European Journal of Preventive Medicine
2024; Vol. 12, No. 2, pp. 35-46
https://doi.org/10.11648/j.ejpm.20241202.12

Review Article

The Significance of Providing the Optimal Micronutrients to the Preterm Low Birth Weight Infants to Prevent Long-Term Health Consequences

Abbas Uddin Khan[1, *], Shohrab Hasan[2], Farzana Siddiqua[3], Sabiha Sultana[4], Moniruzzaman[5], Manir Hossain[6], Shahidul Islam Shaheed[7], Aiyasha Shahid[7]

[1]Department of Paediatric, Tairunnessa Memorial Medical College and Hospital, Dhaka, Bangladesh
[2]Department of Paediatric, International Medical College and Hospital, Dhaka, Bangladesh
[3]Department of Paediatric, Popular Diagnostics Center Gazipur, Dhaka, Bangladesh
[4]Department of Paediatric, Shahid Tajuddin Ahmed Medical College Hospital, Dhaka, Bangladesh
[5]Department of Paediatric, Monno Medical College and Hospital, Manikgonj, Bangladesh
[6]Department of Paediatric, Kumudini Womens Medical College and Hospital, Mirzapur, Bangladesh
[7]Department of Paediatric, Enam Medical College and Hospital, Savar, Bangladesh

Abstract

Premature infants have less nutritional storage capacity and an underdeveloped body, which makes them particularly susceptible to malnutrition. Nutrient surplus and deficiency are possibilities when supplemental feeding is unbalanced. However, little is known about what kids should eat once they are discharged from the hospital. Since many bodily processes depend on micronutrients, it's critical to plan supplemental nutrition with an optimum consumption in mind. This written summary describes the requirements for long-chain polyunsaturated fatty acids (LCPUFA), iron, zinc, vitamin D, calcium, and phosphate for premature newborns receiving supplemental feeding. The scientific community is beginning to acknowledge the advantages of giving premature babies iron and vitamin D supplements. But as of right now, there isn't enough information available to make firm recommendations about the addition of calcium, phosphorus, zinc, and LCPUFAs. Nonetheless, the health of premature infants depends on the following micronutrients: Large chain polyunsaturated fats (LCPUFAs) support the development of the retina and brain, while calcium and phosphorus dosages are necessary to prevent metabolic bone disease (MBD) in preterm infants. It is obvious how understanding the variability of the premature population may help adapt nutritional planning in connection to the development rate, comorbidities, and thorough clinical history of the preterm newborn, even while we wait for consensus on these micronutrients.

Keywords

Premature Infants, Low Birth Weight Infants, Optimizing Nutrition, Enteral Feeding, Expressed Breast Milk, Complementary Feeding, Micronutrients, Fortification

[*]Corresponding author: drabbasuk@yahoo.com (Abbas Uddin Khan)

Received: 29 February 2024; **Accepted:** 1 April 2024; **Published:** 17 April 2024

1. Introduction

The World Health Organization reports that in 62 of the 65 countries where trend data is available, preterm birth rates have grown within the last 20 years. Premature birth complications claim the lives of over a million children annually. Preterm births are the leading cause of newborn mortality and, after pneumonia, the second most prevalent cause of death for children under five. Furthermore, there is a higher chance of unfavorable developmental abnormalities among preterm birth survivors [1]. They had higher rates of adverse health outcomes in early adulthood [2] as compared to their term counterparts.

Because many organs are remarkably flexible throughout fetal development and infancy, and because they are sensitive to environmental cues such as food, this period of development offers a vital temporal window for predicting future health [3]. Newborns' appropriate growth and development depend on their dietary demands being satisfied, yet even brief nutritional deficiencies can have a negative impact on long-term health [4]. Preterm infants (born before 37 weeks of gestation) have higher nutritional needs in terms of both macronutrients and micronutrients because of the lower level of nutrients in the body stores at birth, the immaturity of the body systems, the need for rapid postnatal growth, and the occurrence of acute illnesses. Adequate and prompt nutritional supplementation has been advised for preterm babies in order to prevent malnutrition and limit postnatal growth retardation [5, 6]. By doing this, there will be less of a need for quick growth to catch up, which is linked to worse metabolic outcomes in later life. A growing body of research suggests that effective dietary treatment might lead to excellent neurodevelopmental outcomes while lowering the likelihood of developing comorbidities such sepsis, metabolic bone disease (MBD), and severe retinopathy of prematurity [7, 8].

There is broad agreement about the nutritional requirements for preterm newborns throughout their hospital stay; the pillars of their treatment are early enteral and parenteral assistance [9, 10]. Because breast milk has so many health advantages, it is strongly advised as the first choice for enteral feeding [11, 12]. On the other hand, little is known about the best nutritional therapy for preterm newborns once they leave the hospital [13].

Most people agree that preterm neonates need certain nutrients during their hospital stay; early enteral and parenteral support are the cornerstones of their care [9, 10]. Breast milk is often recommended as the primary option for enteral feeding due to its numerous health benefits [11, 12]. However, once preterm neonates leave the hospital, little is known regarding the optimal nutritional therapy [13]. There are no precise criteria for the introduction of supplemental meals to preterm neonates, despite the fact that recommendations for term newborns cannot be applied to preterm infants due to their unique nutritional demands and neurological trajectories, which include feeding problems [9, 14, 15]. When planning to introduce complementary foods to preterm children, their past feeding histories—which may include exclusive breastfeeding, fortification, the use of post-discharge or conventional formulas—should be taken into account. Growth trends, including the attainment of catch-up growth, and the existence of feeding issues are additional aspects to take into account [9]. After being discharged from the hospital, preterm children get iron and multivitamin supplements; however, the duration and quantity of these treatments vary greatly [18].

2. Nutrition Is One Major Factor Affecting Preterm Newborns' Developmental Outcomes

Nutrition has a critical role in a premature neonatal low birth weight (LBW) child's growth, metabolism, and immunity [19, 20, 21]. In premature babies, poor nutrition is associated with decreased head growth, which results in impaired psychomotor and cognitive development, a higher risk of cerebral palsy, and autism [22]. The aberrant weight and growth of preterm infants is highly associated with poor adult neurodevelopmental outcomes [23]. Furthermore, babies with LBW have an increased risk of type 2 diabetes, hypertension, and coronary heart disease in adulthood, according Barker's idea [24, 25].

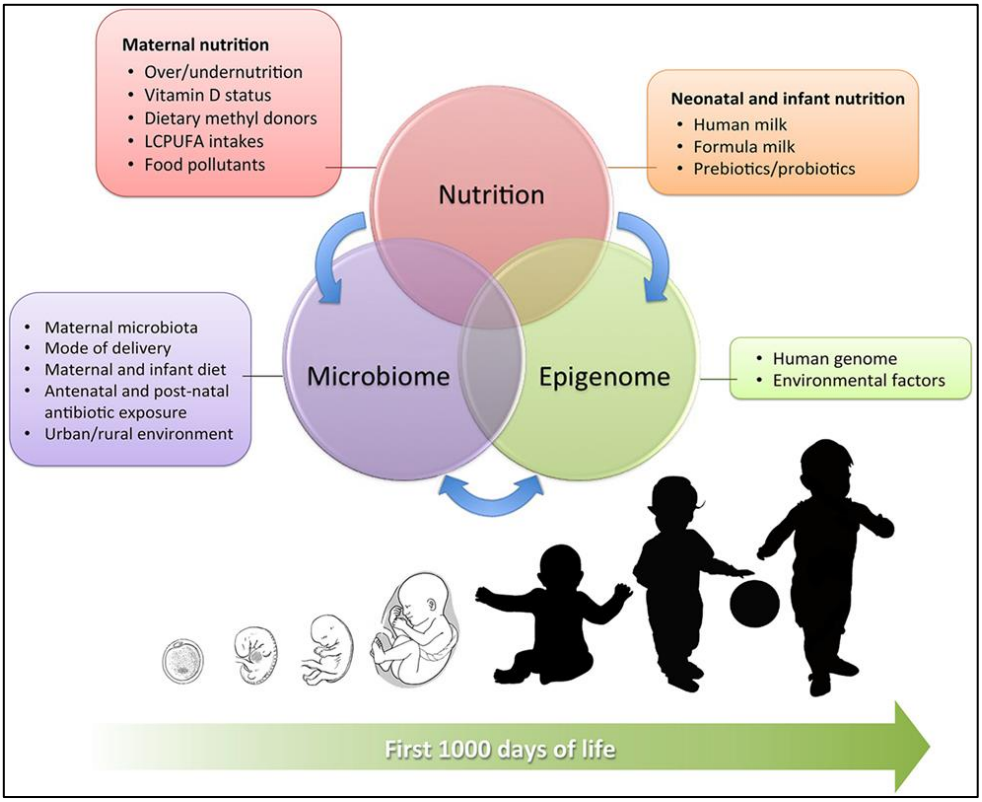

Figure 1. *Nutritional parameters affecting positively or negatively the development of the immune system and the risk of noncommunicable diseases during the first 1000 days of life [96].*

3. Vital Micronutrients for Infants Born Preterm and with Low Birth Weight

3.1. An Important Micronutrient for Preterm LBW Infants Is Iron

Because iron is essential for the synthesis of hemoglobin (Hb), oxygen transport, and other enzymatic processes, such as the generation of cellular energy, it is regarded as a necessary nutrient [26]. Because of the placenta's active transport, the majority of the iron supply accumulates during the second trimester of pregnancy. Approximately 75 mg/kg of iron is present in term newborns; 75–80% of this is found in hemoglobin (Hb), 10% is found in tissues as iron-containing proteins (myoglobin and cytochromes), and the remaining 10-15% is found in forms of stored iron, such as ferritin and hemosiderin [26].

Prenatal variables including the mother's iron status and the likelihood of iron transfer to the unborn child, as well as postnatal events like cord clamping, affect the quantity of iron deposited upon birth. It has been proposed that postponing cord cutting improves both term and preterm newborns' iron status and perinatal hemoglobin transfer [27]. How successfully iron homeostasis is maintained throughout the first 6–9 months of life depends on the baby's iron status at birth since insufficient absorption and the relatively small amount of breast milk create a physiological drop [28].

Because prematurity inhibits placental translocation, preterm neonates' iron reserves upon delivery are decreased based on gestational age and birth weight [29]. Fetal iron storage may be impacted by maternal hypertension, diabetes, iron deficiency anemia in mothers, and intrauterine growth retardation [29, 30]. Other pregnancy-related factors, such obesity and numerous pregnancies, may further decrease the iron stores of premature neonates [31].

Preterm babies have lower iron reserves upon delivery based on birth weight and gestational age because prematurity inhibits placental translocation [29]. Fetal iron storage can be affected by a number of conditions, including intrauterine growth retardation, maternal hypertension, diabetes, and iron deficiency anemia in mothers [29, 30]. Obesity and repeated pregnancies are two more pregnancy-related factors that may further lower the iron levels of premature babies [31].

Given that blood transfusions are given to infants with very low birth weights (ELBW) and very low birth weights (VLBW) at least once during their hospital stay, preterm neonates may be at risk [33]. Due to the established links between early blood transfusion exposure and higher mortality and short-term morbidities, stricter blood transfusion regulations have been called for in recent years, particularly for extremely preterm neonates [34]. The kind of feeding, the quantity and timing of blood transfusions, and the clinical history of the premature child should all be taken into account when planning iron supplementation in this case. If after discharge processed milk is not

supplied or is not fortified, feeding only human milk will not satisfy the high iron requirements [35].

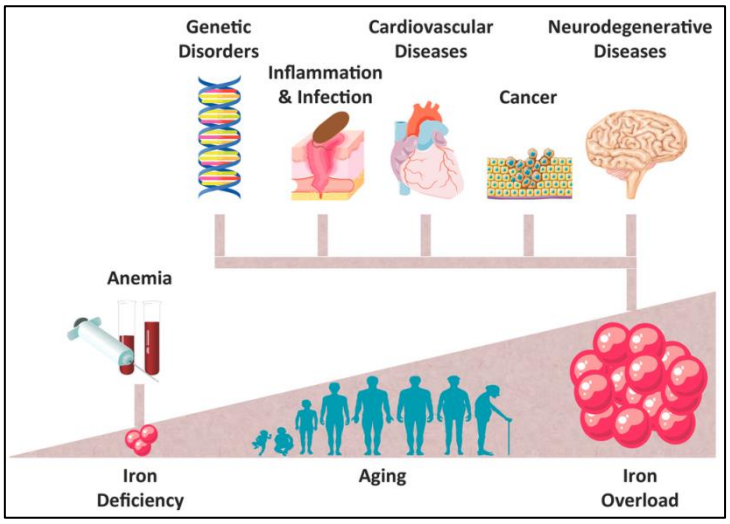

Figure 2. *Iron Homeostasis Disruption and Oxidative Stress in Preterm Newborns [97].*

3.2. Zinc Is an Essential Component for Preterm Low Birth Weight Infants

Zinc's structural, catalytic, and regulatory properties make it necessary for all stages of the cellular life cycle. It is necessary for bone formation, growth hormone regulation, gustatory function, hunger [37-39], immunological modulation (phagocytosis and cellular immunity) [36], and tissue integrity, especially at the respiratory and gastrointestinal levels. Since the body lacks the ability to generate zinc and does not have a suitable mechanism for storing or releasing it, zinc must be eaten frequently [38, 40]. During the first several months of breastfeeding, the amount of zinc in colostrum gradually drops, from 8–12 mg/L to 1-3 mg/L at one month of age [41]. Interestingly, it has been shown that preterm human milk has much less over the first two months of corrected age zinc than term milk [26, 42]. Between 1.5 and 6 mg/L of zinc can be found in baby formula.

At 40 weeks post pregnancy age, preterm newborns have decreased zinc levels than term neonates because their blood zinc concentration falls during the first few months of life [41]. It is challenging to detect zinc deficiency because there are no reliable markers for zinc levels. Serum zinc concentration measurement is still the most accurate biomarker of zinc shortage, despite a number of drawbacks [41, 43].

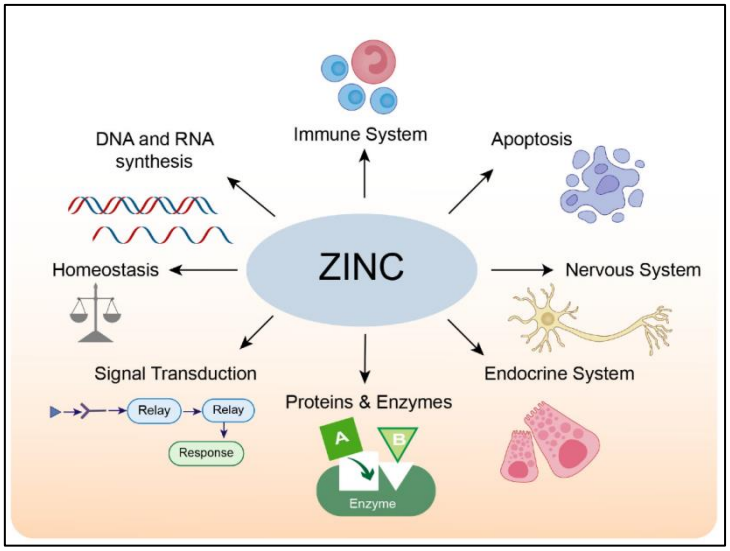

Figure 3. *Zinc role in growth and brain growth and development [98].*

Regarding the quantity, timing, and duration of preventive zinc supplementation, there is no consensus suggestion [44]. Remember that taking zinc supplements could affect the absorption of other microelements like iron and copper, and vice versa [45]. It is unclear how precisely anemia and zinc insufficiency may be caused [46]. According to a study by Griffin et al., copper intakes must be increased up to 250 mcg/kg/d in order to maintain adequate copper retention at the zinc dosages advised 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, it is recommended to administer zinc supplements during the first year of life as zinc does not have pro-oxidant qualities and an overdose seldom has negative implications [47, 48]. Particular consideration should be given to zinc supplementation for prematurely breastfed infants who have stunted growth [49].

3.3. Premature Babies Frequently Experience Early Neonatal Hypocalcemia; This Is Where Calcium and Phosphorus Come in

The third trimester of pregnancy is when the majority of bone mineralization happens [50]. In actuality, osteoblasts deposit 80% of the available bone material during this time. In order to carry out this process, active placental transport of calcium and phosphorus is necessary, resulting in a physiological state known as "fetal hypercalcemia" that is necessary for the formation of bones. To the growing fetus, the placenta transports calcium (120 mg/kg/day) and phosphorus (60 mg/kg/day) [51]. When breathing starts, the pH of the blood rises, which in turn raises the levels of parathormones and lowers the concentration of calcium ions. Due to the beginning of mineral resorption from the aging bone, this process also results in a drop in bone mineral density that can last for up to six months [52].

However, bone integrity is preserved in term newborns. On the other hand, preterm neonates have a noticeably higher prevalence of osteopenia. Premature birth effectively stops this process, effectively stopping the creation of bone material. After delivery, when the body adjusts to life outside the uterus, this deficit gets worse. Actually, a number of variables, including poor gastrointestinal motility and tolerance, the use of drugs like theophylline and furosemide that increase excretion of calcium, and poor gastrointestinal tolerance, cause challenges for premature newborns when it comes to absorbing calcium [52].

MBD, or metabolic bone disease, is a disorder more frequently linked to premature births. In addition to radiographic evidence of bone demineralization and clinical manifestations such rickets, expansion of the cranial sutures, frontal bossing, and softening or fractures of the ribs and other bones, it is typified by hypophosphatemia and hyperphosphatasemia [53]. The increased sensitivity of preterms to MBD can be explained by the combined effect of these risk factors. According to reports, MBD affects 23% of babies with a very low birth weight (VLBW 1500 g) and 55% of neonates with a very low birth weight (ELBW 1000 g). Simultaneously, kids born before 28 weeks of pregnancy seem to experience it more frequently [54].

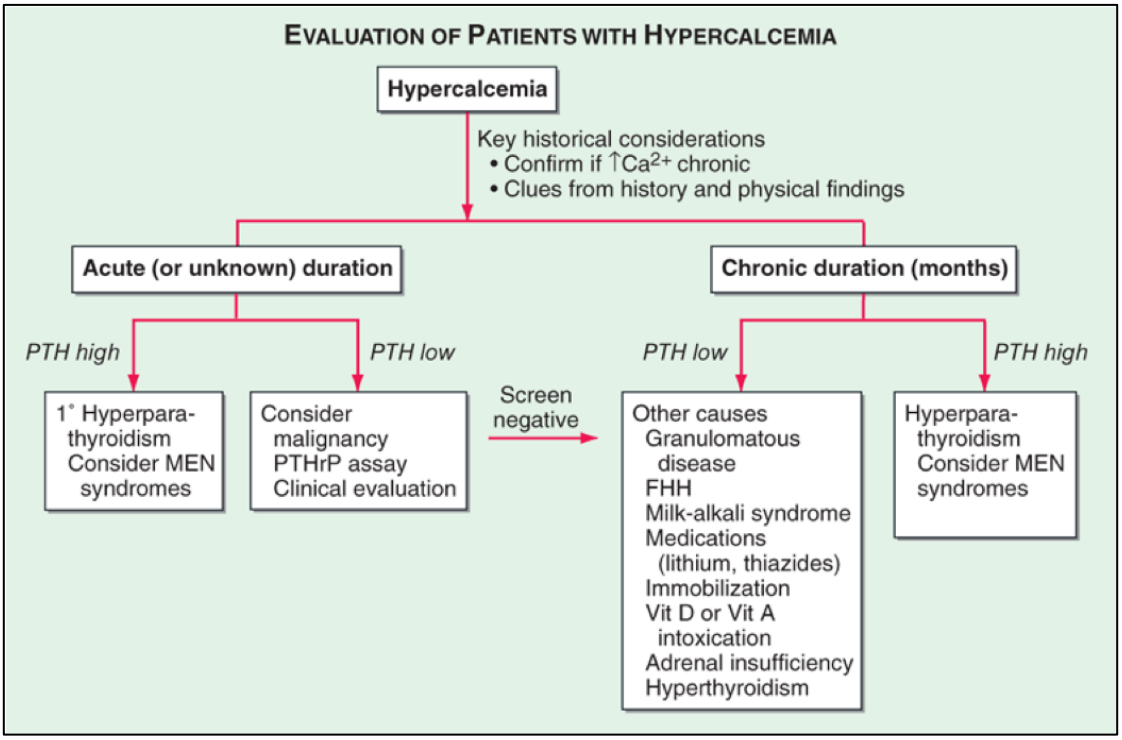

Figure 4. *Diagnostic evaluation for hypercalcemia [99].*

MBD, or metabolic bone disease, is a disorder more frequently linked to premature births. In addition to radiographic evidence of bone demineralization and clinical manifestations such rickets, expansion of the cranial sutures, frontal bossing, and softening or fractures of the ribs and other bones, it is typified by hypophosphatemia and hyperphosphatasemia [53]. The increased sensitivity of preterms to MBD can be explained by the combined effect of these risk factors. According to reports, MBD affects 23% of babies with a very low birth weight (VLBW 1500 g) and 55% of neonates with a very low birth weight (ELBW 1000 g). Simultaneously, kids born before 28 weeks of pregnancy seem to experience it more frequently [54].

4. Vitamin D Insufficiency Occurrence Frequency Is High in Many Regions of the World

The importance of vitamin D and its supplementation has grown over the last several years. Along with its well-documented impact on bone mineralization, many supplementary metabolic processes classified as "extra-skeletal" have also been extensively investigated [55]. The effects of this vitamin outside of the skeletal system have been the focus of further investigation. Many studies have classified vitamin D as a hormone. It has been demonstrated by researchers to control the expression of more than 1250 genes [56]. In fact, among the many recently reported activities, we find anti-tumor actions [57], modulation of the inflammatory function [58], and defense against cardiovascular risk factors [59] through a range of metabolic pathways that are now poorly understood.

The majority (>90%) of vitamin D is produced by skin exposure to sunlight; dietary intake has very little bearing on this process. Despite the great efficiency of the process of synthesising vitamin D from sunshine, the production of vitamin D is compromised during the winter months due to a decrease in solar hours [60]. Moreover, the American Academy of Pediatrics (AAP) advises against exposing a baby to direct sunlight until they are six months old if they are not sheltered from the elements [61]. Over half of neonates have hypovitaminosis D, according to epidemiological research [55]. When the blood concentration of 25-OHD is between 20 and 30 ng/mL, this absence of vitamin D is classified as an insufficiency; if it is less than 20 ng/mL, it is classified as a deficiency [62]. The prevention of vitamin D insufficiency is most important during the first year of life. The ability of the baby to accumulate vitamin D is strongly impacted by the mother's vitamin D status, as seen by the positive correlation found between cordonal or neonatal levels of 25-OHD [63]. There may be additional effects due to maternal supplementation, ethnic background, and birth season [62, 63]. Infants are particularly susceptible to vitamin D insufficiency because of their rapid development, particularly if they are nursed exclusively. This is due to the fact that the 80 UI/L of vitamin D found in human milk is insufficient to prevent deficiency. Moreover, formula milk enriched with 400 UI/L of vitamin D or breast milk alone may not provide an appropriate amount of the vitamin [55].

Prophylaxis must begin during the first few days of life since vitamin D has a half-life of about two to three weeks and neonatal storage is correlated with the mother's condition. When preterm babies reach the term corrected age (40 weeks gestational age), the majority of Neonatal and Pediatric Societies support continuing the same recommended dose of a term neonate (400 UI/day), as indicated in Table 1.

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

A comprehensive evaluation of the risk factors for hypo-vitaminosis D may serve as a useful screening tool to identify a possible deficient state and promptly start the recommended prophylactic treatment. Regardless of the method of feeding, vitamin D supplementation should start in the early stages of life and go well into the neonatal period because even higher dosages of the vitamin don't seem to offer a significant risk of side effects, and overdosing is rare [55].

5. Nutrition's Beneficial Effect in Primitive Stage of Life

Longer-term increases in verbal intelligence quotient (IQ) scores and cognitive function have been associated with improved nutrition in the early postnatal periods of preterm

newborns [64, 65]. When it came to their mental development index scores and likelihood of experiencing growth retardation by the time they were 18 months old, very low birth weight (LBW) neonates who received more protein and calories in the first week after delivery performed better [66]. An increase in head circumference and quicker head growth have also been related to preterm newborns' earlier and greater protein and calorie intake [67, 68]. Improved cognitive results have also been positively correlated with an increase in head circumference [69]. To maintain the growth and developmental outcomes, preterm newborn LBW newborns may receive early, intense nutritional enteral and parenteral treatment [70].

6. Feeding Procedure for Premature Live Births (Low Birth Weight)

6.1. Growth Rate with Basic Nutritional Practices

Enteral basic feedings (10 mL/kg/day) Preterm infants are commonly given enriched human milk, parenteral nutrition with amino acids and lipids, donor milk (in the case that mother milk is not available), and basic enteral feeds [71]. Even with normal treatments, preterm infants may not always reach their full developmental potential. Postnatal growth restriction cannot be avoided by the dietary approaches now used to treat intrauterine growth restriction (IUGR) and preterm neonates [72]. For preterm live birth (LBW) children, extrauterine growth restriction, or EUGR, is a serious issue; the incidences for head circumference, weight, and length are around 28, 34, and 16%, respectively [73]. Preterm and very low birth weight (LBW) newborns hospitalized to the neonatal critical care unit have a growth rate that has a significant impact on their neurodevelopmental and growth outcomes in later life [74].

6.2. Existing 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 milk of choice for supplying nourishment to premature LBW newborns.

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

Recommendations in agreement about the use of breast milk to nourish premature infants:
1) Mother-expressing breast milk is the primary option for human milk used to nourish preterm newborns; donor pasteurized human milk is the second option.
2) The term "donor pasteurized human milk" should be used for donor milk.
3) Human milk should be pasteurized in a pasteurizer; donor human milk should never be served unpasteurized.
4) Donor pasteurized human milk should be screened for bacterial growth, hepatitis B antigen (HBsAg), hepatitis C virus (HCV), HIV, and venereal disease using pertinent tests and cultures.
5) Within six months of donating milk, the donor mother should also be tested for HIV, HCV, HBsAg, and venereal disease.
1) Pooled milk may be utilized if there are local milk banks, as long as the right permissions have been granted.
2) When it comes to pasteurizing pooled tiny aliquots of breast milk, milk banks should communicate with agencies.
3) Although the human milk analyzer is a useful tool to analyze the nutrient content of human milk and enable subsequent fortification, it is currently only being used as a research tool and not in day-to-day clinical practice.
4) Donor human milk may be stored at -20 ℃ for six months. Preterm infants should not be fed milk stored for more than three months. In everyday clinical situations, the conventional fortification technique is advised.

While there are many advantages to nursing human milk, it is important to determine if it can meet the higher nutritional needs of preterm infants. The greatest sources of nutrition for premature children, according to ESPGHAN, are supplemented human milk—ideally from the infant's own mother—or formula milk designed especially for preterm neonates [93].

6.2.2. Improved Human Milk

Fortified breast milk can help when an infant's nutritional demands cannot be met by EBM [76]. The goal of fortification is to increase the nutritional content to the point that the infant's demands may be satisfied with normal feeding volumes [94]. One nutrient (mono-component) or several nutritional combinations (multi-component) can be used in fortification. The National Neonatology Forum of India [95] states that a baby should get multicomponent fortification if they are under 32 weeks gestational age or weighed less than 1,500 g at birth and are not gaining weight while receiving full quantities

of breast milk (up to 180–200 mL/kg/day).

6.2.3. Formula Milk

Formula milk contains all essential nutrients and is specifically designed to meet the requirements of LBW infants [76].

7. Conclusions

Prematurity implies a higher risk of illness and mortality. Preterm newborns need to get early, adequate nutritional supplements to minimize adverse metabolic effects. There is currently a lack of global agreement on the supply of iron, zinc, calcium, phosphate, vitamin D, and LCPUFAs to preterm newborns upon discharge and during their first year of life. Nevertheless, the literature to far documents very few, if any, adverse effects from their supplementation. Furthermore, the positive effects of these substances on the body as a whole become more apparent as our knowledge of these micronutrients expands.

It seems reasonable to us to propose that supplementing preterm infants with these nutrients may provide more benefits than drawbacks. This is particularly valid for breastfed preterm infants. Breast milk is still the best choice for this group, but it is clear that the concentration of a number of micronutrients, especially LCPUFAs, depends entirely on the diet and deposits of the mother. The review highlights the information gap in the literature on premature supplementation and the necessity of large-scale, randomized trials to address these issues.

Abbreviations

LCPUFAs: Long-Chain Polyunsaturated Fatty Acids

Conflicts of Interest

The authors declare no conflicts of interest.

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. https://doi.org/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.

[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.

[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.

[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.

[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.

[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.

[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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/10.1093/ije/31.6.1235

[26] Domellöf, M. Nutritional Care of Premature Infants: Micro-minerals. 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.

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

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

[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 Insuffi-ciency and Chronic Hypoxia. J. Pediatr. 1987, 111, 283–286.

[31] Baker, R. D.; Greer, F. R.; The Committee on Nutrition. Di-agnosis 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] Siddappa AM, Rao R, Long JD, Widness JA, Georgieff MK. The assessment of newborn iron stores at birth: a review of the literature and standards for ferritin concentrations. Neonatol-ogy. 2007; 92: 73–82.

[36] Tuerk, M. J.; Fazel, N. Zinc Deficiency. Curr. Opin. Gastro-enterol. 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 De-ficiency 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.

[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.

[40] Maggini, S.; Wenzlaff, S.; Hornig, D. Essential Role of Vita-min 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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/10.1080/14767050802630169

[72] Puntis JW. Nutritional support in the premature newborn. Postgrad Med J (2006) 82: 192–8. https://doi.org/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. https://doi.org/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. https://doi.org/10.1542/peds.2005-1368

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

[76] 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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/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. https://doi.org/10.1016/j.neuroimage.2013.05.090

[91] Northam GB, Li égeois F, Chong WK, Wyatt JS, Baldeweg T. Total brain white matter is a major determinant of IQ in adolescents born preterm. *Ann Neurol* (2011) 69: 702–11. https://doi.org/10.1002/ana.22263

[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) 67: 357–62. https://doi.org/10.1203/PDR.0b013e3181d026da

[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. https://doi.org/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. Fragkou1, 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 https://doi.org/10.1007/s00223-001-1135-6