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Wyeth Nutrition SCIENCE CENTER

Nourishing the Growing Brain: Early Nutrition for Preterm Infants

Approximately, 1 out of 10 infants are born preterm (before 37 weeks of gestation) every year.[1] Preterm infants are at a higher risk of adverse neurodevelopmental outcomes in later stages of life as compared to term infants.[2] The risk of neurodevelopmental impairments is around 25% in extremely preterm infants (born before 28 weeks of gestation. Multiple studies have highlighted that adequate nutrition in preterm infants during the early stages of life can be the key to healthy brain development and reduced risk of cognitive, behavioural, and neurodevelopmental outcomes.[3,4]

Early life brain development: Constructing a foundation for future

The first 1000 days (270 days of pregnancy+730 days [2 years] after birth) are a critical window of mental growth and development of infants.[5] Most importantly, the brain undergoes a rapid growth trajectory during the third trimester of pregnancy where the brain volume is increased by around 140%.[3] This phase of pregnancy can be marked by multiple brain developmental phenomena such as myelination, neural migration, synaptogenesis, and so on, as shown in Figure 1.[6] Healthy brain development in the early stages of life forms the foundation of complex pathways and behaviours in later stages of life.[7] The brain development of a child during this phase of life may have long-term consequences on learning, education, and mental health.[8]

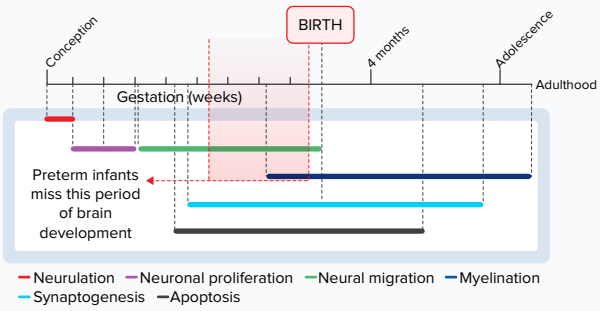

Figure 1: Major events of brain development from gestation to adulthood.

Preterm vs. term infants: Examining the differences in brain development

Studies have documented neurodevelopmental delays in preterm infants as compared to their term counterparts. This might be related to the altered brain structure and morphology of preterm infants.[9] The developmental trajectory of preterm infants is altered from that of term infants during the "third trimester" resulting in reduced global as well as regional growth of the brain.[10] Late preterm infants have been reported to have lower brain volume, differentiated myelination, and neural connectivity than infants born at full term.[9,11,12]

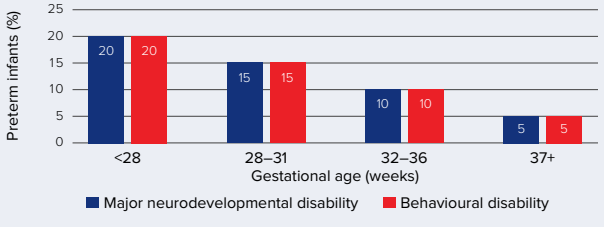

Figure 2: Rate of neurodevelopmental disabilities and behavioural disorders at different gestational ages.

Additionally, research shows that the gestational age of infants is positively associated with a reduced risk of neurodevelopmental disabilities and behavioural disorders.[13] Further, neurodevelopmental delays due to preterm birth may also have a direct effect on the cognitive development, and social–emotional competence of children in later stages of life (Figure 2).[14]

Nutrients that support neurocognitive development

The impact of nutrition on brain development has been highly studied over the course of time. Apart from adequate protein and energy intake, a higher intake of other nutrients such as vitamins, minerals, healthy fats, as well as sphingomyelins, has shown promising neurodevelopmental benefits for preterm infants.[4,15]

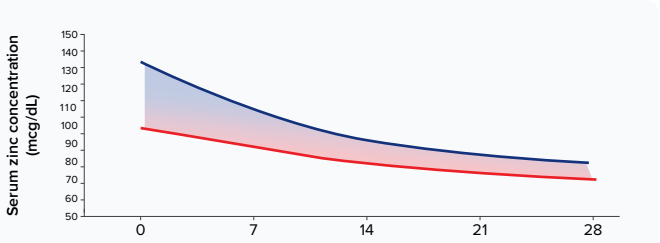

Figure 3: Rate of zinc depletion in preterm infants during the first month after birth.

1. Important macro- and micronutrients

Here is a list of important macro- as well as micronutrients that have shown to have a promising effect on the neurodevelopment of preterm infants:

Protein: Protein intake during the first 7–10 days of life has shown a positive association with the neurodevelopment of preterm infants. Around 3–4 g/kg/day is considered a safe and effective dose of protein for supporting adequate neurodevelopment. Among the amino acids, glutamine supplementation has also been shown to increase the brain volume in preterm infants during the later stages of life.[4,16]

LCPUFAs: As the primary DHA (a long-chain polyunsaturated omega-3 fatty acid) accretion occurs during the third trimester of pregnancy, preterm infants are at a higher risk of DHA and essential fatty acid deficiency.[17,18] DHA plays a vital role in myelination, differentiation and growth of neurons, and neurotransmission.[19] Clinical studies have shown that infant feeds comprising 0.3% DHA and 0.6% AA (long-chain polyunsaturated omega-6 fatty acid) can contribute to healthy brain development in preterm infants.[20]

Iron: Iron is essential for brain development, myelination, and neurotransmission. Most of the iron accumulation in infants occurs during the third trimester of pregnancy. Thus, preterm infants are at risk of iron deficiency. Iron-fortified formulas or feeds that can provide 1–2 mg/kg/day of iron have shown the potential to improve neurocognitive outcomes in preterm infants as breastmilk alone may not be able to fulfil their high iron requirements.[4,21]

Zinc: Zinc plays an important role in brain growth and development. Most of the *in utero* zinc accretion occurs during the third trimester. Preterm infants are, thus, at a higher risk of zinc deficiency. Serum zinc concentration may rapidly decrease in these infants in the absence of zinc supplementation, as shown in Figure 3.[22,23]

Other micronutrients: Preterm infants are at a higher risk of iodine and folate deficiencies that might lead to adverse neurodevelopmental outcomes.[24,25]

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2. Sphingomyelin

Sphingomyelin (SM) supports brain myelination, a process closely associated with cognitive maturation.[26] An 8-week intervention after birth using a formula containing 20% SM from milk phospholipids showed improved neurodevelopmental outcomes in intellectual abilities, sustained attention, and behaviour compared to 13% SM from egg phospholipids.[4]

Breastmilk and infant formula for healthy brain development of preterm infants[27]

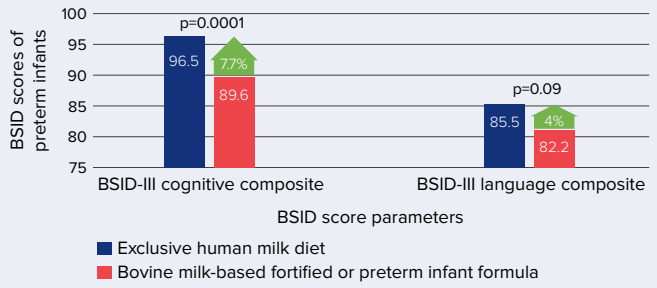

Figure 4: Impact of exclusive human milk diet vs. preterm infant formula on the brain development of preterm infants – Neurodevelopmental outcomes at 18–22 months of age.

Exclusive breastfeeding has been shown to improve cognitive neurodevelopmental scores in preterm infants as compared to preterm infant formulas (Figure 4). Further, research has also shown a positive association between prolonged breastfeeding and cognitive abilities as well as executive brain function scores (working memory, mental flexibility, self-control, etc.) during infancy.[4,28]

Optimizing enteral and parenteral nutrition to support the development of preterm infants

Improving early parenteral and enteral nutrition to reduce energy and nutrient deficits may improve brain growth, brain maturation, and neurodevelopment. The current evidence indicates some benefits of enriched enteral and parenteral nutrition in preterm infants, although the evidence from RCTs is limited.[4]

Key Points

- The first 1000 days of a child's life, from pregnancy to 2 years after birth, are crucial for brain and mental growth and development. Brain development during the third trimester of pregnancy has long-term consequences on learning, education, and mental health.
- Preterm birth can lead to neurodevelopmental delays and altered brain structure, affecting cognitive development and social–emotional competence in later stages of life.
- Adequate protein and energy intake, along with a higher intake of important nutrients such as LCPUFAs, iron, zinc, and SMs have shown promising neurodevelopmental benefits.
- Exclusive breastfeeding has been linked to improved cognitive neurodevelopmental scores in preterm infants compared to preterm infant formulas, with prolonged breastfeeding also positively associated with cognitive abilities during infancy.
- Improving early parenteral and enteral nutrition can potentially reduce energy and nutrient deficits, leading to improved brain growth, maturation, and neurodevelopment in preterm infants.

AA: Arachidonic acid; DHA: Docosahexaenoic acid.

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