

Understanding long-term neurodevelopmental outcomes of very and extremely preterm infants

A clinical review

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This article is the sixth in a series on paediatric health. Articles in this series aim to provide information about diagnosis and management of presentations in infants, toddlers and pre-schoolers in general practice.

Background

Survival of infants born at <32 weeks of gestation has increased over recent years. This has resulted in an increased incidence of neurodevelopmental morbidities in survivors.

Objectives

The aim of this article is to provide a pragmatic clinical review of long-term neurodevelopmental risk experienced by very preterm infants.

Discussion

Very preterm infants have a higher risk of cerebral palsy, cognitive delay, deafness and blindness, and autism spectrum disorder when compared with term controls. The presence of Grade 3 or 4 intraventricular haemorrhage or necrotising enterocolitis increased the risk of cerebral palsy, while magnesium sulphate for threatened preterm labour decreased the risk in the surviving neonate. Most of the neurodevelopmental conditions can be diagnosed in early childhood through regular follow-up. General practitioners need to be vigilant about early signs of developmental problems affecting preterm survivors. Regular follow-up is necessary to identify red flags in early development.

THE WORLD HEALTH ORGANIZATION defines very preterm infants as those born at 28–32 weeks of gestation and extremely preterm as those born at <28 weeks of gestation.¹ Over the past few decades, improvement in the clinical care of preterm infants has resulted in improved survival in the neonatal age group and beyond. Thus, a greater number of premature infants are surviving with major and minor neurodevelopmental morbidities, often resulting in lifelong disability.²

Major neurodevelopmental morbidities in surviving preterm infants include cerebral palsy, deafness, blindness and cognitive delay, with scores of <2 standard deviations below the mean for age.³ Recent reports also indicate a higher risk of autism spectrum disorder (ASD) and emotional behavioural abnormalities such as attention deficit hyperactivity disorder (ADHD).³ While some of the outcomes can be identified in the first two to three years, neurobehavioural and emotional problems evolve later – at school age.

Parents often visit general practitioners (GPs) to get an assessment and understanding of their infant's developmental problems. Regular interactions for immunisations and health checks also provide an opportunity to educate the parents regarding their child's neurodevelopmental conditions. An understanding of the effects of prematurity and the neonatal course is necessary to counsel the family and identify the infant

with an increased neurodevelopmental risk. The aim of this clinical review is to provide a broad understanding of the common neurodevelopmental problems in preterm infants born at <32 weeks of gestation.

Methods

A literature search on PubMed, Cochrane library and Ovid was carried out. Details of the search methodology and results are provided in Appendix 1 (available online only). Recent systematic reviews that reported the overall neurodevelopmental outcome for each neonatal condition were selected. The results are outlined below.

Developmental/cognitive delay and prematurity

Various factors increase the risk of neurodevelopmental delay in very preterm infants (Figure 1). The risks of cognitive delay increase as the gestational age at birth decreases.⁴ A large French study followed up 5567 preterm infants using the Ages and Stages Questionnaire (ASQ) developmental screening at 24 months of corrected age, and it was reported that the risk of scores below two standard deviations were 50.2% for infants born at 24–26 weeks and 40.7% for infants born at 27–31 weeks.⁵ Pascal et al reported that a confirmative test using the Bayley Scales of Infant and

Toddler Development indicated a pooled prevalence of 16.9% for the cognitive delay for preterm infants. The risk of moderate and severe delay in survivors born at 22, 23, 24, 25 and 26 weeks of gestation was 60%, 51%, 34%, 27%, and 16% respectively.⁶ Serenius et al compared the risk of cognitive delay in very preterm infants with term controls and reported that the risk of moderate disability (preterm, compared with term) was 5% and 0.1% and the risk of and severe disability was 6.3% and 0.3%. The IQ scores (mean \pm standard deviation) were 104 ± 10.6 for preterm infants and 94 ± 12.3 for term infants. A total of 58% of infants born at <28 weeks gestation had a mild, moderate or severe disability. Cognitive tests were performed using the Bayley Scales of Infant and Toddler Development, third edition. The results were adjusted for demographic differences.⁷ It has been observed that preterm infants exposed to antenatal administration of corticosteroids for threatened preterm labour showed a lower incidence of cognitive delay.⁸ Neonatal hypoxic ischaemic insult resulting in low Apgar scores, low arterial cord pH, presence of seizures and intraventricular haemorrhage increases the risk of cognitive delay (Figure 1; Table 1).

Preterm infants also have a higher risk of gross motor and speech delay. Pierrat et al reported that at two years of

corrected age, 16.6% of infants born at 24–26 weeks and 9.7% of infants born at 27–31 weeks displayed signs of motor delay, whereas only 5.1% of infants born at 32–34 weeks of gestation displayed the same signs.⁵ At two years of corrected age, speech delay was evident in 33.9% of infants born at 24–26 weeks and 24.1% of infants born at 27–31 weeks, compared with 17.8% of infants born at 32–34 weeks).⁵

Cerebral palsy and prematurity

Cerebral palsy describes a group of permanent disorders affecting the development of movement and posture that cause limitations of activity and are attributed to nonprogressive disturbances that occurred in the developing fetal or infant's brain.⁹ Cerebral palsy occurs in 2–2.5 per 1000 live births.¹⁰ A French cohort study reported that the risk of cerebral palsy was 6.9% in infants born at 24–26 weeks and 4.3% in infants born at 27–31 weeks, whereas in more mature infants born at 32–34 weeks the risk was 1.0%.⁵ The diagnosis of cerebral palsy was made at two years of corrected age in this study. Serenius et al reported that the prevalence of cerebral palsy was 7% in preterm infants born at <28 weeks of gestation and 0.1% in full-term controls (Table 1).⁷ The presence of periventricular leukomalacia, where

there is scarring of white matter around the ventricles of the brain, or severe intraventricular haemorrhage are strong predictors of cerebral palsy.¹¹ Malin et al, in their systematic review, reported that low arterial cord pH increased the risk of cerebral palsy twofold. However, this study did not examine the added risk of prematurity on cerebral palsy.¹²

Blindness, deafness and prematurity

Retinopathy of prematurity (ROP), a condition where blood vessels grow into various layers of the retina, can result in blindness. With improvements in neonatal intensive care, the risk of blindness secondary to ROP has decreased over time.^{2,13} Although the exact aetiology is not known, exposure to prolonged oxygen treatment has been shown to trigger the growth of blood vessels into various layers of the retina, causing blindness if not treated early. Hintz et al reported that the risk of blindness was 2.2% in children born at <25 weeks of gestation.¹⁴ The risk decreased as the gestational age increased. In their cohort, Serenius et al reported that the risk of blindness in very preterm infants, when compared with term infants, was 0.9% versus 0%.⁷ Exposures to ototoxic antibiotics such as gentamicin and diuretics such as frusemide may contribute to hearing impairment.¹⁵ Hintz et al also

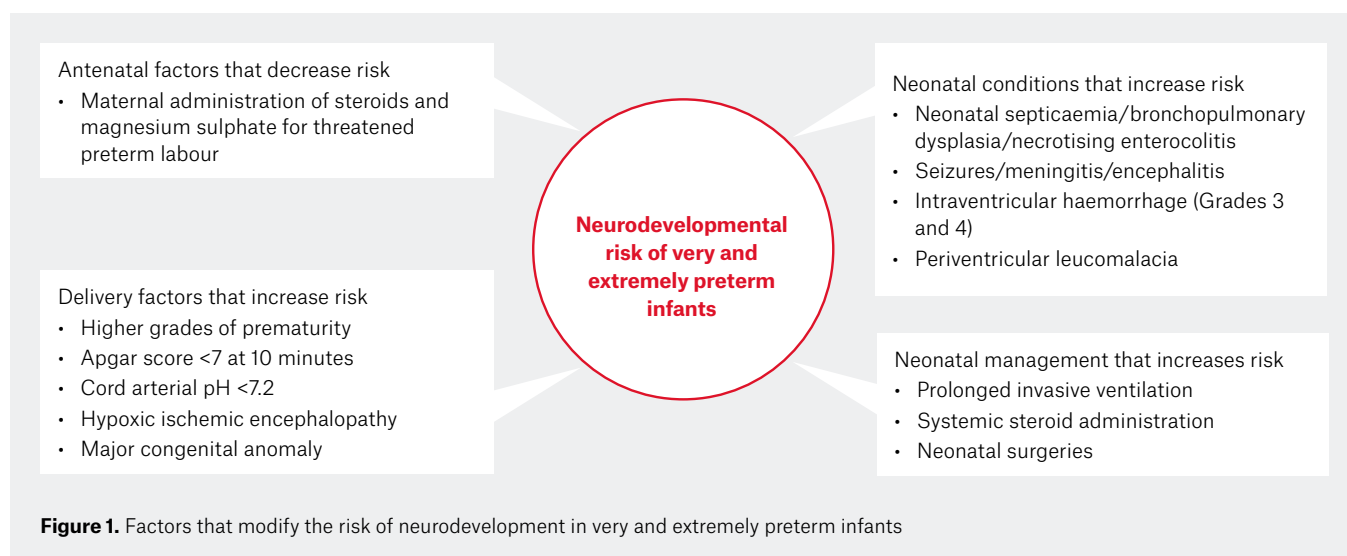


Figure 1. Factors that modify the risk of neurodevelopment in very and extremely preterm infants

reported that the risk of deafness was 1.4% in infants born at 24–26 weeks and decreased as gestation increased.¹⁴ The risk of deafness in infants born at <25 weeks of gestation in an Australian cohort was 2.5%.¹⁶ Hence, very preterm infants are more susceptible to deafness and blindness.

ASD and prematurity

ASD is a lifelong neurodevelopmental disorder comprising social communication and emotional difficulties.¹⁷ Recently, the increased risk of positive autism screening in premature infants has gained much attention. Limeropoulous et al reported that the risk of a positive screen was 25% in infants with a birth weight of <1.5 kg when screened at 22 months of corrected age.¹⁸ Other reports have identified the risk of a positive screen to be 21–41% in infants born at <28 weeks of gestation.^{19–21} However, the results need to be interpreted with caution. Moore et al observed that of 41% of infants who screened positive, coexisting disabilities such as severe motor, visual and cognitive impairment were present in 62% of those

infants. Moreover, sensory difficulties that form a part of autism diagnosis are also observed in preterm infants, which may contribute to false-positive screening results.¹⁹ In a population case control study, Lampi et al reported that the risk of ASD for preterm and term infants was 1.3% and 0.6%.²¹ Difficulties in social, emotional and cognitive domains of development in early infancy could point towards the need for further diagnostic assessments for ASD. This is summarised in Box 1 and Table 2.

Antenatal and neonatal conditions and neurodevelopmental outcomes

Premature gestation at birth is one of the major determinants of increased neurodevelopmental risk in surviving infants. Various antenatal factors, delivery circumstances, neonatal morbidities and management add to the increased risk of neurodevelopmental abnormalities in preterm infants (Figure 1).^{22,23} Each of these conditions is an independent risk factor for adverse long-term

neurodevelopmental outcomes. After discharge from hospital, physical and emotional environments such as parental substance use, not meeting physical and emotional requirements of the child, early childhood trauma, and emotional deprivation also contribute to the increased risk of neurodevelopmental problems.²⁴ Given the scope of the review, only antenatal, birth and immediate postnatal factors that affect the neurodevelopment in surviving very preterm infants is discussed here.

Antenatal administration of corticosteroids during pregnancy for impending preterm labour minimises the risk of cognitive delay and cerebral palsy in the surviving infant at two years of corrected age (Table 1).^{8,22} However, administration of oral or injectable corticosteroids to the premature infant after birth adversely affects brain development and increases the risk of cerebral palsy^{25,26} (Table 1). In a recent systematic review, Shepherd et al reported that early administration of a high dose of postnatal corticosteroids increased the risk of cognitive delay and cerebral palsy

Table 1. Antenatal/neonatal conditions and neurodevelopmental outcomes: Evidence from systematic reviews

Condition	Reference/ measure of effect	Age at assessment	Cognitive/ developmental delay	Cerebral palsy	Deafness	Blindness
Necrotising enterocolitis	Schulzke et al ²⁸ AOR (95% CI)	Corrected 12 months or older	1.65 (1.27, 2.15)	1.59 (1.23, 2.07)	1.74 (0.79, 3.85)	2.75 (1.30, 5.85)
Intraventricular haemorrhage	Mukerji et al ¹¹ AOR (95% CI)	Corrected 18–24 months	2.44 (1.73, 3.42)	3.43 (2.24, 5.25)		
Postnatal steroids (does not include inhaled steroids)	Onland et al ²⁶ Risk ratio (95% CI)	Corrected 2 years or older	3.37 (1.42, 7.99)	2.17 (0.87, 5.37)		
	Zeng et al ²⁵ OR (95% CI)	Unclear		2.30 (1.22, 4.36)		
Antenatal corticosteroids	Sotiriadis et al ⁸ AOR (95% CI)	Corrected 2 years or older	0.83 (0.74, 0.93)	0.68 (0.56, 0.82)		
	Shepherd et al ²² AOR (95% CI)	Corrected 12 months or older		0.60 (0.34, 1.03)		
Antenatal magnesium sulphate	Crowther et al ²⁷ RR (95% CI)	18 months – 2 years	0.99 (0.91, 1.08)	0.68 (0.54, 0.87)	1.10 (0.83, 1.47)	0.83 (0.65, 1.06)

AOR: adjusted odds ratio; CI, confidence interval; OR, odds ratio; RR, relative risk

when compared with low doses.²² Any exposure to corticosteroids, compared with placebo, also resulted in a higher risk of cerebral palsy diagnosis.²² Antenatal administration of magnesium sulphate for threatened preterm labour reduced the risk of cerebral palsy in preterm survivors. Neither magnesium sulphate nor corticosteroids are routinely administered during pregnancy unless there is a threat of preterm labour at <34 weeks of gestation.²⁷ Surviving preterm infants with conditions such as necrotising enterocolitis, severe intraventricular haemorrhage or bronchopulmonary dysplasia are more likely to have cerebral palsy and cognitive delay.^{11,25,28} Although administration of probiotics to very preterm infants is routinely practised in many centres across the world, its neurodevelopmental benefits are still being researched. Akar et al reported that oral probiotics in preterm infants did not affect the neurosensory and cognitive outcomes at 18–24 months of corrected age.²⁹ It is beyond the scope of this article to report and analyse each of these conditions. Hence a brief summary is provided in Table 1.

Being born prematurely disrupts brain development and maturation.³⁰ The last few weeks of pregnancy are associated with a rapid increase in brain maturation and cortical synapse formation. The brain continues to mature after birth,

but the trajectory of maturation is vastly different from in utero maturation because of adverse environmental conditions and interventions in neonatal intensive care units.³⁰ Using magnetic resonance imaging brain techniques at corrected term-equivalent age, Smith et al reported that exposure to stressors during neonatal care is associated with decreased brain size in the frontal and parietal regions and altered brain microstructure and functional connectivity within the temporal lobes.³¹ Alterations in neurobehaviour at term-equivalent age were also associated with increased early exposure to stress. The authors listed various procedures, including blood sampling, as stressors in the neonatal intensive care unit.³¹ Sick infants are often exposed to more interventions; therefore, a sick preterm infant with prolonged admission to neonatal intensive care is at a higher risk of developing neurodevelopmental abnormalities. A brief checklist to identify major problems at clinic visits is provided in Box 1.

Signs and symptoms of developmental delay

Timely identification of signs and symptoms of developmental concerns during follow-up visits assists GPs to facilitate conversation with parents about the further evaluation of the infant's

neurodevelopment. Any delay in achieving milestones at recommended ages requires further evaluation. Various screening questionnaires and checklists are available online for use.³² Some of the red flags for reference are included in Table 2.

Disability-free survival in very preterm infants

Many very preterm infants survive without any major neurodevelopmental disability. Sharp et al reported that >50% of preterm infants born at <24 weeks of gestation in Western Australia showed no major disability, including cerebral palsy and ASD.³³ The median age at diagnosis was 59 months.³³ The study did not examine the risk of mild disability and school problems. Although the risk of neurodevelopmental impairment is high in very preterm infants, it is not inevitable.

Drawbacks of the review

This review has many drawbacks. It is not intended to be an exhaustive systematic review and has been carried out by a single author. Hence, subconscious selection bias in study selection is possible. However, this is a clinical review, and the information provided in the review matches with the clinical experience of the author.

Neonatal care and survival have changed significantly over the past few

Table 2. Red flags in normal infant development: Absence of milestones at different ages³²

Developmental domain	Six months	Nine months	Twelve months	Eighteen months	Two years	Three years	Four years
Gross motor	Head control	Rolling over, sitting, weight-bearing on legs when made to stand	Any mobility (crawl, walk, bottom shuffle)	Walking, standing with support	Walking without support	Walk up and down the stairs	Jump, kick a medium-size ball
Speech and communication	Babbling	Bisyllables (baba, dada), pointing	Babbled phrases	Words, comply simple instructions with gesture	Two-word phrases	Clarity of speech	Two-step instructions
Fine motor, cognition	Palmar grasp, hand regard	Hand-to-hand transfer of objects	Hand-mouth coordination, pincer grasp	Scribbling	Attempt to feed self	Simple dressing, feeding self	Copy a circle
Social emotional	Social smile	Eye contact	Simple interactive games (eg peekaboo)	Interaction	Use of toys for their purpose	Pretend play	Peer interaction

decades. Various antenatal and postnatal interventions and early intervention practices, such as physiotherapy and occupational therapy, have affected the incidence and severity of developmental disabilities in surviving infants. The tests to identify neurodevelopmental disabilities, such as the Bayley Scales of Infant and Toddler Development and the Griffith Mental Development Scales, have also changed over time. Long-term neurocognitive and neurodevelopmental outcomes at school age and beyond depend not only on the neonatal course, but also on the physical and emotional environments at home and school.³³ Hence, one needs to be cautious when interpreting the results of long-term outcome studies.

Follow-up recommendations

Very preterm infants need regular outpatient follow-up to identify neurodevelopmental impairments at corrected ages of four, eight, 12 and 18 months and at two years, to identify early signs of developmental delay.³⁴ Clinical examinations for the identification of neurological abnormalities and the use of screening tools such as the Ages and Stages Questionnaire may guide further referrals to a specialist service.³⁵ National Institute for Health and Care Excellence guidelines recommend routine follow-up of all very preterm infants until four years of age. Further follow-up of infants may be necessary to identify neurobehavioural conditions in early school age.³⁴

Conclusion

The majority of developmental problems in children who were born very preterm can be identified in early childhood through regular follow-up. GPs need to be vigilant about physical as well as early signs of emotional and behavioural problems affecting preterm survivors, and provide follow-up care beyond the first two years of life. A referral to the local child development services pathway for further evaluation and management should be considered for infants with early signs of developmental disabilities.

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Box 1. Examination checklist at every GP clinic visit³⁴

Ask for:

- extent of prematurity, birthweight and Apgar scores
- presence of intraventricular haemorrhage and severity (Grade 3 and 4 are more significant)
- diagnosis of necrotising enterocolitis and need for surgery and laparotomy
- presence of proven neonatal sepsis or meningitis
- presence of hypoxic-ischemic encephalopathy Grade 2 or 3 and exposure to whole-body cooling
- exposure to postnatal steroids (especially before 32 weeks of gestational age)
- presence of any brain lesion (ie periventricular leukomalacia)
- current parental concerns regarding development, feeding, sensory and sleep problems
- difficulties related to attention, concentration, impulsivity and hyperactivity emotional and behavioural problems
- executive function (including organisation skills, thought regulation, impulse control, working memory and planning)
- current ongoing therapies.

Look for early signs and symptoms of developmental problems as appropriate, such as:

- gaze fixing and following
- growth (height and weight)
- head circumference (a rapid increase or static measurement is a concern)
- delayed motor milestones (ie sitting, asymmetry in crawling, delayed standing, tiptoe walking and contractures at ankles and hips)
- persistent feeding problems (including hypersensitivity with certain textures of food)
- abnormalities of tone (ie hypotonia or hypertonia)
- quality of general movements (ie absence or abnormal fidgety movements carried out at four-month visit – this needs special training)
- outcomes of screening questionnaires (eg Ages and Stages Questionnaire, if completed).

Counsel for:

- need for ongoing surveillance
- referral service for formal identification of cognitive abilities, cerebral palsy, autism spectrum disorder, attention deficit hyperactivity disorder and executive functions. The tests can be performed at any age.

- course of antenatal steroids in children born preterm: A systematic review and meta-analysis. *Obstet Gynecol* 2015;125(6):1385–96. doi: 10.1097/AOG.0000000000000748.
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Appendix 1. Details of the search methodology and results

Methods

A literature search on PubMed, Cochrane library and Ovid was carried out on 4 February 2018 and 20 June 2018 using MeSH words 'preterm' OR 'premature' OR 'very preterm' OR 'extremely preterm' AND 'intraventricular haemorrhage', 'corticosteroids', 'bronchopulmonary dysplasia', 'magnesium sulphate', 'probiotics', AND developmental outcome', 'speech delay', 'motor delay', 'cognitive delay', 'autism', 'cerebral palsy', alone and in different combinations. Randomised controlled trials (RCTs), cohort studies and systematic reviews published in English language were selected. Since this is not intended to be a systematic review, quality assessment of studies or meta-analysis was not performed.

Results

The initial search identified 115 systematic reviews. Neonatal and perinatal conditions such as antenatal steroids and chronic lung disease are a subject of many RCTs over the years. Moreover, neonatal care has changed significantly over the last decade. Hence, the results of studies conducted in the past may be vastly different from recent studies. In order to minimise the selection bias, a recent systematic review/RCT or a cohort study that reported the overall neurodevelopmental outcome for each neonatal condition was selected at the author's discretion. Population cohort studies that selected patients based on the gestational age and not on any specific medical condition were also selected for further review.
