

Post-discharge formula feeding in preterm infants: A systematic review mapping evidence about the role of macronutrient enrichment. 2016

Teller et al. *Clin Nutr* 35(4):791–801

Early growth deficits in preterm infants have been associated with neurocognitive impairment at 18 or 24 months of age [1,2]. Many preterm infants experience intra- and extrauterine growth retardation and are unable to recover during hospital stay. Different nutritional intervention studies addressed recovery growth in the post-discharge period aiming for improved growth trajectories. These studies were heterogeneous and differed in more than 20 parameters, which does not allow for a reliable meta-analysis despite insightful efforts [3]. A different approach is mapping the evidence visually as reported and provide collective insights into available data. A novel finding was that preterm infants seem to adjust their volume intake by energy density. This finding increased relevance of nutrient to energy ratios in intervention products. Protein-to-energy ratios were plotted against growth parameters at three, six, and 12 months of age which indicated early impact particularly on length and make the supplemental data of this publication insightful as well [4].

Approach

Whilst meta-analyses provide the highest level of evidence, data paucity and study heterogeneity often result in simplified comparisons bearing the risk of involuntarily superficial conclusions. Nutritional studies are at high risk for this phenomenon because they offer a complex matrix of macro- and micronutrients that are rarely comparable. A less systematic yet inclusive and reproducible approach is “evidence mapping”. This visualizes reported measures of all available studies and differences in study setup.

Methods

A systematic search led to 31 studies from 1980 - to 2016. Multiple publications associated with the same trial were combined. Interventions were grouped according to formula composition per 100 ml even if termed differently in the original paper: standard term formula (STF, 60-70 kcal), preterm formula (PTF, 80+ kcal) and post-discharge formula (PDF, 70-79 kcal). In isoenergetic comparisons, the enriched formula was identified as “e” e.g. ePDF. All studies were included. The authors list 22 factors of heterogeneity and found a high variation in interventions start and duration, observational times, study period and follow-up, which they display in figure 1 and table 1, respectively.

Growth

Weight, length, and head circumference parameters were plotted for each assessment time together with the overall conclusion of the original authors. Isoenergetic STF comparisons did not lead to anthropometric changes although trends early in the intervention were noted. PDF and PTF seemed to achieve more favourable results particularly for weight and lengths although not consistently. Only one study, that was well-conducted, showed consistent unfavourable outcomes at every measurement point.*

Neurodevelopment

Only one of the ten studies observed significant favourable changes in neurodevelopmental outcomes at 24 months.

Volume intake and nutrient-to-energy ratio

Twenty-one studies kept records on volume intake. The collected information suggested that infants adjust volume intake on energy-density as it was noted that higher volumes of less energy-dense formula were consumed. This raised awareness that nutrient-to-energy ratios may be more relevant than each nutrient’s concentration alone. Therefore, the “evidence mappers” plotted protein-to-energy (P:E)-ratios against anthropometric values at three, six, and 12 months of age without statistical adjustments (displayed in figure 6, in the supplemental material of the paper). The graphs indicated that those fed a higher P:E-ratio formula displayed slightly faster gain in weight, length and head circumference especially at earlier times than those on a low(er) P:E ratio formula.

Conclusion

Evidence mapping is a valuable tool to visualize outcomes from heterogenetic studies. It could be especially useful in combination with meta-analyses on the same topic balancing strict statistical approaches with experience-based insights.

Clear conclusions for product composition or the need for individual nutrients were impossible to draw due to the high heterogeneity in products – as well as almost every other parameter documented. The “evidence mappers” illustrated that with a higher caloric density more often favourable outcomes on growth parameters overall or at certain times were reported than not. Neurocognitive development was generally not affected.

Even with all the limitations, slight growth benefits were shown when providing higher P:E ratios (between 2.5 and 3) until six months of corrected age. Since preterm infants seem to be able to adjust their volume intakes based on energy density, the ratio of nutrients to energy seem much more relevant than individual concentrations alone. This should be considered when investigating post-discharge interventions and product compositions.

*Note of the editor: This study affects the outcome of any meta-analysis on the topic heavily.

Post-discharge formula feeding in preterm infants: A systematic review mapping evidence about the role of macronutrient enrichment. 2016

Teller et al. Clin Nutr 35(4):791–801

References

- [1] 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. 2006 Pediatrics 117(4):1253–1261. doi: 10.1542/peds.2005-1368
- [2] Stephens BE, Walden RV, Gargus RA, Tucker R, McKinley L, Mance M, Nye J, Vohr BR. First-week protein and energy intakes are associated with 18-month developmental outcomes in extremely low birth weight infants. 2009 Pediatrics 123(5):1337–1343. doi: 10.1542/peds.2008-0211
- [3] Young L, Embleton ND, McGuire W. Nutrient-enriched formula versus standard formula for preterm infants following hospital discharge. 2016 The Cochrane database of systematic reviews 12:CD004696. doi: 10.1002/14651858.CD004696.pub5
- [4] Teller IC, Embleton ND, Griffin IJ, van Elburg RM. Post-discharge formula feeding in preterm infants: a systematic review mapping evidence about the role of macronutrient enrichment. 2016 Clin Nutr 35(4):791–801. doi: 10.1016/j.clnu.2015.08.006. Supplemental material: [https://www.clinicalnutritionjournal.com/article/S0261-5614\(15\)00227-7/fulltext#supplementaryMaterial](https://www.clinicalnutritionjournal.com/article/S0261-5614(15)00227-7/fulltext#supplementaryMaterial)