Neuroscience meets nurture: the challenges of prematurity and the critical role of family-centred and developmental care as a key part of the neuroprotection care bundle

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What is known about this topic?

1. Preterm survival rates at the lowest gestational ages have improved.
2. Preterm infants spend their most vulnerable period of brain development on the NICU, largely in the absence of positive maternal influences.
3. Severe neurological disability is reducing but morbidity related to prematurity continues to present a global challenge.

What this study adds:

1. Several drug and cell-based neuroprotective therapies are being intensely studied but require more clinical research.
2. Family centred and developmental care therapies promote parent-infant interaction and enhance the preterm experience with the potential to improve neurodevelopmental outcomes.

ABSTRACT:

Advances in neonatal-perinatal medicine have resulted in increased survival at lower gestations. Although the incidence of germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (PVL) are reducing, a new phenotype of preterm brain injury has emerged consisting of a combination of destructive and dysmaturational effects. Consequently, severe neurological disability is reported at a lower rate than previously, but the overall morbidity associated with premature birth continues to present a large global burden and contributes significantly to increased financial costs to health systems and families. In this review, we examine the developmental milestones of fetal brain development and how preterm birth can disrupt this trajectory. We review common morbidities associated with premature birth today. Although drug and cell-based neuroprotective therapies for the preterm brain are under intense study, we outline basic, sustainable and effective non-medical, family-centred and developmental care strategies which have the potential to improve neurodevelopmental outcomes for this population and need to be considered part of the future neuroprotection care bundle.
INTRODUCTION

Despite advances in medical knowledge and techniques, prematurity and its sequelae continue to present a significant global challenge. Here we review the burden of prematurity, preterm brain development and injury, commonly associated neurodevelopmental morbidities, and focus on the evidence in support of developmental and family centred care practices to enhance preterm brain development and neurodevelopmental outcomes.

PRETERM BIRTH AND SURVIVAL

Nearly fifteen million babies are born preterm every year (WHO definition <37 completed weeks gestation). The ten countries with the highest rates of prematurity (mainly sub-Saharan Africa and South Asia) account for 60% of all preterm births worldwide. Although rates are highest on average for low-income countries (11.8%), followed by lower-middle-income countries (11.3%) and lowest for upper-middle- and high-income countries (9.4% and 9.3%), relatively high preterm birth rates are seen in many individual high-income countries where they contribute substantially to neonatal mortality and morbidity. [Fig 1]

For infants born at 22+0–25+6 weeks in the UK, survival to discharge has continued to improve over the decades from 40% in 1995, to 66% in 2014. Several international studies have similarly indicated an incremental improvement in survival for the most premature babies over the last 1-2 decades. The largest changes in outcome are at the lowest gestational ages. At 22 weeks GA, recent cohort studies from the US, UK, Sweden and Germany indicate that approximately 30% of live-born babies who receive active treatment survive to discharge.

PRETERM BRAIN DEVELOPMENT

The human central nervous system (CNS) develops with a pattern similar to all mammals, beginning as a simple neural tube and gradually developing features through hugely complex and strictly regulated processes. The growth rate in the human CNS is higher than any other organ from the 4th postconceptional week (PCW) to the 3rd postnatal year. The association areas of the cerebral neocortex develop more slowly, and the gestation period and childhood are much longer compared to other mammals. This period of dependency and the prolonged developmental course allows, more than any other species, the environment to shape the development of cognition, social and emotional factors. In addition, the developing human brain has larger proliferative areas and diverse subtypes of neural and progenitor cells that lead to increased brain expansion, especially of the neocortex.

Fetal development is the most important period for neurogenetic events, with regards to number of neurons (proliferation), their molecular diversity (molecular specification), allocation
in the cortex (migration), phenotype differentiation (dendritogenesis), and is a time for the growth of axons (axonogenesis) and functional contacts (synaptogenesis). The subplate zone of the telencephalon plays a pivotal role in the development of the human brain and is the most prominent transient compartment of the fetal cortex. It is the major site of synaptogenesis and neuron maturation and is a site for increasing the number of associative and thalamocortical pathways in the human neocortex. Most developmental processes extend into the post-natal period, especially processes associated with interneuron connectivity. Each of these cellular processes may be vulnerable to environmental influences, and their impairment may disrupt brain growth.

The third trimester is a critical period during which global and regional brain volume increases three to fourfold. The general architecture of the human brain is achieved during the first 6 months of fetal life, mostly driven by genetic influences, which are then silenced in the third trimester, when environmental factors, uterine or in the NICU, strongly influence the last phases of prenatal and early postnatal brain development. Prematurity is one of many biological or environmental insults that can push the trajectory of the developing brain to an atypical path, with the resultant increased prevalence of neurodevelopmental and neuropsychiatric disorders.

**SENSORY DEVELOPMENT OF THE FETUS**

The sensory systems of the fetus become functional in the following sequence during early development: tactile > vestibular > chemical > auditory > visual. As a result, the various sensory modalities have markedly different developmental histories at the time of birth. The basic structure of the eyes, ears and olfactory bulb develop early in gestation. Some of the primary receptors for touch, position and motion also develop early. The development of touch starts at around 8 PCW, initially beginning with sensory receptor development in the face, mostly on the lips and nose. Taste buds begin to emerge at 8 PCW and at 13-15 PCW, the fetus has similar taste buds to adults. Smell develops around the same time that the fetus has taste function. The neural architecture of each sensory system is built at 22-40 weeks gestation and further develops in the neonatal period. The hearing system is fully developed at 20 PCW. At 23 PCW, an unborn baby can respond to loud noises. A newborn baby’s eyes are susceptible to bright light but are short-sighted at only 8 to 12 inches in front of their face.

Adverse neonatal experiences can alter brain development and subsequent behaviour in preterm infants. They are exposed to many stimuli from which they would have been protected in-utero, including the NICU environmental and its related stressful events. Calming experiences are few, including lower levels of maternal oxytocin. The nature of delivery of
sensory experience received in the NICU can over stimulate later developing sensory systems (auditory and visual) and under stimulate earlier developing systems (tactile and vestibular), while also reducing the amount and availability of intersensory redundancy. The interplay of these sensory experiences and its influence on future neurodevelopment is not yet well understood.

**BRAIN MRI ABNORMALITIES ASSOCIATED WITH PREMATURITY**

Survival at lower gestations has seen the emergence of new phenotypes of preterm brain injury. With the incidence of germinal matrix haemorrhage-intraventricular haemorrhage (GMH-IVH) and cystic periventricular leukomalacia (PVL) reducing, a more diffuse pattern of white matter injury, characterised by loss of oligodendrocyte precursors, is more frequently seen. Punctate white matter lesions (PWML) are the most common MRI abnormality in preterms imaged at term equivalent age and are associated with an increased risk for poor motor outcome. [Fig 3]

The term “encephalopathy of prematurity” describes the combination of destructive and dysmaturational effects leading to abnormal white matter (WM) and grey matter (GM) development. Neonatal MRI has shown a signature pattern of preterm birth that includes alterations in white and grey matter microstructure, impaired cortical folding and disturbances in regional brain growth. These structural changes reflect a dysconnectivity of neural networks and atypical development of cortical and deep grey matter structures. While MRI has advanced our understanding of preterm brain injury, predicting neurodevelopmental outcome based on lesions other than PVL and haemorrhagic periventricular infarction (HPI), is still elusive.

**Brain growth:** Although brain growth is rapid between 25 and 40 weeks in a preterm baby on the NICU, the growth trajectory is less than in a healthy fetus over the same duration. MR imaging studies of preterm infants have identified reduced cortical [Fig 4] and subcortical grey matter volumes diminished cerebellar volumes and alterations in thalamo-cortical development at term-equivalent age. The long-term effects of prematurity are observed by alterations in WM and GM volumes seen in adolescence.

**Microstructural brain development of white and grey matter:** Diffusion MRI (dMRI) has demonstrated altered WM development in preterm infants without focal lesions, which is related to neurodevelopmental performance in early childhood and adolescence. Using dMRI to assess macrostructural connectivity the organisation of structural brain networks during the preterm period has been characterised, demonstrating a relative preservation of
specific core connections at term equivalent age. Of great interest, Batalle and colleagues recently demonstrated relative preservation of these specific core connections whereas regional connectivity involving thalamus, cerebellum, superior frontal lobe, cingulate gyrus and short-range cortico-cortical connections were related to the degree of prematurity.

Compared to term-born infants, preterm infants at term corrected age have impaired cortical development with decreased cortical folding; reduced GM volumes are associated with foetal growth restriction and slower postnatal growth.

Factors associated with the preterm birth signature have been elegantly reviewed by Boardman and Counsell 2020. Maternal factors associated with altered brain development include chorioamnionitis, fetal growth restriction, socioeconomic deprivation and prenatal alcohol, drug and stress exposures; fetal factors include nutrition, pain and medication and variation conferred by the genome/epigenome.

**NEURODEVELOPMENTAL OUTCOMES OF PRETERM INFANTS**

Although rates of severe neurological disability, cerebral palsy (CP) and intellectual disability, are reduced compared to previously reported, 5-15% of very preterm survivors are still affected. Milder cognitive disabilities, learning difficulties, and behavioural problems are detected in 25-50% of preterm survivors at preschool and school age.

Whilst the extremely preterm and very preterm infants are found to have disadvantages across all domains of development; the moderately preterm infants have more favourable developmental trajectories. The motor, cognitive, behavioural, and psychiatric disabilities in the moderate and late preterm population, however, have a greater impact being the larger proportion of the preterm population. An estimated 0.9 million post-neonatal survivors suffer long-term neurodevelopmental impairment with 345,000 being moderately or severely affected, presenting a large global burden.

Impairment is often defined as a composite of neurosensory (CP, blindness, deafness) and developmental outcomes. However, there may be variation in the aspects of these outcomes included and the cut offs used for defining the developmental delay. Of babies born in the UK before 27 weeks GA in 2006, 13.4% (n=77) were categorised as having a severe impairment and 11.8% (n=68) moderate impairment at three years. Outcomes for most neonatal networks and national studies are similar, although differences in cohort and impairment definitions make it challenging to compare the data between countries. [Fig 5]
Outcomes at school age or beyond are more valid compared to earlier assessments.\textsuperscript{41, 45, 47} Male gender and lower maternal education are associated with both lower early learning composite scores and a decline in scores over time.\textsuperscript{42} Bronchopulmonary dysplasia is found to be a crucial factor for cognitive outcome.\textsuperscript{50}

**Motor:**
Motor impairments are common in the preterm population and include CP, developmental coordination disorder (DCD), and other disorders of movement and its control. CP is the most well defined and the most severe form.\textsuperscript{41}

Prematurity is the most frequent cause of CP, with an incidence of 9.1\% in adults born at 23 to 27 weeks' gestation inclusive. The spastic subtype accounts for 96\% of CP in preterm infants, with 60\% being spastic diplegia, and 17\% spastic quadriplegia.\textsuperscript{51}

Motor difficulties associated with DCD, although often considered "minor" can have a significant impact on the child's abilities.\textsuperscript{41}

**Cognitive:**
Cognitive impairment is well recognised after extreme preterm birth but is complex and influenced by multiple processes and not easily predicted by brain injury. Limitations of the available assessments make it difficult to accurately estimate long term cognitive challenges.\textsuperscript{51}

Cognitive scores at school age and beyond are 11 to 12 points lower in children born preterm, with mean IQ being 5 to 7 points lower than in controls. Those with executive dysfunction have difficulty in tasks such as initiating activities, organisation, flexibility in generating ideas and problem solving, working memory, inhibition, and attention problems. Weaknesses in working memory and visuo-motor integration are particular challenges in preterm survivors.\textsuperscript{41}

**Behaviour:**
Approximately 40\% of preterm infants have an overall atypical pattern of behaviour with respect to processing sensory stimuli, and almost 90\% have a probable or definite abnormality in one or more sensory processing domains (e.g., oral, auditory, tactile, visual).\textsuperscript{41}

Extremely preterm infants are at 4 times the risk of attention deficit hyperactivity disorder as compared to term infants with a four-fold increase in risk of autistic spectrum disorder.\textsuperscript{52} Psychiatric disorders occur in approximately 25\% of those born preterm.\textsuperscript{41, 51}
**Speech and language:**
Language development is seen to be more delayed than motor or cognitive abilities in early childhood. Expressive language, receptive language processing, and articulation difficulties with deficits in phonologic memory are seen at an older age.\(^{41}\)

**Academic achievements:**
Preterm children are 2.85 times more likely than their term-born peers to receive special education and score significantly worse in arithmetic, reading, and spelling. Weaknesses in attention, executive functioning, visual-motor skills, and verbal memory in preterm children may all be contributing factors. Socioeconomic status is an important modifier of the relationship between prematurity and IQ. \(^{41}51\)

**STRATEGIES TO IMPROVE OUTCOMES, AND THE CRITICAL ROLE OF FAMILY CENTRED AND DEVELOPMENTAL CARE**

**Medical therapies:**
Optimising outcomes for premature babies starts with good obstetric care to promote fetal growth and well-being. Use of antenatal corticosteroids and magnesium sulphate are recommended for fetal neuroprotection. Attention to detail with appropriate expertise and facilities at delivery and in everyday management are essential for healthy brain development.\(^{53}\) Caffeine, used for apnoea of prematurity is neuroprotective in pre-clinical models \(^{54}\) and improves survival without neurodevelopmental disability.\(^{55}\) Delayed cord clamping may allow improved cardiovascular transition with improved cerebral autoregulation but meta-analysis failed to demonstrate a significant benefit in major neonatal neurological morbidities.\(^{56}\)

Researchers around the world are keenly focused on developing pharmacological therapies to protect the preterm brain. Disappointingly, even though erythropoietin showed neuroprotective effects in preclinical models,\(^{57}\) high-dose early erythropoietin administration to extremely preterm infants did not lower the risk of severe neurodevelopmental impairment or death at 2 years of age.\(^{58}\) Stem cell or exosomal therapies are particularly promising for protection, regeneration and repair of the injured developing brain. Mesenchymal Stem Cells (MSC) are attractive because of their low immunogenicity, self-renewing capacity, multi-lineage differentiation and secretome. Animal models suggest that administration of MSCs significantly reduces brain injury and post haemorrhagic hydrocephalus after IVH by reducing inflammation, gliosis and apoptosis of the immature brain.\(^{59}60\) Administration of MSC is
possible intranasally, with stem cells migrating or "homing" to the injured regions within 2 hours; this opens up great possibilities for treatment of preterm babies over the course of their stay in NICU. A recent report highlights the presence of stem cells in breast milk and the intriguing possibility that nasal breast milk might exert neuroprotective effects in preterm infants. However further clinical research is needed; on recent systematic review of clinical studies, there is no evidence of benefit of stem cell- or exosome-based therapies for treatment of GMH-IVH, or any other brain injury in the preterm infant.

**Non-Medical therapies:**

Admission to NICU has been associated with poor psychological functioning in mothers and fathers and negative parenting behaviours. The technical environment of the baby and NICU architecture may pose barriers to physical closeness. Animal data suggests that prolonged physical separation between parent and newborn alters brain development and results in higher cortisol levels in the infants and is associated with stress and anxiety in parents.

Family-Centred and Developmental Care practices are promising therapies with the potential to enhance the preterm baby experience and ameliorate the trajectory towards preterm birth MRI signature and phenotype.

**Developmental care** is defined as the wide range of medical and nursing interventions that help to decrease the stress of preterm neonates in neonatal intensive care units. These interventions are designed to allow optimal neurobehavioral development of the infant. A large variety of interventions and environmental tools have been extensively studied - light and noise levels, scheduling of care according to the baby's behaviour and state of sleep, limiting painful procedures, general motor containment, quality oral feeding.

Neonatal individualised developmental care and assessment programme (NIDCAP) is an individualised approach that integrates a number of interventions and is based on the synactive theory model. NIDCAP has been developed to interact with preterm infants at levels adapted to their degree of neurological maturity. Increase in support to the infant's behavioural self-regulation has been shown to improve medical, behavioural and developmental outcomes and has a positive impact on neurophysiology and brain structure, likely due to prevention of inappropriate inputs during a highly sensitive period of brain development.

Improved long-term outcomes in infant cognitive, motor and emotional functioning due to NIDCAP in the NICU has been reported up to school age. Enhanced parent confidence and
competence is also well documented. Meta-analysis of studies thus far has, however, failed to show significant benefits, likely due to lack of good quality large trials.

Skin-to-skin contact (SSC) and Kangaroo mother care (KMC) are the two most studied, multisensory parent interventions. A multitude of positive effects have been observed, such as supporting infant physiological stability, preventing pain, strongly promoting infant growth and neurobehavioral development, improving breastfeeding, reducing neonatal morbidities, parental anxiety, neonatal stress scores, nosocomial infections, hypothermia and length of stay. Earlier and longer contact provides greater benefit and studies have alluded to a dose-response relationship.

SSC and KMC have been shown to confer several benefits to the preterm brain with increased brain maturation, improved connectivity, improved cerebral blood flow, and a positive influence on brain networks and synaptic efficacy up to adolescence. KMC is also shown to increase oxytocin levels and decrease cortisol reactivity in term infants. Studies elude to a lasting impact on self-regulation skills later in infancy, improved executive functioning at 5 and 10 years of life, and significant, long-lasting social and behavioural protective effects even after 20 years of the intervention. Further longer-term effect studies of KMC on cognitive and motor development, socioemotional skills, and temperament are needed.

Exposure to neonatal pain has been linked to impaired brain development in preterm infants, neonatal pain experience in animals may lead to physical damage or even death of young neurons in the brain. The activation of the hypothalamic-pituitary-adrenal (HPA) axis, in response to stressors during the critical periods of brain development, has been associated with many acute and long-term adverse bio-behavioural outcomes. KMC accelerates neurophysiological maturation of premature neonates and reduces the HPA axis response to pain and reduced maternal care leading to typical development of the HPA axis and brain with normal cognitive functioning and behavioural outcomes.

The exact biological mechanism of how KMC results in the large range of beneficial outcomes however remains largely unknown. The relatively limited sample sizes of the studies thus far, heterogeneity in strategies and outcome measures and the potential for confounding variables highlight the need for further trials with clearly defined and similar outcomes.

Breastfeeding is well known to have a range of social, emotional and health benefits for both the term and preterm infant and mother. The cognitive and developmental advantages to breastfed infants have been acknowledged in the literature as early as the 1970s.
positive impact of breastfeeding on intellectual development has subsequently been established with evidence of a lasting impact through to adulthood.\textsuperscript{89} Improvement in cognitive development is even greater in preterm and very low birth weight infants.\textsuperscript{90,91}

Adolescents that were breastfed in infancy have an increase in total white matter, sub-cortical grey matter and parietal lobe cortical thickness. Studies using evoked potentials suggest delayed or immature myelination of early neural pathways in formula-fed infants as compared to breastfed ones. More recently, imaging studies of preterm infants at term equivalent age demonstrate an association between higher exposure to breast milk feeding with improved microstructural properties of white matter tracts and cerebral structural connectivity. These effects had a dose-dependent relationship with breast milk exposure.\textsuperscript{92,93}

**Family-Centred Care** (FCC) interventions are based on the principle of recognising the parents as integral members of the care team, who work in partnership and collaboration with healthcare professionals in the planning and delivery of their infant’s care.\textsuperscript{64}

By encouraging parental presence, FCC facilitates parent-infant closeness, including skin-to-skin contact and breastfeeding, and synchronises cortisol variation between the preterm infant and mother. Several mechanisms maybe involved in improving outcomes from parent-infant contact such as improved sleep, pain management with moderated needs for pain medication, infant touch and massage with resultant brain growth-promoting factors and oxytocin, interactive communication with the parent, positive auditory experience,\textsuperscript{94} all enhancing neurological, neurobehavioural and neurocognitive outcomes in preterm infants.\textsuperscript{71,95} Close physical and emotional contact between parent and preterm infant, also reduces short and long term parental stress\textsuperscript{96} and decreases infant's cortisol levels and pain responses.\textsuperscript{71}

EEG assessments indicate that cerebral cortical development is promoted by parent-infant interaction and brain maturation may also be accelerated, particularly in frontal brain regions, which have been shown to be involved in regulation of attention, cognition and emotion; domains known to be deficient in preterm infants.\textsuperscript{97} Other reported benefits of FCC include reduction in length of stay, and moderate to severe bronchopulmonary dysplasia, which in itself is a strong predictor of poor neurodevelopmental outcome.\textsuperscript{64,65}

**Family Integrated Care** (FIC) is a more recent concept which draws on all the essential elements of Family-Centred Care but advances it further by enabling parents to become their infant's primary caregiver and to actively participate in their care. In a recent large multi-centre randomised controlled trail, FIC significantly improved infant weight gain and parental stress
and anxiety. Other centres have reported improvement in breastfeeding rates and length of stay.

CONCLUSIONS:
The third trimester is a critical period of brain development. Prematurity and its related experiences can push the trajectory of the developing brain to an atypical path during this most vulnerable period, which is spent largely on the NICU, in the absence of positive maternal influences. FCC and developmental care promote parent-infant interaction and are safe and feasible in most settings and socioeconomic conditions. They have the potential to enhance the preterm baby experience and improve neurodevelopmental outcomes globally in the high-risk preterm population. These practices should be considered part of the neuroprotection care bundle and are important considerations in future clinical trials of pharmacological therapies for brain protection in preterm infants.

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