Promoting healthy growth and nutrition in preterm infants: A challenge for clinicians and researchers

Christoph Fusch and **Samira Samiee-Zafarghandy**

Division of Neonatology, Department of Pediatrics, McMaster University, Hamilton, Ontario, Canada

Background

The ultimate goal of the quality post-natal care of premature infants is to provide an extra-uterine environment with high resemblance to intra-uterine life and primed for an undisrupted growth and development. Ideally, neonatal intensive care shall provide premature infants with equal chances in all aspects of development compared to as their counterparts in utero until they reach term age. However, in real life, preterm birth causes major deviations in various aspects of physiology:

- Disruption of a fast growing body from the placental supply.
- Immature postnatal transition; its major determinant is pulmonary adaptation, with high demand for various degrees of support over a variable period of time.
- Perinatal pathology leading to preterm birth with varying degrees of severity and healing time.

Furthermore, different management strategies within and amongst neonatal intensive care units (NICU) as well as various degrees of experience, consistency of care and team functionality contribute to nosocomial complications at different levels [1,2]. All of which, affect the integrity and potential of the body of the premature infant in different aspects of development and intact organ function, such as:

- Pulmonary system (pulmonary inflammation, persistent pulmonary hypertension, pulmonary hypercirculation);
- Vascular endothelial system (sepsis/neonatal inflammatory response syndrome with or without periventricular leucomalacia);
- Central nervous system (germinal matrix hemorrhage grade 2);
- Gastrointestinal system (necrotizing enterocolitis) and
- Nutrition.

Each of the above conditions alone or in combination with the other factors affects the potential to establish an anabolic metabolism, which is essential for optimal growth and otherwise would lead to postnatal growth restriction.

Improvement of perinatal management, from intrauterine conditioning and timing of birth to less invasive ventilatory management, to more efficient feeding strategies and infection prevention has resulted to higher survival rates, with centers of excellence achieving >92% disease free survival amongst very low birth weight (VLBW) infants, but not necessarily paying a price for potential morbidity [3,4].

Improved organ function challenges currently defined the patterns of appropriate postnatal growth and development and of optimum delivery of macro- and micronutrients to these vulnerable infants.

What is appropriate postnatal growth?

As a first step the definition of appropriate postnatal growth needs to be elucidated. There is little doubt that prematurely born infants should ideally continue to follow the intrauterine rate of growth. There are also robust data available determining the required nutritional supply, specifically protein and calorie intake, which translates into this optimum pattern of growth [5]. The accepted reference daily intake of protein, which determines the rate of accretion of lean mass (longitudinal growth), is 3.5–4.5 g/kg/day. The dietary reference intake for daily calorie is 135–145 kcal/kg/day [6].

The protein–energy intake needs to be in a reasonable balance, as excess calorie intake, while protein intake is not optimized, will promote accretion of fat mass. On the other hand, when caloric intake is not optimized, excess intake of protein will lead to protein oxidation and formation of urea for excretion of excess nitrogen. This process not only costs energy for synthesis and renal excretion but also requires extra water, as urea is a strong osmolyte. Moreover, it is unclear if carbohydrate- or fat-based calorie should be the main composite of non-protein calorie intake. Kashayp et al. found challenging effects on the body composition of three study groups while varying the fat: carbohydrate ratio in an otherwise isocaloric and isoproteinic diet [7,8].

Postnatal adaptation and body weight

Apart from the provided basic data, the growth trajectory that the premature infant will be adjusted to, after the post-natal adaptation, needs to be addressed. Two factors shift the weight of an infant across the growth percentile:

1. The loss of body water, mostly due to contraction of extracellular fluid space
2. Insufficient nutrient intake, until the infant is on fully fortified enteral nutrition.

The first factor is an inevitable process and its effect size is defined by physiology. The effect size of the second factor is determined by underlying pathology as well as the skills and nutritional competence of the managing center and is in part evitable. Unfortunately, the current components of parenteral nutrition may achieve up to 100 kcal/kg/day and are thus not suited to fulfill the nutritional needs of an extremely low birth weight (ELBW) infant with target growth rate of 17–22 g/kg/day.

What is the optimum postnatal growth trajectory?

There are justifications to assume that preterm infants should follow a percentile below their birth percentile. Our recent data suggest an offset of approximately 0.8 Z-score [9]. Let us illustrate the course of healthy term or late preterm infants as examples: After contraction of extracellular space (i.e. maximum weight loss), these infants grow on trajectories that are parallel, but have a visible offset from their birth percentile. This is also reflected by standard growth curves that smooth in this offset over a period of 1–2 months [10]. It is our current understanding that it will become important to identify the individual postnatal trajectory in order to adjust nutritional intake appropriately. Observed deviations from optimal growth might go along with altered body composition and thus increase in the risk of early onset adult diseases (DOHaD hypothesis) [11]. Of interest, postnatal growth trajectories may be different for preterm infants exposed to intrauterine conditions that deflect the fetal growth from its genetic potential.

For the future we see a challenge for clinical chemists to provide neonatologists and nutritionists with validated biomarkers to monitor and adjust nutrition for the healthiest growth pattern.

The role of target fortification (TFO)

There is little doubt that mother's own milk is the best in tolerance and bio-digestibility. Breast milk provides a variety of factors (hormones, oligosaccharides, vitamins, cellular components, growth factors, etc.) that, although not fully understood, seem to be important. However, human milk has been “engineered” by evolution to meet the needs of term (growth rate of 5–9 g/kg/d), but not preterm infants (15–22 g/kg/d). Hence, breast milk needs to be fortified. Commercially available fortifiers have been designed assuming that they provide average macronutrient content of breast milk (fat 3.6, protein 1.5, lactose 6.5 g/dl). However, in real life there is a huge variation in their composition ranging from 1 to 9 g/dl for fat, 0.5–2.3 g/dl for protein and 4.0–8.8 g/dl for lactose (Fig. 1). This means that only 75% of the preterm infants, on standard fortified breast milk (STBF), receive sufficient amount of nutrients while 25% of them don't. Indeed, recent reports state that up to 58% of preterm infants on STBF experience postnatal growth restriction [12]. Especially babies on donor breast milk or those on breast milk from late lactation periods are at risk.

One approach to increase the nutrient supply is to measure the breast milk content on an individual basis and selectively fortify the missing nutrients with modular components. We have recently published the first results of a pilot study that implemented the procedure of:

- Validation of cow's milk infrared milk analyzers,
- Establishment of the infrastructure of daily measurements at bedside (including osmolality),
- Daily prescription of target fortification and
- Proper handling of milk fortification [13].

The results of this study (Fig. 2) showed that growth was closely related to milk intake in the target fortification group ($r^2 = 0.68$) whereas it was not related in the standard fortification group ($r^2 = 0.02$). During this project we have also established and validated micro-methods that enabled us to measure all macronutrient content of breast milk in 1.5 ml of sample volume [14]. We also established a new ultra performance liquid chromatography (UPLC)/mass spectrometry (MS)/MS method for the rapid determination of lactose [15].

At present time, all milk analyzers need further validation to be approved by the Food and Drug Administration (FDA) and thus may be introduced in the routine clinical practice. Currently, there are some challenges for clinical chemistry to provide a differential measurement of the carbohydrate fraction, namely lactose and oligosaccharides, as their nutritional value is different. We also feel that it would be beneficial that fast micro-methods for breast milk analysis could be developed and implemented in the clinical laboratory in order to follow Good Laboratory Practice (GLP) and Good Clinical Practice (GCP).

References

1. Rogowski JA, Horbar JD, Staiger DO, Kenny M, Carpenter J, Geppert J. Indirect vs direct hospital quality indicators for very low-birth-weight infants. *JAMA*. 2004; 29:202–9.
2. Phibbs CS, Baker LC, Caughey AB, Danielsen B, Schmitt SK, Phibbs RH. Level and volume of neonatal intensive care and mortality in very-low-birth-weight infants. *NEJM*. 2007; 35:2165–75.
3. van Haastert IC, Groenendaal F, Uiterwaal CS, Termote JU, van der Heide-Jalving M, Eijssers MJ, et al. Decreasing incidence and severity of cerebral palsy in prematurely born children. *J Pediatr*. 2011; 159:86–91. [PubMed: 21367430]
4. LS http://www.klinikum.uni-heidelberg.de/uploads/media/GBA_Report_2012.pdf.
5. Ziegler EE, Thureen PJ, Carlson SJ. Aggressive nutrition of the very low birthweight infant. *Clin Perinatol*. 2002; 29:225–44. [PubMed: 12168239]
6. Agostoni C, Buonocore G, Carnielli VP, De Curtis M, Darmaun D, Decsi T, et al. Enteral nutrient supply for preterm infants: commentary from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition Committee on Nutrition. *JPGN*. 2010; 50:85–91. [PubMed: 19881390]
7. Kashyap S, Towers HM, Sahni R, Ohira-Kist K, Abildskov K, Schulze KF. Effects of quality of energy on substrate oxidation in enterally fed, low-birth-weight infants. *AJCN*. 2001; 74:374–80.
8. Kashyap S, Ohira-Kist K, Abildskov K, Towers HM, Sahni R, Ramakrishnan R, et al. Effects of quality of energy intake on growth and metabolic response of enterally fed low-birth-weight infants. *Pediatr Res*. 2001; 50:390–7. [PubMed: 11518827]
9. Preeya, Raja. Open Access Dissertations and Thesis. Hamilton, Ontario: Department of Medical Sciences, McMaster University; 2013. Developing predictive models for postnatal growth of preterm infants during and after unimpaired postnatal adaptation. (<http://digitalcommons.mcmaster.ca/opendissertations/8161/>)
10. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013; 13:59. [PubMed: 23601190]
11. Barker DJ. Fetal origins of cardiovascular disease. *Ann Med*. 1999; 31(Suppl 1):3–6.
12. Henriksen C1, Westerberg AC, Rønnestad A, Nakstad B, Veierød MB, Drevon CA, et al. Growth and nutrient intake among very-low-birth-weight infants fed fortified human milk during hospitalisation. *Br J Nutr*. 2009; 102:1179–86. [PubMed: 19445820]
13. Rochow N, Fusch G, Choi A, Chessell L, Elliott L, McDonald K, et al. Target fortification of breast milk with fat, protein, and carbohydrates for preterm infants. *J Pediatr*. 2013; 163:1001–7. [PubMed: 23769498]
14. Choi, A., Fusch, G., Rochow, N., Sheikh, N., Fusch. Establishment of micromethods for macronutrient contents analysis in breast milk. *Matern Child Nutr*. Jun 18. 2013 <http://dx.doi.org/10.1111/mcn.12053> [Epub ahead of print]

15. Fusch G, Choi A, Rochow N, Fusch C. Quantification of lactose content in human and cow's milk using UPLC-tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2011; 879:3759–62.

Fig. 1.

True variation of protein content in standard fortified breast milk of 10 lactating mothers. The numbers on the x-axis represent the number of subsequent 12-hour batches analyzed for this study. There is a considerable inter- and intraindividual variation of protein content. Dashed line indicates upper limits for ESPGHAN recommendations [5], the shaded area represents the recommended range. A large number of standard fortified feedings do not fulfill the recommendations. The data are similar for the other two macro-nutrients fat and lactose (data not shown).

Data taken from [13] and reproduced with permission.

Fig. 2.

Effect of target fortification on growth rates: squares represent 10 ELBW infants with target fortification (TFO), crosses represent 20 matched pair infants (± 1 week of gestation, ± 100 g of birth weight) with standard fortification. Growth rates of infants on TFO are closely related to the volume of milk intake ($R^2 = 0.68$) while babies on standard fortification are not ($R^2 = 0.02$). TFO prospectively identifies mother–infant pairs with insufficient levels of macronutrients in breast milk.

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