Abstract
Low birthweight (LBW) is defined by the World Health Organization (WHO) as body weight less than 2,500 g at birth based on epidemiological observations that infants with a birthweight less than 2,500 g are 20 times more likely to die than ‘heavier’ babies [1]. Moreover, according to the WHO, a birthweight below 2,500 g contributes to poor health outcomes. Worldwide, the incidence of LBW is estimated to be 15.5% with a range from 7 to 18.6% based on more developed, less developed and least developed countries. In addition to discussing causes and consequences of LBW, this chapter will discuss specific nutrients that need particular attention in this cohort of infants: calcium, phosphorus, magnesium, vitamin D, iron, copper, zinc and issues related to feeding these infants including the use of human milk. Since LBW is an important public health indicator of long-term maternal malnutrition, maternal health, poor prenatal care and, in addition, poses significant challenges in feeding and growth, this large population, globally, deserves particular attention.

Introduction
Low birthweight (LBW) defined as birthweight <2,500 g, remains a major public health problem since it is estimated that over 20 million infants (15.5% of all births) worldwide are born with LBW, and the overwhelming majority of these infants are born in developing countries. The definition adopted by the World Health Organization (WHO) is also based on epidemiological observations that LBW infants are about 20 times more likely to experience mortality compared to larger infants. In developed countries, LBW is largely due to premature birth, whereas in developing countries it is due to intrauterine growth restriction [2]. Moreover, LBW is
associated with fetal and neonatal morbidity and mortality, poor growth, impaired cognitive development and chronic diseases in adult life [3]. According to the WHO report, half of all LBW infants are born in South-Central Asia followed by Sub-Sahara Africa, Middle East and North Africa, Latin America and the Caribbean, Central and Eastern Europe, Commonwealth of Independent States and East Asia and the Pacific [4]. Various maternal factors including poor protein and energy intakes, prepregnancy weight and body mass index determine LBW, and discussion of these factors is beyond the scope of this paper [5]. An intergenerational cycle of growth failure has also been described, making attention to preconception nutrition a very important intervention in preventing LBW [6].

LBW infants are very heterogeneous from being premature to being small for age at term. The strategies to feed these infants differ because the initial goals are different. For example, the LBW premature infant does not get the benefit of placental transport of various nutrients including protein, essential fatty acids, calcium, phosphorus, magnesium, iron and zinc [7]. The delivery of such an infant then causes abrupt cessation of nutrient delivery, and postnatal nutrition practices can result in negative nitrogen balance very early in life. Aggressive nutritional practices including early parenteral and enteral nutrition have been shown to promote positive nitrogen balance and, in addition, shorten the interval to return to birthweight, a critical factor in reducing extrauterine growth restriction [8–10].

**Nutrient Recommendations**

Current nutrient recommendations are summarized in table 1, and table 2 summarizes the macronutrient composition of human milk, term, preterm and donor milk.
As seen in Table 1, preterm milk would have to be fed in excessive quantities to meet the nutrient recommendations set forth, thus highlighting the need for appropriate fortification. In Table 2, the major differences between preterm, term and donor milk are highlighted.

As will be discussed later in this chapter, feeding premature and LBW infants is challenging especially when feeding them human milk, an accepted global standard. The macro- and micronutrients needed have to be provided in the form of fortification.

**Table 2. Macronutrient composition of term, preterm and donor milk**

<table>
<thead>
<tr>
<th></th>
<th>Protein, g/dl</th>
<th>Fat, g/dl</th>
<th>Lactose, g/dl</th>
<th>Energy, kcal/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>1.2 (0.9–1.5)</td>
<td>3.6 (2.2–5)</td>
<td>7.4 (7.2–7.7)</td>
<td>70 (57–83)</td>
</tr>
<tr>
<td>Donor</td>
<td>1.2 (0.7–1.7)</td>
<td>3.2 (1.2–5.2)</td>
<td>7.8 (6–9.6)</td>
<td>65 (43–87)</td>
</tr>
<tr>
<td>Donor</td>
<td>0.9 (0.6–1.4)</td>
<td>3.6 (1.8–8.9)</td>
<td>7.2 (6.4–7.6)</td>
<td>67 (50–115)</td>
</tr>
<tr>
<td>Reference</td>
<td>0.9</td>
<td>3.5</td>
<td>6.7</td>
<td>65–70</td>
</tr>
<tr>
<td>Preterm &lt;29 weeks</td>
<td>2.2 (1.3–3.3)</td>
<td>4.4 (2.6–6.2)</td>
<td>7.6 (6.4–8.8)</td>
<td>78 (61–94)</td>
</tr>
</tbody>
</table>

Adapted from Ballard and Morrow [14].

Calcium, Phosphorus and Magnesium

Most of the fetal accretion of calcium, phosphorus and magnesium occurs in the third trimester of pregnancy [15]. Fetal accretion of calcium and phosphorus approximates 20 and 10 g, respectively, during the last trimester, which translates to accretion rates of 100–120 mg/kg per day for calcium and 50–65 mg/kg per day for phosphorus [16]. In the blood, calcium ions exist in three forms: nondiffusible complex with protein (~40%), diffusible complex with citrate, bicarbonate and phosphate (~5%) and as free ionized calcium (~55%). The nondiffusible calcium is bound to albumin and is highly pH dependent, and alterations in acid-base homeostasis will affect free ionized calcium. In the fetus, parathyroid hormone (PTH), PTH-related peptide and 25-hydroxy vitamin D play important roles in the transplacental influx of calcium and bone remodeling; the latter is important since 90% of total calcium is found in teeth and bones especially in the adult [17]. LBW infants, either from prematurity or intrauterine growth restriction, have lower calcium and phosphorus stores compared to their term counterparts. Postnatally, optimal calcium and phosphorus homeostasis is important to diminish the incidence of metabolic bone disease, the spectrum of which ranges from osteopenia to frank rickets and fractures. After birth, there is
an increase in calcium flux from the bone to extracellular space and if calcium stores are low, as in prematurity, unless exogenous calcium is provided, hypocalcemia will occur. Very LBW infants exhibit the lowest nadirs of ionized calcium, but in most cases, low levels are not associated with symptoms [18]. Calcium absorption depends on calcium and vitamin D intakes as well as absorbed phosphorus. Thus, the calcium to phosphorus ratio may be an important determinant of calcium absorption and retention [16]. Phosphorus accretion is related to both calcium and protein retention; phosphorus absorption is very efficient (~90%) in infants fed either human milk or formula. However, human milk does not have adequate amounts of calcium and phosphorus to sustain bone health in a small preterm infant and will need fortification. If calcium retention of 60–90 mg/kg per day is achieved with a nitrogen retention of 350–450 mg/kg per day, then an intake of phosphorus of 65–90 mg/kg per day along with a Ca:P ratio of 1.5–2:1 will achieve appropriate phosphate levels [19].

Similar to calcium, plasma concentrations of magnesium in the fetus exceed those of the mother [20]. Little is known about the mechanisms of placental magnesium transport, but they appear to be different from those for placental calcium transport [21].

Fetal growth disturbances are seen in diabetic pregnancies, both in humans and in animals. In rats, fetal growth restriction is a consistent finding [22]; however, human infants may be large for gestational age or growth restricted depending on the timing of the diabetes [23]. The pathophysiology of these disturbances in placental transport of calcium and magnesium during diabetic pregnancy is likely a result of altered placental transport and fetal accretion of calcium and magnesium. Both hypo- and hypermagnesemia are common in diabetic pregnancies [24].

In preterm infants, feeding with human milk is a very effective means of intervention, especially for short-term morbidities such as necrotizing enterocolitis and infections. There are however, numerous nutritional challenges in providing human milk to premature infants. These include inadequate supply, variability in nutritional content between and among mothers, and the nutrient limitations in human milk itself. Figure 1 illustrates the limitations of human milk in providing calcium and phosphate. For preterm infants, the suggested enteral requirements for calcium for example, of 25–40 mmol/kg per day cannot be met by preterm or term human milk and must be fortified. In addition, it is well recognized that it is virtually impossible to meet the requirements of these two minerals through parenteral nutrition, and thus infants on prolonged parenteral nutrition and then on unfortified human milk would be at the greatest risk of deficiencies including slower growth. The entire topic of human milk for premature infants is covered elsewhere [7, 26, 27].
The last Cochrane review [28] concludes that multicomponent fortification of human milk is associated with short-term improvements in weight gain, linear and head growth. Further, fortification of human milk for preterm infants after hospital discharge has not been extensively studied. A recent review by Young et al. [29] found limited evidence that feeding preterm infants with fortified milk impacted growth rates during infancy. One study did not find any statistically significant effects on neurodevelopmental outcomes at 18 months. In a cohort of preterm infants, 750- to 1,800-gram birthweight, human milk-fed infants were randomized to receive either half of the feedings with fortified human milk (n = 19) or all their feedings with unfortified human milk (n = 20) for 12 weeks after hospital discharge. The infants fed fortified human milk were longer (p < 0.001) and had a greater bone mineral content (p = 0.02) at 12 months corrected age, and in infants less than 1,250 g, head circumference remained large (p < 0.001) through the first year of life [30]. In long-term studies, very LBW infants attain a suboptimal peak bone mass and subnormal skeletal mineralization [31]. Fewtrell et al. [32] measured whole and regional bone mineral content and bone mineral density using dual-energy X-ray absorptiometry and single-photon absorptiometry and bone turnover in 244 preterm infants at 8–12 years of age. These infants had been fed either banked human milk (n = 87) or preterm formula (n = 96) or expressed breast milk supplemented with preterm formula (n = 36). Preterm children were shorter and lighter than term children and had significantly lower whole-body bone mineral content. However, the bone mineral content was appropriate for bone and body size, suggesting that early diet despite large differences in mineral intake did not affect bone mass at 8–12 years of age.
Magnesium

Similar to calcium, magnesium has a high accretion rate in utero during the third trimester. The magnesium requirement estimated to be 8–15 mg/kg per day is higher than that of term infants. It has been calculated that with human milk feeding (Mg content ~1.3 mmol/l), preterm infants will receive 5.5–7.5 mg/kg per day, and magnesium absorption is better with human milk than formulas (73 vs. 48%). Effects of the greater magnesium accretion in premature formula-fed infants than intrauterine estimates are not known. No functional criteria of magnesium status have been demonstrated that reflect dietary changes in infants. The recommended intakes are based on an adequate intake that reflects mean intake from human milk [33]. Transient hypomagnesemia is associated with both hypocalcemia and hyperphosphatemia and is common in growth-restricted infants and in infants of diabetic mothers.

Vitamin D

Requirements of vitamin D may be affected by the availability of substrates such as calcium, phosphorus, magnesium and vitamin D itself. In humans, 25-hydroxyvitamin D [25(OH)D] is the major circulating form of vitamin D after it is hydroxylated in the liver and is also the form that is involved in transplacental passage [34]. The ideal definition of requirement and optimal levels of vitamin D should be based on functional markers, such as absorption, bone mineralization and PTH concentrations. The major biologic function in humans is to maintain serum calcium and phosphorus within the normal range. The vitamin D available to the infant (term) during the first 6 months of life depends on the vitamin D status of the mother during pregnancy and later on the infant’s exposure to sunlight and availability of vitamin D in the diet. Human milk contains low amounts of vitamin D, and colostrum contains an average of 397 ± 216 ng/l of vitamin D. Low vitamin D levels are not uncommon in neonates fed human milk of formula. Although there is no compelling evidence, it is accepted that a serum 25(OH)D concentration of <50 nmol/l is consistent with deficiency, 50–80 nm/l is insufficiency and >80 nm/l is considered sufficient. The Institute of Medicine [35] defines sufficiency as 50 nm/l, risk of deficiency <30 nm/l and inadequacy as 30–50 nm/l. In premature infants, the requirements and levels are extrapolated from adult studies. Premature infants are at particular risk for developing metabolic bone disease because of the difficulty in achieving adequate intakes of calcium, phosphorus and vitamin D, relative immobili-
ity, prolonged total parenteral nutrition, feeding of unfortified human milk and adverse effects of commonly used medications such as diuretics and steroids. Suggested intakes vary from 400 IU/day [36, 37] to a recommended upper level of 1,000 IU/day from the Institute of Medicine [38]. The American Academy of Pediatrics has recently published new guidelines for premature infants: <1,500 g birthweight: 200–400 IU of vitamin D/day, >1,500 g: 400 IU/day to a maximum of 1,000 IU/day [39]. Evidence from a randomized controlled study demonstrated that 200–400 IU/kg per day maintains normal vitamin D status [40]. Higher doses may accelerate bone turnover [41]. However, the short-term benefits of increased vitamin D intake on bone mineral status in preterm infants disappear at 9–11 years, similar to the effects seen with different doses of calcium [42].

Iron

LBW and preterm infants are at high risk for iron deficiency since iron is an endowment and is transported in the last trimester of pregnancy. The body content of iron in the term infant is estimated to be ~75 mg/kg. Premature infants have higher iron requirements partially because of the rapid postnatal growth and the depletion of iron stores by bloodletting for laboratory determination. Human milk contains 0.5 mg/l of elemental iron, and breastfed preterm infants remain in negative iron balance for at least the first 30 days of life [43]. Iron deficiency is the most common micronutrient deficiency worldwide, and risk factors include LBW, high cow’s milk intake, low intake of iron-rich diets and lower socioeconomic status. Observational studies have shown an association between iron deficiency and poor neurodevelopment in infants [44]. A recent Cochrane review concluded that enteral iron supplementation of both preterm and LBW infants confers an improvement in hemoglobin and ferritin status at 8 weeks of age [45]. A limited number of studies suggest that early iron deficiency may also adversely affect neurologic function and neurodevelopment in preterm infants. Compared with nonanemic, iron-replete infants, preterm infants with anemia (Hgb ≤10 g/dl) and low iron stores (serum ferritin ≤76 μg/l) had an increased number of abnormal neurologic reflexes at 37 weeks’ postmenstrual age [46]. It has also been shown that mild neurologic abnormalities at 5 years of age in preterm infants occur more often in infants who received iron supplementation from 2 months of age, compared with those supplemented from 2 weeks after birth [47].

As stated above, human milk has a low content of iron and must be fortified. Similarly, iron-fortified formulas need to be fed if human milk is not
used. Formulas containing 5–9 mg/l of iron appear to meet the iron requirements of erythropoiesis in healthy preterm infants during the first 6 months of life [48]. However, 18% of the infants receiving the 9 mg/l formula and 30% of those receiving the 5 mg/l formula developed iron deficiency (serum ferritin concentration <10 μg/l) between 4 and 8 months of age in that study [48]. Current recommendations are to provide a dietary iron intake of 2 mg/kg per day for infants with a birthweight of 1,500–2,500 g and 2–3 mg/kg per day in infants less than 1,500 g. Iron should be started after 2 weeks of age. If erythropoietin is used, higher amounts of iron at 6 mg/kg per day will be needed during the period of its use [49]. Another strategy to reduce the risk of iron deficiency is the timing of umbilical cord clamping. Andersson et al. [50] randomized 400 term Swedish infants to delayed (>3 min) or early (<10 s) cord clamping and showed a significant effect on neonatal iron status and also a significant reduction in the proportion of iron-deficient infants at 4 months of age (0.6 vs. 5.7%, p = 0.01). There were no increases in neonatal jaundice or any other adverse effects. A Cochrane analysis, based on studies performed in low-income countries, also concluded that late cord clamping improves infant iron status [51].

**Copper**

Copper is essential in physiologically important enzymes such as lysyl oxidase, elastase, monoamine oxidases, ceruloplasmin and copper-zinc superoxide dismutase. Copper deficiency is related to the impaired activities of these enzymes. Further, copper transporters have been described (ATP7A, ATP7B, Ctr1) and may have a role in genetic disorders of copper metabolism. Severe copper deficiency is a rare condition associated with anemia, neutropenia, thrombocytopenia and osteoporosis [52]. Human milk contains low amounts of copper, 0.2–0.4 mg/l [53]. The most recent recommendations for copper intakes are between 120 and 150 μg/kg per day [12, 54]. More recently, a calculation based on 9 clinical studies suggested that enteral copper requirements may be 210–232 μg/kg per day if zinc intake is 2–2.25 mg/kg per day to achieve a net retention of copper of 30 μg/kg per day [19].

An x-linked recessive disorder of copper metabolism, Menkes syndrome, is rare, but is manifested soon after birth and is characterized by anemia, steely hair and progressive brain degeneration [55]. Wilson disease is another autosomal recessive disorder of copper metabolism and results in toxic effects of copper; copper accumulates in the liver and brain, and symptoms include cirrhosis, eye lesions (Kayser-Fleischer ring), and neurological problems [56].
Zinc

Zinc is abundant in the human body second only to iron among the trace elements. It is essential for many enzymes and is part of metalloproteins or zinc-binding proteins. Zinc plays an important role in growth, tissue differentiation, apoptosis and signal transduction. Severe zinc deficiency in infants and children is characterized by a typical skin rash, diarrhea and slow growth [57]. Zinc homeostasis is maintained by regulation of zinc absorption and endogenous secretion in the gastrointestinal tract. Marginal zinc deficiency is difficult to diagnose due to a lack of reliable markers of zinc status [58]. Current recommendations for zinc in preterm infants are in the range of 1–2 mg/kg per day. Lot is not known about zinc accretion rate in the fetus, effects of zinc intake on other micronutrients and effect of disease states. A summary of significant findings from supplementation trails has been recently published [19]. The estimated requirement for zinc is approximately 400 μg/kg per day for premature infants 30–32 weeks’ gestation. Extrapolating data from various metabolic studies, an intake of 2.0–2.25 mg/kg per day should achieve zinc retention [19]. Term breastfed infants are relatively protected from zinc deficiency since zinc concentrations are high in colostrum and decline over the next 3 months. However, in premature infants and in those with diarrheal losses due to short bowel syndrome, zinc deficiency is of importance. Complementary foods should be high in zinc similar to iron especially when infants are weaned from breast milk. Domellof [49] recommends an enteral intake of 1.4–2.5 mg/kg per day and a parenteral intake of 400 μg/kg per day.

Long-Chain Polyunsaturated Fatty Acids

During the last trimester of pregnancy and for the first 18 months after birth, arachidonic and docosahexaenoic acids are accumulated in the cerebral cortex [59, http://journal.frontiersin.org/Journal/10.3389/fnhum.2013.00774/full, 60]. This stage of human development with its brain growth spurt [61] is particularly vulnerable to nutritional insufficiencies [62]. Long-chain polyunsaturated fatty acids (LC-PUFA) are critical for neurodevelopment, and the subject has been extensively studied. In preterm infants, the LC-PUFA are of particular importance since they do not get the benefit of placental transfer and are dependent on sources of these fatty acids in their diet. Possible effects of LC-PUFA supplementation include visual and cognitive effects. Numerous studies have reported on the effects of LC-PUFA on the developing brain [63]. A Cochrane review [64] concluded that no clear benefits or harms were demonstrated for preterm in-
fants receiving LC-PUFA-supplemented formula. Various studies reporting outcomes of LC-PUFA supplementation are summarized by Lapapillonne et al. [63]. Studies using higher doses of docosahexaenoic acid supplementation (0.5% total fatty acids compared to 0.2–0.4% previously used) reported improved growth and, in addition, improved neurodevelopment in boys [65]. Other studies have shown controversial effects [66, 67]. In a more recent meta-analysis, LC-PUFA supplementation failed to show any significant effect on early infant cognition [68]. Thus, as stated by Lapillonne et al. [63], the ‘essentiality’ of arachidonic acid and docosahexaenoic acid has been recognized and that the current recommendations should remain [12].

Feeding Low-Birthweight and Growth-Restricted Infants

The specific requirements of this cohort of infants are unknown. Therefore, the stated goals [69] are similar to that for premature infants. WHO evaluated studies of infants <2,500 g or gestational ages <37 weeks. Nutritional requirements were not distinguished for growth-restricted infants. Breastfeeding or provision of breast milk was highly recommended.

In summary, nutrition in premature and LBW infants is a continuum from birth through discharge and after. Although this chapter focused on enteral nutrition, particular attention is needed during parenteral nutrition, human milk feedings and choice of formulas appropriate for birthweight. Current recommendations need to be followed as most deficiency states are preventable and the goal is to promote optimal growth and development as much as possible.

Disclosure Statement

The author declares that no financial or other conflict of interest exists in relation to the contents of the chapter.

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Role of Specific Nutrients in Low-Birthweight Infants


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