International Journal of Nutrition and Food Sciences
2023; 12(5): 148-157
http://www.sciencepublishinggroup.com/j/ijnfs
doi: 10.11648/j.ijnfs.20231205.15
ISSN: 2327-2694 (Print); ISSN: 2327-2716 (Online)

Review Article

The Necessity of Providing Optimal Micronutrients to the Preterm Low Birth Weight Infants for Preventing Long-Term Health Complications in Perspective of Bangladesh

Azizul Hossain[1, *], Abu Nayeem Mohammad Shahidul Islam Bhuiyan[1], Iftekhar-Ul-Haque Khan[1], Mohammad Yousuf Faruqi Parvez[2], Farah Chowdhury[3], Firoza Akter[3], Shanta Datta[3], Ziaur Rahman[3]

[1]Pediatric Department, Cumilla Medical College and Hospital, Cumilla, Bangladesh
[2]Pediatric Department, SA Health Care, Amanbazar, Chattagram, Bangladesh
[3]Pediatric Department, Chattagram Maa Shishu O General Hospital, Chattagram, Bangladesh

Email address:
tasbiul@yahoo.com (Azizul Hossain), riponbhuiyan.bd@gmail.com (Abu Nayeem Mohammad Shahidul Islam Bhuiyan), iftekhar1284jx@gmail.com (Iftekhar-Ul-Haque Khan), myfp40@gmail.com (Mohammad Yousuf Faruqi Parvez), chyfarah@gmail.com (Farah Chowdhury), dr.feroza1979@gmail.com (Firoza Akter), shantad782@gmail.com (Shanta Datta), ziaul.rahman123@gmail.com (Ziaur Rahman)

To cite this article:
Azizul Hossain, Abu Nayeem Mohammad Shahidul Islam Bhuiyan, Iftekhar-Ul-Haque Khan, Mohammad Yousuf Faruqi Parvez, Farah Chowdhury, Firoza Akter, Shanta Datta, Ziaur Rahman. The Necessity of Providing Optimal Micronutrients to the Preterm Low Birth Weight Infants for Preventing Long-Term Health Complications in Perspective of Bangladesh. *International Journal of Nutrition and Food Sciences*. Vol.12, No. 5, 2023, pp. 148-157. doi: 10.11648/j.ijnfs.20231205.15

Received: September 17, 2023; **Accepted**: October 04, 2023; **Published**: October 30, 2023

Abstract: Preterm newborns are more likely to experience malnutrition because they have undeveloped body systems and lower levels of body storage for nutrients. Complementary feeding that is out of balance increases the risk of nutritional excesses and deficiencies. However, there is little information on their dietary needs after leaving the hospital. Appropriate micronutrient intake should be taken into account when planning supplemental feeding because of their crucial role in supporting numerous bodily processes. This narrative review provides an overview of the requirements for long-chain polyunsaturated fatty acids (LCPUFAs), iron, zinc, vitamin D, calcium, and phosphate supplementation in preterm babies during supplemental feeding. The scientific community is beginning to comprehend the benefits of giving iron and vitamin D supplements to specific subgroups of preterm infants. On the other hand, there isn't enough information yet to provide precise suggestions for the inclusion of LCPUFAs, zinc, calcium, and phosphorus. But the preterms' health depends on these micronutrients: While calcium and phosphorus supplements are important to prevent metabolic bone disease (MBD) in preterm infants, LCPUFAs can promote the development of the retina and the brain. While we wait for consensus on these micronutrients, it is clear how knowledge of the heterogeneity in the premature population may help modify nutritional planning in connection to the growth rate, comorbidities, and detailed clinical history of the preterm baby.

Keywords: Preterm Low Birth Weight Infants, Optimizing Nutrition, Enteral Feeding, Expressed Breast Milk, Complementary Feeding, Micronutrients, Fortification

1. Introduction

Preterm birth rates have increased over the past 20 years in 62 of the 65 nations with trend data available, according to the World Health Organization. Every year, problems from premature delivery kill over a million kids. The major cause of neonatal mortality and the second most common cause of death in children under the age of five, behind pneumonia, are preterm births. Additionally, preterm birth survivors are more likely to experience negative progressive infirmities [1]. Compared to their term peers, they have greater rates of unfavorable health outcomes in early adulthood [2].

Fetal development and infancy offer a key temporal window for predicting future health since many organs are extremely flexible at this period of development and are sensitive to diet and other environmental signals [3]. The normal growth and development of newborns depends on their dietary needs being met, but nutritional shortfalls, even those that last only a short time, can have detrimental effects on long-term health [4]. Due to the lower level of nutrients in the body stores at birth, the immaturity of the body systems, the requirement for rapid postnatal growth, and the occurrence of acute illnesses, preterm infants (born before 37 weeks of gestational age) have high nutritional requirements in terms of both macronutrients and micronutrients. Preterm babies should get appropriate and timely nutritional supplements, according to recommendations [5, 6], in order to avoid malnutrition and limit postnatal development retardation. This will lessen the need for rapid catch-up growth, which is associated with poor metabolic outcomes in the late stages. According to an increasing body of evidence, proper nutritional therapy greatly reduces the risk of contracting comorbid conditions including sepsis, metabolic bone disease (MBD), and severe retinopathy of prematurity while improving neurodevelopmental outcomes [7, 8].

It is commonly accepted that preterm neonates require early enteral and parenteral support as the cornerstone of their nutritional care throughout their hospital stay [9, 10]. Breast milk is explicitly recommended as the primary choice for enteral feeding due to its many health benefits [11, 12]. However, research on the appropriate nutritional management for preterm neonates after hospital discharge is scant [13].

According to the kind and rate of catch-up growth, nutritional requirements, and neurodevelopmental and metabolic problems, it has been suggested to use a tailored approach [9]. The supplemental feeding phase has received little attention in this context, despite the fact that it increases the risk of nutritional excesses and deficiencies in preterm children, particularly if they have postnatal growth retardation and aberrant body composition [14]. Although recommendations for term infants cannot be applied to preterm infants due to their specific dietary needs and neurological trajectories, which include feeding problems [9, 14, 15], there are no clear guidelines for the introduction of supplementary meals to preterm newborns. Preterm infants' prior feeding history (exclusive breastfeeding, fortification, use of post-discharge or standard formulas), growth patterns, including the achievement of catch-up growth, and the presence of eating difficulties, should all be taken into consideration when planning the introduction of complementary foods [9]. Preterm children are given iron and multivitamin supplements after being released from the hospital, while the length of time and amount of these supplements varies substantially [18].

2. Nutrition: A Key Aspect Affecting Preterm Infants' Developmental Outcomes

For growth, metabolism, and immunity in a preterm neonatal low birth weight (LBW) kid, feeding is essential [19-21]. Poor nutrition is linked to slower head growth in preterm infants; this leads to worse psychomotor and cognitive development, greater incidence of cerebral palsy, and autism [22]. Preterm babies' abnormal weight and growth are strongly linked to poor neurodevelopmental outcomes in adulthood [23]. Additionally, according to Barker's theory [24, 25], As adults, type 2 diabetes, hypertension, and coronary heart disease are more likely to affect neonates with LBW.

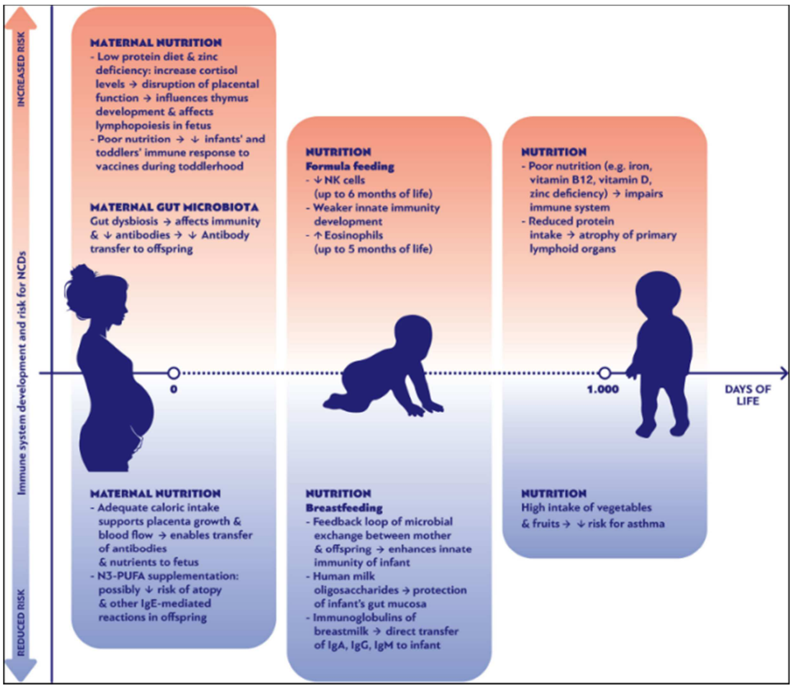

Figure 1. *Nutrition-related factors influencing the immune system's growth and the risk of noncommunicable illnesses during the first 1000 days of life [96].*

3. Important Micronutrients for the Preterm Low Birth Weight Infants

3.1. Iron – An Essential Micronutrient for Pre-Term LBW Infant

Due to its critical function in the synthesis of hemoglobin (Hb), oxygen transport, and a number of enzymatic activities, including the creation of cellular energy, iron is regarded as an important nutrient [26]. The bulk of the iron supply increases during the third trimester of pregnancy as a result of active transport in the placenta. A term newborn's iron concentration is typically approximately 75 mg/kg, of which 75-80% is found in hemoglobin (Hb), 10% is present in tissues as iron-containing proteins (myoglobin and cytochromes), and the remaining 10-15% is stored iron (ferritin and hemosiderin) [26]. How much iron is stored at birth depends on prenatal factors including the mother's iron status and the possibility of iron transfer to the baby, as well as perinatal events like cord clamping. Delaying cord clamping has been hypothesized to improve perinatal Hb transfer and improve the iron status of both term and preterm neonates [27]. A good iron status at birth is essential for maintaining iron homeostasis throughout the first 6–9 months of life, when a physiological decline occurs due to poor absorption and the comparatively low content in breast milk [28].

The iron reserves of preterm newborns at delivery are lowered according to gestational age and birth weight because prematurity prevents placental transfer [29]. Intrauterine growth retardation, maternal hypertension, diabetes, and iron deficiency anemia in mothers may all have an impact on the fetal iron storage [29, 30]. The iron reserves of the preterm newborn may be further depleted by additional pregnancy-related variables such repeated pregnancies and obesity [31].

In actuality, all of these diseases, which are frequently linked to preterm delivery, might result in chronic placental insufficiency, which reduces prenatal iron transport. Additionally, the body's iron reserves may be further depleted by preterm newborns' quick growth recovery, the requirement to start erythropoiesis early in development, and frequent infusions [32].

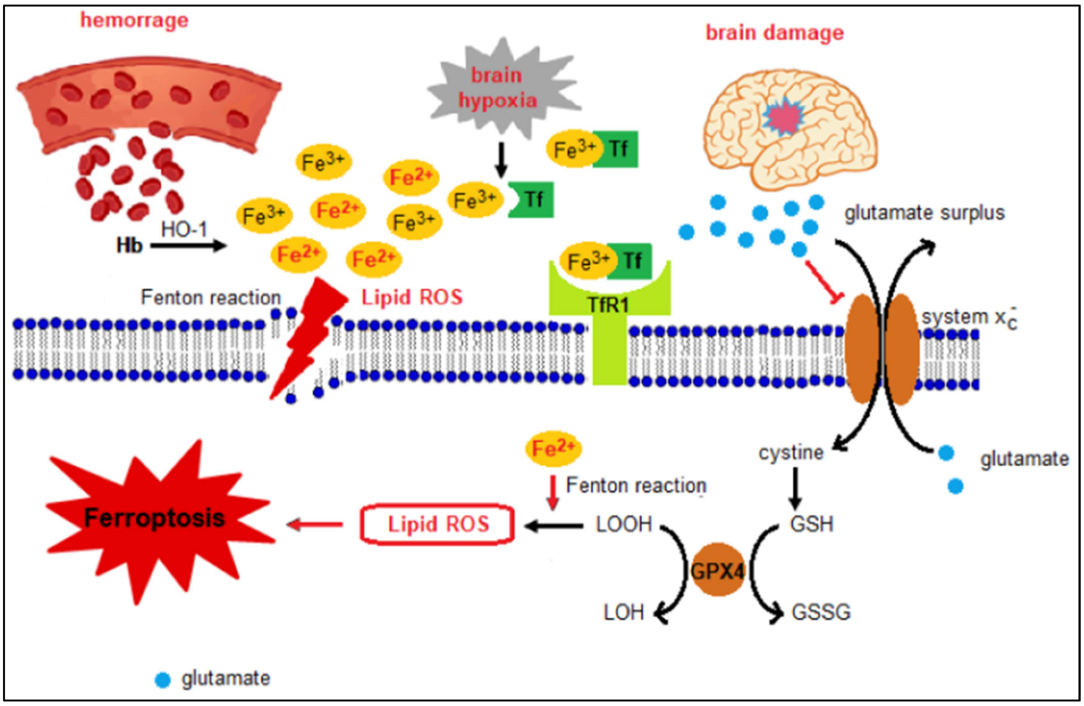

Figure 2. *Oxidative Stress and Iron Homeostasis Disruption in Preterm Newborns [97].*

Blood transfusions may be risky for preterm babies given that infants with extremely low birth weight (ELBW) and very low birth weight (VLBW) get at least one blood transfusion at least once during their hospital stay [33]. More rigorous blood transfusion rules have been asked for in recent years, notably for the extremely preterm neonates, as a result of the correlations between early exposure to blood transfusions and greater mortality and short-term morbidities that have been documented [34]. Planning iron supplementation in this situation, including the amount and timing of blood transfusions as well as the kind of feeding, should consider the preterm newborn's medical history. Feeding purely on human milk does not provide such high iron requirements if post-discharge formula milk is not supplemented or if it is not fortified [35].

3.2. Zinc Plays Key Role for Preterm Low Birth Weight Infants

Zinc plays a crucial role in every phase of the cellular life cycle thanks to its catalytic, structural, and regulatory capabilities. It is essential for tissue integrity, particularly at the respiratory and gastro-intestinal levels, and supports immunological regulation (phagocytosis and cellular immunity) [36], bone development, growth hormone control, gustatory function, and appetite [37, 38, 39]. Zinc must be consumed often since the body cannot produce it and does not have an appropriate mechanism for storing and releasing it [38, 40]. Over the first several months of breastfeeding, zinc content progressively decreases from 8–12 mg/L in colostrum to 1-3 mg/L at one month of age [41]. Surprisingly, through the first two months of corrected age, it has been shown that the zinc content in preterm human milk is much lower than that in term milk [26, 42]. Zinc concentrations in infant formula range from 1.5 to 6 mg/L.

At 40 weeks post-conceptional age, preterm newborns have lower zinc levels than term neonates because the blood zinc content in preterm infants falls throughout the first few months of life [41]. Due to the absence of reliable indicators for zinc status, the diagnosis of zinc insufficiency is not simple. The strongest indicator of zinc shortage is still serum zinc concentration evaluation, notwithstanding some of its drawbacks [41, 43].

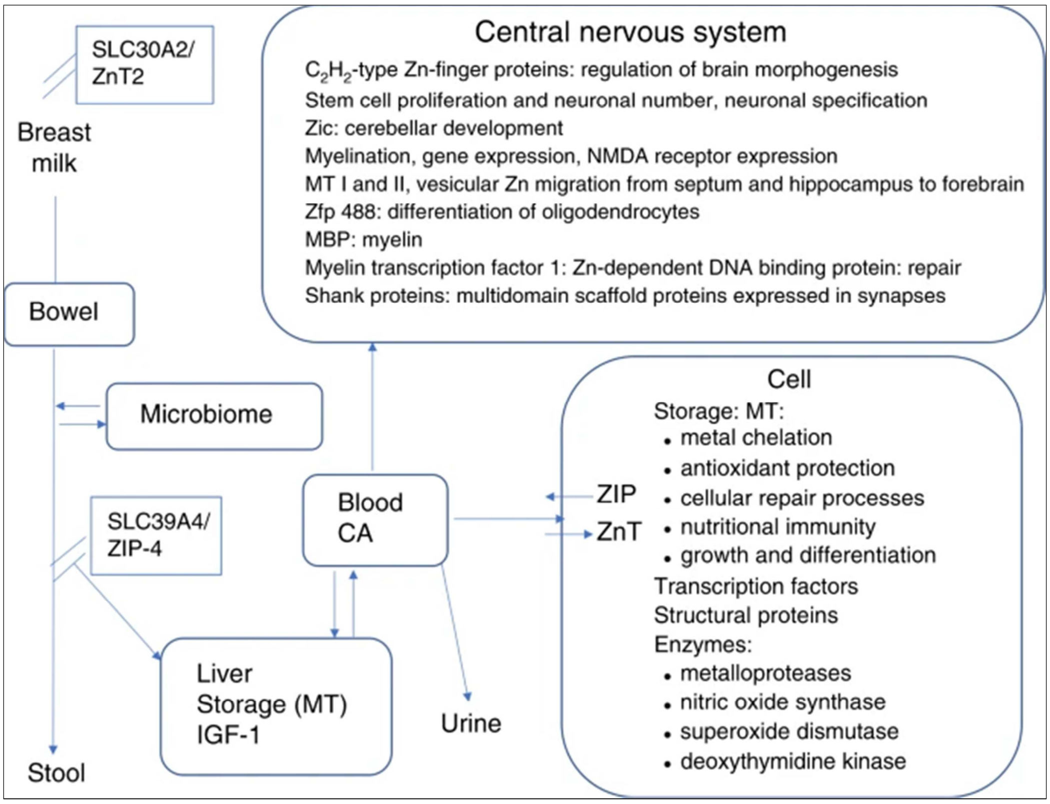

Figure 3. *Zinc role in growth and brain growth and development [98].*

Regarding the dosage, frequency, and duration of preventive zinc supplementation, there is no consistent guidance [44]. It must be remembered that when supplemented, zinc might affect the absorption of other microelements, such as iron and copper, and vice versa [45]. Uncertainty surrounds the mechanism through which copper shortage and anemia may be caused by zinc [46]. According to a research by Griffin et al., copper intakes must be increased up to 250 mcg/kg/d to maintain sufficient copper retention at the zinc intakes recommended by the authors (1.8-2.4 mg/kg/d for formula-fed newborns and 2.3-2.4 mg/kg/d for breastfed infants) [47].

Based on the information currently available [47], it is recommended to give zinc supplements throughout the first year of life because zinc does not have pro-oxidant qualities and seldom can an overdose create negative effects [48]. In particular, preterm breastfed infants with stunted development should be thought about using zinc supplements [49].

3.3. Early Neonatal Hypocalcemia Is a Common Problem in Prematurely Born Infants and the Role of Calcium and Phosphorus

In the third trimester of pregnancy, the majority of bone mineralization takes place [50]. In actuality, osteoblasts function during this time to deposit 80% of the bone mineral stock. The obtainability of calcium and phosphorus through active placental transport, which results in a physiological "fetal hypercalcemia" necessary for bone development, is a need for this process. 120 mg/kg/day of calcium and 60 mg/kg/day of phosphorus are transferred to the embryo through the placenta [51]. When breathing begins at birth, blood pH rises, which lowers the amount of calcium ions in the blood and raises parathormone levels. The beginning of mineral resorption from the bone that occurs along with this process results in a drop in bone mineral density that lasts for up to 6 months of age [52].

However, in term babies, bone integrity is maintained. On the other hand, preterm newborns have a much higher risk of developing osteopenia. This process is abruptly stopped with a premature delivery, which effectively prevents the creation of bone mineral. This deficiency becomes worse after a baby is born because of the transition to extrauterine life. In truth, in addition to the mechanisms already mentioned for term newborns, the absorption of calcium in preterm infants is additionally hampered by poor gastrointestinal tolerance and motility as well as by the use of drugs that increase its excretion, such as diuretics (furosemide) and theophylline [52].

Metabolic bone disease (MBD) is characterized by hypophosphatemia, hyperphosphatasemia, and, in later stages, radiological findings of bone demineralization or clinical features like softening or fractures of the ribs and other bones, enlargement of the cranial sutures, frontal bossing, and rickets [53]. Preterms are more likely to develop this condition. The combination of these risk factors explains why preterms are more vulnerable to MBD. MBD reportedly affects 23% of infants with very low birth weights (VLBW 1500 g) and 55% of newborns with very low birth weights (ELBW 1000 g), according to studies. In addition, babies born prematurely—before 28 weeks of gestation—seem to experience it more commonly [54].

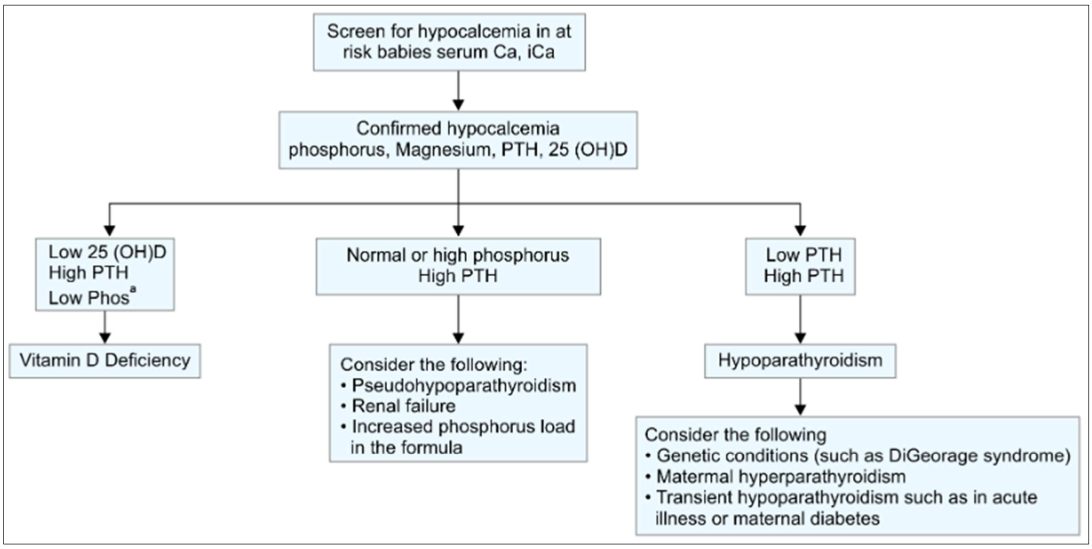

Figure 4. *Diagnostic evaluation for hypercalcemia [99].*

Given the importance of these two minerals for the health of the preterm baby and the increased risk of developing MBD, it seems reasonable to urge that blood tests be used to evaluate the metabolic status of the bone during the follow-up after discharge. This may lead to an early diagnosis of osteopenia and the start of adequate supplements. Additionally, it can help identify kids who could require greater or longer-term supplementation due to dietary variances, coexisting diseases, or drug use.

4. The Prevalence of Vitamin D Deficiency in Preterm Infants Is High in Several Parts of the World

Over the past several years, the significance of vitamin D and its supplementation has increased. Additional metabolic processes labeled as "extra-skeletal" have also been thoroughly studied, in addition to its well-known effect on bone mineralization [55]. The focus of research has subsequently shifted to how this vitamin affects tissues other than the skeletal system. According to some research, vitamin D is a hormone. Researchers have established that it can regulate the expression of more than 1250 genes [56]. In fact, among the numerous recently discovered functions, we find defense against cardiovascular risk factors [59], regulation of inflammatory function [58], and anti-tumor activities [57] through a variety of metabolic pathways that are now poorly understood [57].

The majority (>90%) of vitamin D is created by skin exposure to sunlight, with little or no effect from food intake. The generation of vitamin D is impaired during the winter months due to a reduction in solar hours, despite the high efficiency of vitamin D synthesis from sunlight exposure [60]. Additionally, the American Academy of Pediatrics (AAP) cautions against exposing young children who are unprotected from the elements and under the age of six months to direct sunlight [61].

Epidemiological studies have shown that almost 50% of neonates have hypovitaminosis D [55]. This lack of vitamin D is categorized as an insufficiency when the blood concentration of 25-OHD is between 20 and 30 ng/mL, and as a deficiency when it is less than 20 ng/mL [62]. The first year of life is crucial for preventing the vitamin D shortage. The positive link between cordonal or neonatal levels of 25-OHD [63] shows that the maternal vitamin D status directly influences the neonatal store of vitamin D. Maternal supplementation, ethnic background, and birth season may also have an impact [62].

Because of their fast growth, infants are especially vulnerable to a vitamin D deficiency, especially if they are exclusively breastfed because human milk only provides a small amount of vitamin D (80 UI/L) to avoid deficiency. A suitable amount of vitamin D may not be provided by breast milk alone or formula milk that has been fortified with 400 UI/L of vitamin D [55].

Since neonatal storage of vitamin D is influenced by maternal condition and has a half-life of two to three weeks, prophylaxis must begin within a few days of delivery. When preterm neonates reach the term corrected age (40 weeks gestational age), the majority of Neonatal and Pediatric Societies advise to continue the same recommended dose of a term neonate (400 UI/day), as shown in Table 1.

A thorough evaluation of the risk factors for hypovitaminosis D may serve as a useful screening tool to identify a possible deficiency and start the recommended prophylaxis as soon as possible. Even higher doses of vitamin D do not seem to appear to offer a large risk of harmful effects, and an overdose is not frequent, therefore vitamin D supplementation should start in the early days of life regardless of the method of feeding and continue well into the neonatal age [55].

Table 1. *Summary of Vitamin D supplementation in preterm infants up to term corrected age [26, 32].*

AAP 2013	ESPGHAN 2010 Other	Guidelines
Birth Weight <1500 g: 200-400 IU/day Birth Weight >1500 g: 200-400 IU/day	400—800UI/day	800—1000UI/day

AAP: American Academy of Pediatrics; g: grams; UI: International Unit; ESPGHAN: European Society for Paediatric Gastroenterology Hepatology and Nutrition

5. Beneficial Role of Nutrition in Early Strategies

Long-term gains in cognitive function and verbal intelligence quotient (IQ) scores of preterm neonates have been associated to better nutrition throughout the early postnatal periods [64, 65]. Extremely LBW infants with more protein and calorie intake in the first week after birth scored higher on the mental development index and were less likely to experience growth retardation at 18 months [66]. Early and higher protein and calorie intake in preterm infants has also been associated with faster head growth and an increase in head circumference [67, 68]. Additionally, an increase in head size has been positively associated with improved cognitive results [69]. Early aggressive nutritional enteral and parenteral support may be given to preterm newborn LBW newborns in order to improve growth and developmental outcomes [70].

6. Feeding Process for Preterm LBW Infants

6.1. Growth Rate with Standard Nutritional Practices

Basic enteral feeds (10 mL/kg/day), donor milk (in the absence of mother milk), enhanced human milk, feed advances of 20 mL/kg/day, and parenteral nutrition with amino acids and lipids are frequently given to preterm neonates [71]. The development of preterm neonates may not always go as planned, even when standard protocols are followed. The dietary strategies now employed to treat intrauterine growth restriction (IUGR)/preterm newborns cannot prevent postnatal growth restriction [72]. Extrauterine growth restriction (EUGR) is a significant problem in premature LBW newborns, with incidence rates for head circumference, weight, and length of around 28, 34, and 16%, respectively [73]. The growth rate of preterm and extremely LBW neonates hospitalized in the neonatal critical care unit has a significant impact on neurodevelopmental and growth outcomes in later life and consequences for neurodevelopment and growth in later life [74].

6.2. Present Nutritional Strategies

EBM, EBM that has been supplemented, and formula milk are the enteral feeding alternatives for preterm newborns (75).

6.2.1. Expressed Breast Milk

Due to its many intrinsic benefits, breast milk should be the optimal milk for supplying nourishment to premature LBW newborns.

Table 2. *Consensus recommendations on the use of mother's milk for feeding preterm infants [76-92].*

Consensus recommendations on the use of mother's milk for feeding preterm infants:
• The first choice of human milk for feeding preterm infants is expressed breast milk from the mother; the second choice is donor pasteurized human milk.
• "Donor pasteurized human milk" should be the term used for donor milk.
• A pasteurizer should be used for pasteurization of human milk; unpasteurized milk should not be used in case of donor human milk.
• Donor pasteurized human milk should be screened for human immuno-deficiency virus (HIV), hepatitis C virus (HCV), hepatitis B antigen (HBsAg). venereal disease, and bacteria, using relevant tests/cultures.
• The donor mother should also be screened for HIV, HCV, HBsAg, and venereal disease within 6 months of donating milk.
• If milk banks exist locally, pooled milk may be used, provided proper consent has been obtained.
• Milk banks should liaise with agencies for pasteurization of pooled small aliquots of breast milk.
• Donor human milk may be steed at -20°C for 6 months, preterm infants should not be fed milk stored for more than 3 months.
• Although the human milk analyzer is a useful tool to analyze the nutrient content of human milk and enable subsequent fortification, it is currently being used as only a research tool and not in day-to-day clinical practice. The standard fortification method is recommended in daily clinical settings.

Although there are several benefits of giving human milk, it is crucial to ascertain whether it can satisfy the greater nutritional requirements of premature newborns. ESPGHAN states that formula milk made specifically for preterm newborns or supplemented human milk, ideally from the infant's own mother, are the best sources of nourishment for premature children [93].

6.2.2. Fortified Human Milk

When EBM is insufficient to meet an infant's nutritional demands, fortifying breast milk helps [76]. The idea behind fortification is to raise the nutritional concentration to levels where the infant's demands can be satisfied with normal feeding quantities [94]. Fortification may involve a single nutrient (mono-component) or a number of nutrient combinations (multi-component). According to the National Neonatology Forum of India [95], infants who are under 32 weeks gestational age or who were born weighing less than 1,500 g should be given multicomponent fortification if they are not gaining weight despite receiving full volumes of breast milk (up to 180-200 mL/kg/day).

6.2.3. Formula Milk

Formula milk is created particularly to satisfy the needs of LBW newborns and provides all vital elements [76].

7. Conclusions

A higher potential for morbidity and death is implied by prematurity. To prevent negative metabolic consequences, preterm babies must get early, appropriate nutritional supplementation. The provision of iron, zinc, calcium, phosphate, vitamin D, and LCPUFAs in the preterm newborn after discharge and during the first 12 months of life is still not a topic of widespread worldwide consensus. However, little to no negative consequences resulting from their supplementation are currently documented in the literature. Additionally, as our understanding of these micronutrients grows, so do the favorable benefits of these compounds on the body as a whole.

We believe it's safe to suggest that giving these supplements to preterm newborns can have more positive effects than negative ones. This is especially true for preterm babies who are breastfed. For this group, breast milk is still the best option, but it is obvious that the concentration of several micronutrients, particularly LCPUFAs, is solely reliant on maternal diet and deposition. This review emphasizes the need for sizable, randomized studies to address these concerns and the knowledge gap that exists in the information on premature supplementing.

References

[1] March of Dimes, Partnership for Maternal Newborn and Child Health, Save the Children, World Health Organization. Howson CP, Kinney MV, Lawn JE, editors. *Born Too Soon: the Global Action Report on Preterm Birth* (2012). Available from: http://www.who.int/pmnch/media/news/2012/201204_born-toosoon-report.pdf

[2] Doyle LW, Anderson PJ. Adult outcome of extremely preterm infants. *Pediatrics* (2010) 126: 342–51. doi: 10.1542/peds.2010-0710.

[3] Colombo, J.; Gustafson, K. M.; Carlson, S. E. Critical and Sensitive Periods in Development and Nutrition. Ann. Nutr. Metab. 2019, 75, 34–42.

[4] Langley-Evans, S. C. Nutrition in Early Life and the Programming of Adult Disease: A Review. J. Hum. Nutr. Diet 2015, 28, 1–14.

[5] Ruys, C. A.; van de Lagemaat, M.; Rotteveel, J.; Finken, M. J. J.; Lafeber, H. N. Improving Long-Term Health Outcomes of Preterm Infants: How to Implement the Findings of Nutritional Intervention Studies into Daily Clinical Practice. Eur. J. Pediatri. 2021.

[6] Cooke, R. J. Improving Growth in Preterm Infants during Initial Hospital Stay: Principles into Practice. Arch. Dis Child. Fetal Neonatal Ed. 2016, 101, F366–F370.

[7] Gidi, N. W.; Mekasha, A.; Nigussie, A. K.; Goldenberg, R. L.; McClure, E. M.; Worku, B.; Amaru, G. M.; Tazu Bonger, Z.; Demtse, A. G.; Kebede, Z. T.; et al. Preterm Nutrition and Clinical Outcomes. Glob. Pediatric Health 2020, 7, 2333794X2093785.

[8] Cormack, B. E.; Harding, J. E.; Miller, S. P.; Bloomfield, F. H. The Influence of Early Nutrition on Brain Growth and Neurodevelopment in Extremely Preterm Babies: A Narrative Review. Nutrients 2019, 11, 2029. [CrossRef]

[9] Crippa, B. L.; Morniroli, D.; Baldassarre, M. E.; Consales, A.; Vizzari, G.; Colombo, L.; Mosca, F.; Giannì, M. L. Preterm's Nutrition Sfrom Hospital to Solid Foods: AreWe Still Navigating by Sight? Nutrients 2020, 12, 3646.

[10] Hay, W. W. Nutritional Support Strategies for the Preterm Infant in the Neonatal Intensive Care Unit. Pediatric Gastroenterol. Hepatol. Nutr. 2018, 21, 234–247. [CrossRef] [PubMed]

[11] Cerasani, J.; Ceroni, F.; De Cosmi, V.; Mazzocchi, A.; Morniroli, D.; Roggero, P.; Mosca, F.; Agostoni, C.; Giannì, M. L. Human Milk Feeding and Preterm Infants' Growth and Body Composition: A Literature Review. Nutrients 2020, 12, 1155.

[12] Boquien, C.-Y. Human Milk: An Ideal Food for Nutrition of Preterm Newborn. Front. Pediatr. 2018, 6, 295.

[13] Morgan, J. A.; Young, L.; McCormick, F. M.; McGuire, W. Promoting Growth for Preterm Infants Following Hospital Discharge. Arch. Dis Child. Fetal Neonatal Ed. 2012, 97, F295–F298. [CrossRef] [PubMed]

[14] Giannì, M.; Bezze, E.; Colombo, L.; Rossetti, C.; Pesenti, N.; Roggero, P.; Sannino, P.; Muscolo, S.; Plevani, L.; Mosca, F. Complementary Feeding Practices in a Cohort of Italian Late Preterm Infants. Nutrients 2018, 10, 1861. [CrossRef] [PubMed]

[15] Baldassarre, M. E.; Giannì, M. L.; Di Mauro, A.; Mosca, F.; Laforgia, N. Complementary Feeding in Preterm Infants: Where Do We Stand? Nutrients 2020, 12, 1259. [CrossRef] [PubMed]

[16] Obbagy, J. E.; English, L. K.; Psota, T. L.; Wong, Y. P.; Butte, N. F.; Dewey, K. G.; Fox, M. K.; Greer, F. R.; Krebs, N. F.; Scanlon, K. S.; et al. Complementary Feeding and Micronutrient Status: A Systematic Review. Am. J. Clin. Nutr. 2019, 109, 852S–871S. [CrossRef]

[17] Brion, L. P.; Heyne, R.; Lair, C. S. Role of Zinc in Neonatal Growth and Brain Growth: Review and Scoping Review. Pediatr. Res. 2020.

[18] Oliver, C.; Watson, C.; Crowley, E.; Gilroy, M.; Page, D.; Weber, K.; Messina, D.; Cormack, B. Vitamin and Mineral Supplementation Practices in Preterm Infants: A Survey of Australian and New Zealand Neonatal Intensive and Special Care Units. Nutrients 2019, 12, 51.

[19] Hanson C, Sundermeier J, Dugick L, Lyden E, Anderson-Berry AL. Imple-mentation, process, and outcomes of nutrition best practices for infants <1500 g. *Nutr Clin Pract* (2011) 26: 614–24. doi: 10.1177/0884533611418984.

[20] Donovan R, Puppala B, Angst D, Coyle BW. Outcomes of early nutrition support in extremely low-birth-weight infants. *Nutr Clin Pract* (2006) 21: 395–400. doi: 10.1177/0115426506021004395.

[21] Ganapathy S. Long chain polyunsaturated fatty acids and immunity in infants. *Indian Pediatr* (2009) 46 (9): 785–90.

[22] Lee KA, Hayes BC. Head size and growth in the very preterm infant: a litera-ture review. *Res Rep Neonatol* (2015) 5: 1–7. doi: 10.2147/RRN.S74449.

[23] Vinall J, Grunau RE, Brant R, Chau V, Poskitt KJ, Synnes AR, et al. Slower post-natal growth is associated with delayed cerebral cortical maturation in preterm newborns. *Sci Transl Med* (2013) 5: 168ra8. doi: 10.1126/scitranslmed.3004666.

[24] Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet* (1989) 2: 577–80. doi: 10.1016/S0140-6736(89)90710-1.

[25] Barker DJ, Eriksson JG, Forsén T, Osmond C. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol* (2002) 31: 1235–9. doi: 10.1093/ije/31.6.1235.

[26] Domellöf, M. Nutritional Care of Premature Infants: Microminerals. In World Review of Nutrition and Dietetics; Koletzko, B., Poindexter, B., Uauy, R., Eds.; S. KARGER AG: Basel, Switzerland, 2014; Volume 110, pp. 121–139. ISBN 978-3-318-02640-5.

[27] Chaparro, C. M. Timing of Umbilical Cord Clamping: Effect on Iron Endowment of the Newborn and Later Iron Status. Nutr. Rev. 2011, 69, S30–S36. [CrossRef]

[28] Cao, C.; O'Brien, K. O. Pregnancy and Iron Homeostasis: An Update. Nutr Rev. 2013, 71, 35–51. [CrossRef] Life 2021, 11, 331 11 of 13.

[29] Domellöf, M.; Georgieff, M. K. Postdischarge Iron Requirements of the Preterm Infant. J. Pediatr. 2015, 167, S31–S35. [CrossRef]

[30] Chockalingam, U. M.; Murphy, E.; Ophoven, J. C.; Weisdorf, S. A.; Georgieff, M. K. Cord Transferrin and Ferritin Values in Newborn Infants at Risk for Prenatal Uteroplacental Insufficiency and Chronic Hypoxia. J. Pediatr. 1987, 111, 283–286. [CrossRef]

[31] Baker, R. D.; Greer, F. R.; The Committee on Nutrition. Diagnosis and Prevention of Iron Deficiency and Iron-Deficiency Anemia in Infants and Young Children (0–3 Years of Age). Pediatrics 2010, 126, 1040–1050.

[32] Raffaeli, G.; Manzoni, F.; Cortesi, V.; Cavallaro, G.; Mosca, F.; Ghirardello, S. Iron Homeostasis Disruption and Oxidative Stress in Preterm Newborns. Nutrients 2020, 12, 1554.

[33] Ghirardello, S.; Dusi, E.; Cortinovis, I.; Villa, S.; Fumagalli, M.; Agosti, M.; Milani, S.; Mosca, F. Effects of Red Blood Cell Transfusions on the Risk of Developing Complications or Death: An Observational Study of a Cohort of Very Low Birth Weight Infants. Amer. J. Perinatol. 2016, 34, 88–95.

[34] Kelly, A. M.; Williamson, L. M. Neonatal Transfusion. Early Hum. Dev. 2013, 89, 855–860.

[35] Rao R, Georgieff MK. Iron therapy for preterm infants. Clin Perinatol.2009, Mar; 36(1): 27-42., doi: 10.1016/j.clp.2008.09.013. PMID: 19161863; PMCID: PMC2657918.

[36] Tuerk, M. J.; Fazel, N. Zinc Deficiency. Curr. Opin. Gastroenterol. 2009, 25, 136–143.

[37] International Zinc Nutrition Consultative Group (IZiNCG); Brown, K. H.; Rivera, J. A.; Bhutta, Z.; Gibson, R. S.; King, J. C.; Lönnerdal, B.; Ruel, M. T.; Sandtröm, B.; Wasantwisut, E.; et al. International Zinc Nutrition Consultative Group (IZiNCG) Technical Document #1. Assessment of the Risk of Zinc Deficiency in Populations and Options for Its Control. Food Nutr. Bull. 2004, 25, S99–S203.

[38] Hambidge, K. M.; Krebs, N. F. Zinc Deficiency: A Special Challenge. J. Nutr. 2007, 137, 1101–1105. [CrossRef]

[39] Harris, T.; Gardner, F.; Podany, A.; Kelleher, S. L.; Doheny, K. K. Increased Early Enteral Zinc Intake Improves Weight Gain in Hospitalised Preterm Infants. Acta Paediatr. 2019, 108, 1978–1984. [CrossRef] [PubMed].

[40] Maggini, S.; Wenzlaff, S.; Hornig, D. Essential Role of Vitamin C and Zinc in Child Immunity and Health. J. Int. Med. Res. 2010, 38, 386–414.

[41] Terrin, G.; Berni Canani, R.; Di Chiara, M.; Pietravalle, A.; Aleandri, V.; Conte, F.; De Curtis, M. Zinc in Early Life: A Key Element in the Fetus and Preterm Neonate. Nutrients 2015, 7, 10427–10446.

[42] Sabatier, M.; Garcia-Rodenas, C. L.; De Castro, C. A.; Kastenmayer, P.; Vigo, M.; Dubascoux, S.; Andrey, D.; Nicolas, M.; Payot, J. R.; Bordier, V.; et al. Longitudinal Changes of Mineral Concentrations in Preterm and Term Human Milk from Lactating Swiss, Women. Nutrients 2019, 11, 1855.

[43] Lowe, N. M.; Fekete, K.; Decsi, T. Methods of Assessment of Zinc Status in Humans: A Systematic Review. Am. J. Clin. Nutr. 2009, 89, 2040S–2051S.

[44] Pediatric Nutrition in Practice, 2nd ed.; Koletzko, B. (Ed.) World Review of Nutrition and Dietetics; Karger: Basel, Switzerland; New York, NY, USA, 2015; ISBN 978-3-318-02690-0.

[45] Maret, W.; Sandstead, H. H. Zinc Requirements and the Risks and Benefits of Zinc Supplementation. J. Trace Elem. Med. Biol. 2006, 20, 3–18.

[46] Hess, S. Y.; Brown, K. H. Impact of Zinc Fortification on Zinc Nutrition. Food Nutr. Bull. 2009, 30, S79–S107.

[47] Griffin, I. J.; Domellöf, M.; Bhatia, J.; Anderson, D. M.; Kler, N. Zinc and Copper Requirements in Preterm Infants: An Examination of the Current Literature. Early Hum. Dev. 2013, 89, S29–S34.

[48] Fewtrell, M.; Bronsky, J.; Campoy, C.; Domellöf, M.; Embleton, N.; Fidler Mis, N.; Hojsak, I.; Hulst, J. M.; Indrio, F.; Lapillonne, A.; et al. Complementary Feeding: A Position Paper by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition. J. Pediatric Gastroenterol. Nutr. 2017, 64, 119–132.

[49] Krebs, N. F. Update on Zinc Deficiency and Excess in Clinical Pediatric Practice. Ann. Nutr. Metab. 2013, 62, 19–29.

[50] Kovacs, C. S. Bone Development and Mineral Homeostasis in the Fetus and Neonate: Roles of the Calciotropic and Phosphotropic Hormones. Physiol. Rev. 2014, 94, 1143–1218.

[51] Koo, W. Maternal Calcium Supplementation and Fetal Bone Mineralization. Obstet. Gynecol. 1999, 94, 577–582.

[52] Bozzetti, V.; Tagliabue, P. Metabolic Bone Disease in Preterm Newborn: An Update on Nutritional Issues. Ital. J. Pediatr. 2009, 35, 20.

[53] Faienza, M. F.; D'Amato, E.; Natale, M. P.; Grano, M.; Chiarito, M.; Brunetti, G.; D'Amato, G. Metabolic Bone Disease of Prematurity: Diagnosis and Management. Front. Pediatr. 2019, 7, 143.

[54] Chacham, S.; Pasi, R.; Chegondi, M.; Ahmad, N.; Mohanty, S. B. Metabolic Bone Disease in Premature Neonates: An Unmet Challenge. JCRPE 2020, 12, 332–339.

[55] Saggese, G.; Vierucci, F.; Boot, A. M.; Czech-Kowalska, J.; Weber, G.; Camargo, C. A.; Mallet, E.; Fanos, M.; Shaw, N. J.; Holick, M. F. Vitamin D in Childhood and Adolescence: An Expert Position Statement. Eur. J. Pediatr. 2015, 174, 565–576.

[56] Boy, E.; Mannar, V.; Pandav, C.; de Benoist, B.; Viteri, F.; Fontaine, O.; Hotz, C. Achievements, Challenges, and Promising New Approaches in Vitamin and Mineral Deficiency Control. Nutr. Rev. 2009, 67, S24–S30.

[57] Negri, M.; Gentile, A.; de Angelis, C.; Montò, T.; Patalano, R.; Colao, A.; Pivonello, R.; Pivonello, C. Vitamin D-Induced Molecular Mechanisms to Potentiate Cancer Therapy and to Reverse Drug-Resistance in Cancer Cells. Nutrients 2020, 12, 1798.

[58] Charoenngam, N.; Holick, M. F. Immunologic Effects of Vitamin D on Human Health and Disease. Nutrients 2020, 12, 2097.

[59] de la Guía-Galipienso, F.; Martínez-Ferran, M.; Vallecillo, N.; Lavie, C. J.; Sanchis-Gomar, F.; Pareja-Galeano, H. Vitamin D and Cardiovascular Health. Clin. Nutr. 2020, S0261561420307007.

[60] Abrams, S. A. Vitamin D in Preterm and Full-Term Infants. Ann. Nutr. Metab. 2020, 76, 6–14.

[61] Council on Environmental Health and Section on Dermatology. Ultraviolet Radiation: A Hazard to Children and Adolescents. Pediatrics 2011, 127, 588–597.

[62] Saggese, G.; Vierucci, F.; Prodam, F.; Cardinale, F.; Cetin, I.; Chiappini, E.; de' Angelis, G. L.; Massari, M.; Miraglia Del Giudice, E.; Miraglia Del Giudice, M.; et al. Vitamin D in Pediatric Age: Consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, Jointly with the Italian Federation of Pediatricians. Ital. J. Pediatr. 2018, 44, 51.

[63] Kovacs, C. S. Maternal Vitamin D Deficiency: Fetal and Neonatal Implications. Semin. Fetal Neonatal Med. 2013, 18, 129–135.

[64] Isaacs EB, Gadian DG, Sabatini S, Chong WK, Quinn BT, Fischl BR, et al. The effect of early human diet on caudate volumes and IQ. Pediatr Res (2008) 63: 308–14. doi: 10.1203/PDR.0b013e318163a271.

[65] Franz AR, Pohlandt F, Bode H, Mihatsch WA, Sander S, Kron M, et al. Intrauterine, early neonatal, and postdischarge growth and neurodevel-opmental outcome at 5.4 years in extremely preterm infants after intensive neonatal nutritional support. Pediatrics (2009) 123: e101–9. doi: 10.1542/ peds.2008-1352.

[66] Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, et al. First-week protein and energy intakes are associated with 18-month devel-opmental outcomes in extremely lowbirth weight infants. Pediatrics (2009) 123: 1337–43. doi: 10.1542/peds.2008-0211.

[67] Brandt I, Sticker EJ, Lentze MJ. Catch-up growth of head circumference of very low birth weight, small for gestational age preterm infants and mental development to adulthood. J Pediatr (2003) 142: 463–8. doi: 10.1067/mpd. 2003.149.

[68] Morgan C, McGowan P, Herwitker S, Hart AE, Turner MA. Postnatal head growth in preterm infants: a randomized controlled parenteral nutrition study. Pediatrics (2014) 133: e120–8. doi: 10.1542/peds.2013-2207.

[69] Leppänen M, Lapinleimu H, Lind A, Matomäki J, Lehtonen L, Haataja L, et al. Antenatal and postnatal growth and 5-year cognitive outcome in very preterm infants. Pediatrics (2014) 133 (1): 63–70. doi: 10.1542/peds.2013-1187.

[70] Ehrenkranz RA. Early, aggressive nutritional management for very low birth weight infants: what is the evidence? Semin Perinatol (2007) 31: 48–55. doi: 10.1053/j.semperi.2007.02.001.

[71] Ziegler EE, Carlson SJ. Early nutrition of very low birth weight infants. J Matern Fetal Neonatal Med (2009) 22: 191–7. doi: 10.1080/14767050802630169.

[72] Puntis JW. Nutritional support in the premature newborn. Postgrad Med J (2006) 82: 192–8. doi: 10.1136/pgmj.2005.038109.

[73] Clark RH, Thomas P, Peabody J. Extrauterine growth restriction remains a serious problem in prematurely born neonates. Pediatrics (2003) 111: 986–90. doi: 10.1542/peds.111.5.986.

[74] Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics (2006) 117: 1253–61. doi: 10.1542/peds.2005-1368.

[75] Su BH. Optimising nutrition in preterm infants. Pediatr Neonatol (2014) 55: 5–13. doi: 10.1016/j.pedneo.2013.07.003.

[76] 53. Preterm and low birth weight babies. In: Bentley D, Aubrey S, Bentley M, editors. *Infant Feeding and Nutrition for Primary Care*. Abingdon: Radcliffe Medical Press Ltd (2004). p. 47–51.

[77] Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* (2012) 129: e827–41. doi: 10.1542/peds.2011-3552.

[78] Schanler RJ, Shulman RJ, Lau C. Feeding strategies for premature infants: beneficial outcomes of feeding fortified human milk versus preterm formula. *Pediatrics* (1999) 103: 1150–7. doi: 10.1542/peds.103.6.1150.

[79] Ganapathy V, Hay JW, Kim JH. Costs of necrotizing enterocolitis and cost-effectiveness of exclusively human milk-based products in feeding extremely premature infants. *Breastfeed Med* (2012) 7: 29–37. doi: 10.1089/ bfm.2011.0002.

[80] Vohr BR, Poindexter BB, Dusick AM, McKinley LT, Higgins RD, Langer JC, et al. Persistent beneficial effects of breast milk ingested in the neonatal inten-sive care unit on outcomes of extremely low birth weight infants at 30 months of age. *Pediatrics* (2007) 120: e953–9. doi: 10.1542/peds.2006-3227.

[81] Zhou J, Shukla VV, John D, Chen C. Human milk feeding as a protective factor for retinopathy of prematurity: a meta-analysis. *Pediatrics* (2015) 136: e1576–86. doi: 10.1542/peds.2015-2372.

[82] Singhal A, Cole TJ, Lucas A. Early nutrition in preterm infants and later blood pressure: two cohorts after randomised trials. *Lancet* (2001) 357: 413–9. doi: 10.1016/S0140-6736(00)04004-6.

[83] Singhal A, Cole TJ, Fewtrell M, Lucas A. Breastmilk feeding and lipoprotein profile in adolescents born preterm: follow-up of a prospective randomised study. *Lancet* (2004) 363: 1571–8. doi: 10.1016/S0140-6736(04)16198-9.

[84] Lewandowski AJ, Lamata P, Francis JM, Piechnik SK, Ferreira VM, Boardman H, et al. Breast milk consumption in preterm neonates and cardiac shape in adulthood. *Pediatrics* (2016) 138 (1): e20160050. doi: 10.1542/peds.2016-0050.

[85] Fewtrell MS, Williams JE, Singhal A, Murgatroyd PR, Fuller N, Lucas A. Early diet and peak bone mass: 20 year follow-up of a randomized trial of early diet in infants born preterm. *Bone* (2009) 45: 142–9. doi: 10.1016/j.bone.2009. 03.657.

[86] Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet* (1992) 339: 261–4. doi: 10.1016/0140-6736(92)91329-7.

[87] Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr* (1999) 70: 525–35.

[88] Horta BL, Loret de Mola C, Victora CG. Breastfeeding and intelligence: a sys-tematic review and meta-analysis. *Acta Paediatr* (2015) 104: 14–9. doi: 10.1111/ apa.13139.

[89] Belfort MB, Rifas-Shiman SL, Kleinman KP, Guthrie LB, Bellinger DC, Taveras EM, et al. Infant feeding and childhood cognition at ages 3 and 7 years: effects of breastfeeding duration and exclusivity. *JAMA Pediatr* (2013) 167: 836–44. doi: 10.1001/jamapediatrics.2013.455.

[90] Deoni SC, Dean DC III, Piryatinsky I, O'Muircheartaigh J, Waskiewicz N, Lehman K, et al. Breastfeeding and early white matter development: a cross-sectional study. *Neuroimage* (2013) 82: 77–86. doi: 10.1016/j.neuroimage. 2013.05.090.

[91] Northam GB, Liégeois F, Chong WK, Wyatt JS, Baldeweg T. Total brain white matter is a major determinant of IQ in adolescents born preterm. Ann Neurol. 2011 Apr; 69(4): 702-11. doi: 10.1002/ana.22263. Epub 2011 Mar 9. PMID: 21391229.

[92] Isaacs EB, Fischl BR, Quinn BT, Chong WK, Gadian DG, Lucas A. Impact of breast milk on intelligence quotient, brain size, and white matter development. Pediatr Res. 2010 Apr; 67(4): 357-62. doi: 10.1203/PDR.0b013e3181d026da. PMID: 20035247; PMCID: PMC2939272.

[93] ESPGHAN Committee on Nutrition, Agostoni C, Braegger C, Decsi T, Kolacek S, Koletzko B, et al. Role of dietary factors and food habits in the devel-opment of childhood obesity: a commentary by the ESPGHAN Committee on Nutrition. *J Pediat.*

[94] Di Natale C, Coclite E, Di Ventura L, Di Fabio S. Fortification of maternal milk for preterm infants. J Matern Fetal Neonatal Med (2011) 24 (Suppl 1): 41–3. doi: 10.3109/14767058.2011.607569.

[95] National Neonatology Forum, India. Bhakoo ON, Kumar P, Jain N, Thakre R, Murki S, Venkataseshan S, editors. Evidence Based Clinical Practice Guidelines. (2010). Available from: http://www.nnfi.org/images/pdf/nnf_cpg_consoli-dated_file-january102011.pdf

[96] Paraskevi C. Fragkou, Dareilena Karaviti, Michael Zemlin and Chrysanthi Skevaki: Impact of Early Life Nutrition on Children's Immune System and Noncommunicable Diseases Through Its Effects on the Bacterial Microbiome, Virome and Mycobiome: March 2021: Frontiers in Immunology 12: 644269.

[97] Francesca Manzoni, Valeria Cortesi, Giacomo Cavallaro, Fabio Mosca, Stefano Ghirardello: Iron Homeostasis Disruption and Oxidative Stress in Preterm Newborns: *Nutrients* 2020, *12*(6), 1554; https://doi.org/10.3390/nu12061554

[98] Brion, L.P., Heyne, R. & Lair, C.S. Role of zinc in neonatal growth and brain growth: review and scoping review. Pediatr Res 89, 1627–1640 (2021). https://doi.org/10.1038/s41390-020-01181-z

[99] S. H. Ralston, R. Coleman, W. D. Fraser, S. J. Gallagher, D. J. Hosking, J. S. Iqbal, E. McCloskey, D. Sampson; Medical Management of Hypercalcemia: Calcif Tissue Int (2004) 74: 1–11 DOI: 10.1007/s00223-001-1135-6.