Definition and Frequency of Preterm Birth

Preterm births are increasing in the United States and the world. Preterm infants are also surviving long-term at ever-earlier gestational ages. (Rodriguez 2016; Younge et al 2017)

According to the World Health Organization, **preterm** is defined as babies born alive before 37 weeks of pregnancy are completed. Of those births, there are multiple subcategories based on gestational age, as follows:

- Preterm: 32 to <37 weeks’ gestation
- Very preterm: 28 to <32 weeks’ gestation
- Extremely preterm: <28 weeks’ gestation (WHO 2015)

Common causes of preterm births include multiple pregnancies, infections, chronic conditions such as diabetes and high blood pressure, prior preterm birth, and genetic influences; some ethnic communities (eg, African-Americans, Hispanic Americans) have higher rates of preterm birth in the U.S. versus the general population. (Rodriguez 2016; Younge et al 2017). However, in many cases no cause for preterm birth can be determined. (WHO 2015)
Both preterm infants and full-term infants experience high rates of growth in early life. Preterm infants have traditionally been expected to achieve a growth rate similar to the intrauterine growth rate (AAP 2014). Emerging research suggests that this goal may be inappropriate. Rather than tracking along the birth centile, preterm newborns can be allowed to experience the initial weight loss and then be assigned a new target centile based on the weight at 2-3 weeks (Cole et al 2014) (Figure 1). Others suggest a 0.8 Z-score drop following birth that then becomes the new slope of growth on an appropriate growth chart (Rochow et al 2016).

Figure 1: Graphic representation of mean neonatal growth (weight and longitudinal) rates of UK neonates versus 1990 British growth weight reference. (Cole et al 2014)

Currently accepted infant growth standards can be especially challenging for preterm infants to achieve due to nutritional deficits that often occur in these very small infants that affect both physical growth and brain/neurological development. Regardless of the target centile chosen, poor growth is unacceptable. Growth failure frequently occurs in sick newborns due to inadequate nutritional intake and/or absorption, and can result in poor neurodevelopmental outcomes. Growth failure in neonates often starts in the first weeks of life and tends to worsen over time. Current estimates indicate that 80% of preterm infants go home from the hospital with impaired growth. (Riskin 2015). Expected growth velocity for preterm infants is approximately 15-20 g/kg per day (Ehrenkrantz 2006).

In addition to an astounding rate of physical growth, significant brain development occurs during early life. Impairment of growth rate and/or neurodevelopment, with potentially lifelong effects, can occur in preterm infants if nutritional needs are not met.

Figure 2 is a graphic illustration of the exponential expansion that occurs in the auditory cortex, receptive language areas, speech production and higher cognitive functions over the first 1000 days of prenatal and early postnatal life. The brain continues to develop after the first 1000 days, but never again achieves this exponential level of growth.
The controversy over weight gain patterns emerged in part because of a gestational-age-related differences in how preterm infants lose or gain weight after birth. Preterm babies born after 29 weeks experience initial weight loss due to the irreversible, physiological loss of extracellular fluid during postnatal adaptation to extrauterine conditions. Meanwhile, postnatal weight loss is generally absent in preterm infants born prior to 29 weeks. (Rochow et al 2016; Cole et al 2014). Revised, evidence-based preterm growth guidelines that reflect these extrauterine variations according to gestational age do not yet exist, presenting challenges for clinicians.
The Centers for Disease Control and Prevention (CDC) has identified pervasive nutritional problems in infants and young children in the United States which may be further exacerbated in preterm infants. (Reinold 2009; Polhamus 2007) While there is no clinical dispute that breastfeeding is the gold standard in infant nutrition, a unique set of challenges for both mother and baby exist for breastfeeding preterm infants. These include:

- Difficulty of initiating and maintaining an adequate breast milk supply during a time of unusual stress and prolonged mother-infant separation
- Hormone-related changes affecting breastmilk composition and supply in a preterm nursing mother versus a full-term nursing mother (eg, lower protein and fat levels, differences in foremilk/hindmilk consistency, etc.)
- Increased nutritional needs of the preterm infant compared to that available in a preterm mother’s milk and/or donor milk.

The nutritional requirements of preterm infants exceed those of term, healthy newborns. Protein and mineral needs are of particular concern and difficult to meet. Selected nutrient requirements are listed in the table below. (Koletzko 2014):

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Preterm Infant Needs (Range)</th>
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<tbody>
<tr>
<td>Energy</td>
<td>110-130 kcal/kg</td>
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<tr>
<td>Protein</td>
<td>3.5-4.5 g/kg</td>
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<tr>
<td>Vitamin A</td>
<td>400-1100 mcg RE/kg</td>
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<tr>
<td>Vitamin D</td>
<td>400-1000 IU/day</td>
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<tr>
<td>Vitamin E</td>
<td>2.2-11 IU/kg</td>
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<tr>
<td>Calcium</td>
<td>120-200 mg/kg</td>
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<tr>
<td>Phosphorous</td>
<td>60-140 mg/kg</td>
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<tr>
<td>Iron</td>
<td>2-3 mg/kg</td>
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<tr>
<td>Zinc</td>
<td>1.4-2.5 mg/kg</td>
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Human milk and breastfeeding have strong advantages for all infants, but for the preterm newborn, the benefits of human milk are even greater. In addition to all the traditional benefits of breastmilk, human milk can decrease the risk of sepsis and life-threatening necrotizing enterocolitis in preterm infants. Human milk also has the potential to improve cognitive, metabolic, cardiovascular and visual outcomes during both the nursing period and throughout life. Human milk is the only evidence-based therapy that can offer these benefits to all babies. (O’Ballard et al 2013) Despite the significant advantages listed above, human milk requires fortification to meet the nutritional needs of preterm, very low birth weight (VLBW) infants. (AAP 2012)

Composition of human milk varies from mother to mother in general, and according to gestational/corrected age of infants in particular. For example, the mother of a preterm infant generally makes milk that is higher in protein than the mother of a full-term infant of the same postnatal age. Even considering this early compositional difference, human milk often cannot meet the additional protein needs required for preterm infants in order to achieve appropriate growth targets. Supplementation with human milk fortifier and/or commercial preterm formula may then be appropriate; this will be discussed in detail in a later section. Furthermore, mineral composition—especially calcium, phosphorus, zinc, and sodium—of human milk alone is inadequate for preterm infants to achieve growth and development targets at a rate that puts them on pace to eventually catch up with full-term infants.

Factors that can influence the composition of human milk include:

- **Length of gestation**, Preterm milk has higher protein and sodium content compared to term milk;
- **Stage of lactation**, including colostrum, transitional, and mature;
- **Within feeding variation**, For example, fat and energy content are higher in hind vs. foremilk;
- **Maternal factors**, including BMI, diet, and health can affect milk composition; between-mother milk variability is also significant;
- **Processing**, such as pasteurization and sterilization of donor milk, storage of expressed milk in the refrigerator and/or freezer, and feeding methods (eg, breast versus expressed human milk via tube or bottle delivery.)

The following chart illustrates how protein composition can vary widely across several pairs of human milk categories. Protein is particularly important for preterm infants due to its direct impact on growth rates. As noted in the table, protein concentrations between preterm and term milk and even mother-to-mother vary widely; this variation is generally not observed for most other nutrients. Mother’s own milk is also generally higher in protein than pooled donor milk, because donor milk is often provided by mothers in later stages of lactation. (Picciano 2001; Wojcik 2009; Gross et al. 1980; Saarela T, et al. 2005; Groh-Wargo et al 2014.)
Pooled donor milk is used when mother’s own milk is not available or mother’s milk supply is insufficient. While donor milk may reduce the risk of necrotizing enterocolitis in preterm infants, it unfortunately is associated with slower growth than the feeding of mother’s own milk. Consequently, many NICUs use donor milk as a bridge to full feeding and then transition to a more nutrient dense preterm formula if mother’s own milk supply is not sufficient. Donor milk is safest when procured via vetted commercial and/or hospital-based sources that screen milk donors and pasteurize/sterilize the donor milk against transmission of disease and/or metabolites of drugs or other substances that may harm infants.

Fortified human milk (FHM). Human milk is the preferred option for feeding infants but requires fortification to meet the nutritional needs of preterm newborns. (AAP 2012; Schanler 2015)

There are 3 options currently available in the United States to fortify expressed human milk for preterm infants:

- **Pre measured, individual packets of powdered or concentrated liquid human milk fortifier.** Preterm infants generally start at 50% strength via mixing ratio of 1 packet to 50 ml of expressed human milk, increased as tolerated to full strength; or 1 packet to 25 ml expressed human milk.
- **Mixing a high calorie/high nutrient density preterm formula with expressed human milk.** This option works well when the volume of human milk is insufficient to meet the fluid needs of the baby. Different mixing ratios can be used for meeting the needs of each individual preterm infant’s nutritional condition.
- **Commercial human milk based human milk fortifier.** This product is available from a commercial manufacturer. The fortifier is concentrated donor human milk enriched with minerals and is available as a frozen liquid, which can then be added to expressed human milk.

Human milk fortification is generally initiated when a baby reaches about 60-80 ml per kg per day of enteral feeding, but this can vary by institution, by infant, and by clinician and/or parent preferences; there is no singular set of clinical guidelines for this topic. Evidence suggests that the transition from parenteral to enteral nutrition is a period of nutrition risk and that fortification early in the course of enteral feedings is well tolerated (Miller et al 2014; Tillman et al 2012). Overall current trends are moving toward earlier initiation of FHM feeding. It is generally accepted that commercial human milk fortifiers can be used safely until an infant weight of about 3.6 kg is achieved.
The Human Milk Banking Association of North America (https://www.hmbana.org/) (HMBANA) provides information about human milk banks in the United States as well as the safe collecting, processing, and distribution of donor milk from properly vetted sources. Donor human milk is available locally from about 16 regional HMBANA milk banks, and nationally for shipment from Prolacta Bioscience (http://www.prolacta.com/) and from Medolac Laboratories through the Mothers Milk Cooperative. (http://www.mothersmilk.coop/)

Procurement of donor breast milk from unvetted sources (eg, informal sharing among friends/relatives/neighbors; purchase from unknown/unvetted sources) is a growing problem, and the American Academy of Pediatrics issued a position statement about the issue in 2017. The purchase of human milk from non-vetted private sellers through the internet and/or procured via informal milk sharing among relatives, neighbors, or friends is not recommended (AAP 2017) because this donor milk has not been properly screened for contamination with infectious diseases transmittable via breastmilk (eg, HIV) or metabolites of drugs (caffeine, tobacco/nicotine, over-the-counter substances, illegal substances) that may be harmful to infants. Donor milk procured from unvetted sources also may be adulterated with non-human-milk substances (eg, cows' milk, water, other substances) that can dilute essential nutrition or may even be harmful or toxic to infants. Several recent studies highlight the risk of purchasing human milk that has not been stored, packaged, and shipped under strict conditions from donors who have not been screened. Milk that has not been transported under sterile conditions may contain potentially dangerous bacteria (eg, salmonella). (Geraghty et al 2013; Keim et al 2013; Keim et al. 2015; Geraghty SR et al 2015; Keim SA 2015a)
Some preterm infants may not be able to achieve growth targets with human milk alone, or even when using fortified human milk. This is especially a challenge when donor milk is the only human milk available. (Koletzko et al 2014) Further, human milk from the mother or from vetted donor sources is not always available. These preterm infants are therefore candidates to receive one or more commercially available preterm formulas, both inside the NICU unit and/or post-discharge into the community prior to transitioning to a commercial term formula once parity with term growth and weight targets is obtained.

Commercial preterm formulas for enteral feeding are manufactured in liquid ready-to-feed forms with caloric densities of 20-30 kcal per ounce. Preterm formulas offer preterm infants many advantages over standard formulas. These include faster growth, better nitrogen retention, more lean body mass accretion, improved bone mineralization, and superior long term outcomes. (Lucas et al. 1998; Ehrenkrantz et al 2007; Bishop NJ 1993; Brunton et al. 1998).

**Preterm formulas** are generally dispensed within the neonatal intensive care unit, though some very small preterm babies and others with special nutritional needs may also receive them at discharge. High-protein versions of preterm formulas, which are appropriate for all very low birth weight infants, are also available. Preterm formulas contain macronutrients that are distinct from standard-term formulas regarding both composition and nutrient density, and increased concentrations of most micronutrients. Preterm formulas can be safely used until a baby weighs about 3.6 kg.

**Preterm discharge formulas** (also called nutrient-enriched formulas) are designed to meet the needs of larger preterm babies, such as those born between 1800-2500 grams, and/or for the continued feeding of former very low birth weight infants at the time of NICU discharge. Preterm discharge formulas can be safely used until 9-12 months corrected age, although only the most preterm, extremely low birth weight infants may need these enriched formulas for that long.

<table>
<thead>
<tr>
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<th>Preterm(High Protein)</th>
<th>Preterm discharge</th>
<th>Standard milk-based</th>
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<tbody>
<tr>
<td>Kcal/oz</td>
<td>24</td>
<td>22</td>
<td>19-20</td>
</tr>
<tr>
<td>Pro (gm)</td>
<td>3-3.3 (3.3-3.6)</td>
<td>2.8</td>
<td>2.1</td>
</tr>
<tr>
<td>A (IU)</td>
<td>1000-1350</td>
<td>350-450</td>
<td>300</td>
</tr>
<tr>
<td>B₆ (µg)</td>
<td>150-250</td>
<td>60-100</td>
<td>60</td>
</tr>
<tr>
<td>Ca (mg)</td>
<td>165-180</td>
<td>105-120</td>
<td>80</td>
</tr>
<tr>
<td>Zn (µg)</td>
<td>1300-1500</td>
<td>1000-1200</td>
<td>750-1000</td>
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Selected Nutrient Levels (per 100 kcal) for Available Preterm, Preterm Discharge, and Standard Formulas
Over the past two decades, significant progress has been made in the clinical understanding of the biochemical dietary needs of preterm and term infants. For example, ongoing advances in research have enabled clinicians to examine the value of long-chain polyunsaturated fatty acids (LCPUFAs) in relation to brain and vision development. (Clandinin 2005; Birch 2002; Morale 2005; Uauy 2003) Compared to infants who received infant formula that was not supplemented with LCPUFAs, a meta-analysis of infants who received infant formula supplemented with LCPUFAs demonstrated that infants’ visual acuity (measured via either visual evoked potential or behaviorally) improved at 2, 4, and 12 months of age. (Qawasmi 2013) A six-year study by Willatts and colleagues, however, found that when infants fed LCPUFA-enriched formulas were compared with infants fed unsupplemented formula and breastfed infants, no statistically significant differences in IQ or attention control were observed. (Willatts 2013)

While the benefits of postnatal supplementation of docosahexaenoic acid, or DHA, remain somewhat controversial, there is no controversy that both preterm and very low birth weight (VLBW) infants are deficient in DHA. DHA is one type of LCPUFA critically important to neurodevelopment and visual acuity. DHA is found in all human milk, including donor human milk, and pasteurization does not alter DHA concentrations; however, the overall levels of DHA in banked donor milk appear to be lower than in mothers’ own milk. (Valentine CJ 2010) Further research is needed to determine whether DHA deficiencies in preterm and VLBW infants may also be based in part on formula composition and/or possibly socioeconomic factors.
In recent years, a growing body of research interest has studied the possible role of prebiotics and probiotics in preterm, term infant, and toddler nutrition to improve overall gastrointestinal health as well as to prevent the development of various food allergies. (Hol 2008; Srinivasjois 2009; West 2009) A 2014 Cochrane review found that supplementation of preterm infants’ diets with prebiotics and probiotics contributed positively to the development of a healthy gut microbiome, and may reduce overall risk of developing necrotizing enterocolitis in this population. (AlFaleh & Anabrees 2014) Human milk oligosaccharides (HMOs) are important prebiotics that exist naturally in human milk and may also help to prevent NEC by influencing the intestinal microbiota in premature infants. These HMOs may serve to decrease pathogens associated with sepsis and NEC. (Pacheco 2015) Some commercial formulas have synthetic-yet-chemically-identical oligosaccharides added to their nutritional composition as a result of this research, but it is too early to determine whether or not these commercial formula products supplemented with HMOs will net similar results. However, a 2016 study found that purified sialylated bovine milk oligosaccharides (S-BMOs) improved the inadequate gut microbiota of severely undernourished Malawian term infants, so it is possible either S-BMOs and/or laboratory-created HMOs may play an important role in future feeding standards for preterm infants. (Charbonneau et al 2016)
The Importance of Nutritional Counseling for Parents and Caregivers of Preterm Infants

Parents and caregivers of preterm infants encounter numerous barriers in providing proper nutrition to their high-risk newborns when the time of discharge approaches. These include, for example, educational barriers, such as lack of knowledge, and communication challenges with NICU clinical staff during a time of extreme stress. Other identified systems-related barriers include time constraints, patient noncompliance, and cost/reimbursement issues. (Kushner 1995) While human breastmilk is the gold standard for infant feeding, mothers of preterm infants often struggle with insufficient milk supply and difficulty with the transition from tube and bottle feedings to feedings at the breast.

Even in well-supported clinical settings, preterm and term infants who do not receive at least some breast-milk-based nutrition face an increased risk of infections. (Stuebe 2010) Support for the mother during the nursing period is often overlooked and/or under-resourced, especially among mothers of preterm infants. This can result in poor outcomes for both mother and infant. For example, mothers who elect to feed their infants with formula report negative emotions, such as guilt and sense of failure, which may add to the overall stress of having an infant in the NICU. (Lakshman 2009)

Achieving the proper nutritional balance for preterm infants post-discharge further complicates the issue of breast-versus-bottle feeding challenges for new mothers. Often, it is unclear which formulas are best to use for preterm infants following discharge from the hospital and as the infant grows. Mothers choosing a combination of breast milk and formula have particularly expressed a need for additional information and guidance on infant nutrition from clinicians. (Greenberg Quinlan Rosner Research 2009) Mothers also report receiving misinformation from the community and/or from family members and a general lack of referral to evidence-based resources that could help improve their knowledge when faced with breastfeeding challenges. (Cross-Barnet 2012) Physicians, nurses, and pediatric dietitians with expertise in preterm infant care, nutrition, and growth are best-positioned to provide this additional support and guidance to parents and caregivers of preterm infants as they transition out of the NICU and into the community.
Enteral feeding of preterm infants according to the best clinical nutritional evidence is an essential component of achieving positive long-term growth and development outcomes for preterm infants and their families. While new clinical evidence surrounding preterm nutrition continues to emerge and some components remain controversial, the overall evidence base regarding safe, optimal feeding options, nutritional components, and methods for preterm enteral feeding is strong. Not only that, there are myriad clinically acceptable options for achieving optimal nutrition and outcomes for preterm infants, ranging from human milk and fortified human milk to a range of commercially available preterm infant formulas, preterm discharge formulas, and standard formulas. Recent evidence suggests that growth targets be established around 2-3 weeks of age. Human milk is the best feeding for all newborns but requires fortification to meet the nutritional needs of preterm infants. If human milk is not available, preterm and preterm discharge formulas are the best alternative. Some very small preterm infants may benefit from a continued nutrient-dense diet at discharge. New clinical nutrition and outcomes data continue to emerge and will likely continue to support the development of improved nutritional strategies and products for preterm infants that clinicians, parents, and caregivers can consider in the context of both the best available evidence and their own unique clinical circumstances.


