquired by an immature brain being exposed to an ex-utero environment which is different from where it would normally develop. Injury can come from many exposures including hypoxia–ischemia, infection/inflammation, and/or other insults that lead to combined toxicities attributable to glutamate, free radicals, and cytokines [46].

Growth and development of the brain occurs rapidly in the second half of development. At 34 weeks, the brain is only at 65% of total term weight [47]. Volumetric magnetic resonance during late gestation has shown a four-fold increase in the cerebral cortical volume between approximately 30 and 40 weeks gestational age [48]. In addition, there is a five-fold increase in myelinated white matter volume between 35 and 41 weeks [48]. The cerebellum is also actively growing and developing with about 25% of its growth occurring after late preterm gestations [49]. Underlying these growth changes, major cellular and regional events in the development of neurons, oligodendrocytes, astrocytes, microglia, and blood vessels are occurring [50].

The brain's growth and development occurs in very specific orders and time frames. It also occurs at different rates during different gestational ages, which creates critical periods of development during which cells are susceptible to insults or injuries. If injury occurs during a critical period of growth and differentiation of brain structures, it can change the trajectory of brain development, resulting in different patterns of brain injury and repair which manifest as unique neurologic outcomes. Brain growth has been shown to be altered simply by being born preterm, as evidenced by studies showing differences in magnetic resonance imaging (MRI) between late preterm and FTI [51].

The late preterm brain is still immature and more likely to experience noxious stimuli from medical complications after birth such as respiratory distress syndrome, hypoglycemia, hyperbilirubinemia, and apnea. Evidence from animal models reveals that these factors can promote or precipitate neuronal cell death in the immature brain [52]. There is some evidence that it is unable to defend against such toxicities. For example, antioxidant enzyme expression differs with age so that LPI have less expression of superoxide dismutases which must be optimized for proper protection from injury from oxygen free radicals in hypoxic–ischemic injury [53].

Magnetic resonance imaging may help us to determine which brain structures have altered developmental patterns in children born late preterm. Researchers are starting to use MRI to associate brain differences between LPI and FTI and associate them with neurodevelopmental outcomes. There is increasing evidence that changes in brain growth and development may underlie some of the developmental issues described.

One such study explored the association of brain volumes, maturation, and injury at term-equivalent age with 2-year cognitive, language, and motor development. In a sample of 197 infants, larger total brain tissue volumes were associated with higher cognitive and language scores. Similar relationships were documented for white matter volumes with cognitive and language scores, multiple cerebral structures with language scores, and cerebellar volumes with motor scores. Larger cerebellar volumes were independently associated with better language and motor scores, after adjustment for several factors (maternal pre-eclampsia, gestational age at birth, sex, birth-weight *z*-score, multiple birth, maternal antenatal corticosteroids, respiratory support, higher social risk, and gestational age at MRI). They concluded that brain volumes may be an important marker for neurodevelopmental deficits described in moderate and late preterm infants [54]. Similar relationships between brain volumes at term-equivalent and long term outcomes have been described for very preterm children [55–57].

There have been few other reports of brain volumes and functional outcomes in late preterm children. Rogers et al. [58] reported that total, right temporal, and parietal gray matter volumes were decreased in late preterm children aged 6–12 years compared with full term controls. LPI had more anxiety symptoms at school age compared to FTI and anxiety was correlated with the decreased percentage of gray matter volume in the right temporal lobe. Brumbaugh et al. [59] performed a cohort study to evaluate brain function, structure, and cortical trajectories at school age. They found more parental reported behavior difficulties, more difficulty with processing speed, visual–spatial perception, and memory compared to full term children. They had similar performance in language, executive function, and motor skills. Structurally, late preterm children had less total brain tissue and more cerebrospinal fluid than full term children. They also had a different tissue volume growth trajectory than full term children [59]. Using functional MRI, one group found altered neural activity in the primary motor and sensory regions in late preterm children compared with full term controls [60].

5. Conclusions

This review demonstrates that LPI have significantly worse performance across a range of cognitive and educational measures compared with FTI. Given the high prevalence of late preterm births, even small differences in abilities, special education, and length of education may have broader consequences. There are still many questions that remain unanswered. First, we do not know which subpopulation of these infants is at the highest risk. Is there a certain vulnerable subgroup, such as those who have the most complicated medical courses, or does the risk extend to those who had uneventful neonatal and prenatal histories? The studies are mostly retrospective and all have found some increased risk to different populations, such as small-for-gestational-age infants, but none have been consistent. Second, it is unclear whether risks for suboptimal outcomes in LPI are limited to specific areas of development or are more global in nature. Third, do these observed delays demonstrate a lag in normal development such that correcting for prematurity may be helpful, or are they associated with longer, possibly life-long issues? Finally, is there an opportunity to proactively intervene to help LPI reach their fullest potential similar to the gains seen with early intervention in more preterm infants? LPI may benefit from increased monitoring of neurodevelopment, academic performance, and behavior.

It is clear at this stage that there needs to be more research into this problem. Future research focusing on defining the specific risks experienced by LPI as well as identifying high-risk groups within late preterm gestations is essential. Studies should adopt uniform gestational age categories, use FTI as controls, and utilize standardized and validated outcome measures so that risk for poor outcomes can be appropriately assessed. Analyses should also be longitudinal, identifying how neurodevelopment changes over time and where we can identify difficulties early, allowing for timely, focused therapeutic interventions. This type of research would help inform public health policy so that appropriate therapeutic interventions, which have been shown to mitigate some of these adverse neurodevelopmental deficits in other populations [61], could be delivered at an appropriate time, allowing LPI to reach their greatest potential.

6. Research directions

- Define the specific risks experienced by late preterm infants.
- Identify high-risk groups within the late preterm gestation.
- Studies should adopt uniform gestational age categories, use full term infants as controls, and use standardized and validated outcome measures.
- Analyses should be longitudinal to follow neurodevelopment over time and identify points for therapeutic intervention.

Conflicts of interest

None declared.

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