Nutrient-enriched formula versus standard term formula for preterm infants following hospital discharge

01 March 2013

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1. INTRODUCTION

Preterm babies continue to remain at high risk for poor growth and nutritional challenges not only during infancy and early childhood, but also in later life. Despite having a higher potential for growth during the first few months after birth, preterm infants do not grow as well as their term counterparts at 3 and 8 years, and in adulthood (1–3).

In the majority of preterm infants, there is a large discrepancy between daily recommended dietary intakes and actual intake during the first few weeks of life, resulting in substantial nutritional deficits. At discharge from hospital, preterm infants may have low body stores of nutrients, deficient bone mineralization, and an accumulated energy deficit (4). This concern has driven neonatologists and nutritionists to search for better feeding options for achieving growth similar to fetal growth rates with similar body composition and satisfactory functional development (5).

The present Cochrane (6) review aimed “to determine the effect of feeding nutrient-enriched formula compared with standard term formula on growth and development for preterm infants following hospital discharge.”

2. METHODS OF THE REVIEW

The authors planned to include controlled trials that had used random or quasi-random patient allocation. Only studies conducted on preterm infants, who were at least partially formula milk-fed following discharge from hospital, were eligible for inclusion in this review. For the purpose of inclusion in the review, intervention was defined as feeding with nutrient-enriched formula milk with at least 72 kcal/100 ml, and at least 1.6 grams protein/100 ml versus standard term formula milk with energy content less than 72 kcal/100 ml, and protein content less than 1.6 grams/100 ml. While selecting the research articles care was taken that infants in the intervention group had received similar care other than the type of formula milk.

The primary outcomes considered were growth and development. For growth, the measures included rates of weight gain during the trial period, and long-term growth measured as weight, height and head circumference at 18 months and beyond. For development, neurodevelopmental outcomes at 12 months or above, severe neurodevelopmental disability, and cognitive or educational outcome at 5 years or more were
considered.

The authors used the standard search strategy of the Cochrane Neonatal Review Group, which included searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL, conference proceedings, and previous reviews. Trials reported only as abstracts were included if sufficient information was available from the report, or from contact with the authors, to fulfill the inclusion criteria. The UK National Research Register and Current Controlled Trials websites were searched for completed or ongoing trials.

**3. RESULTS OF THE REVIEW**

The authors could identify only seven trials which fulfilled all the eligibility criteria. The total number of newborns included in the analysis was 631. All the infants included in the study were less than 1850 grams. The identified studies differed considerably in terms of measured outcomes (both primary and secondary). Therefore, the authors faced difficulty during data synthesis.

For growth the authors analysed together studies based on the duration of follow-up. Meta-analysis of two trials with follow-up of six months post-term, infants fed with nutrient-enriched formula had statistically significantly lower weight [weighted mean difference (WMD) 601, 95% confidence interval (CI) ?1028 to ?174 grams], length (WMD ?18.8, 95% CI ?30.0 to ?7.6 mm), and head circumferences (WMD ?10.2, 95% CI ?18.0 to ?2.4 mm) compared with infants fed standard term formula. Meta-analysis for two trials with follow-up up to nine months post-term and for another meta-analysis for three trials with follow-up up to 12–18 months post-term did not show any significant difference in the growth parameters between the two groups.

Authors performed subgroup analyses of trials using “post-discharge” formula and “preterm formula” separately. Subgroup analysis for studies using “post-discharge formula” versus standard term formula did not find a statistically significant difference in weight or length at 12–18 months post-term. However, the head circumference in the enriched-formula group was statistically significantly lower than in the standard term formula group (WMD ?4.5, 95% CI ?9.1 to ?0.04 mm). Subgroup analysis of the trials that had used “preterm” formula, found a significantly higher weight in babies in the enriched-formula group compared with the standard term formula group (mean difference 500, 95% CI 25–974 grams).

Only two trials had measured development of children using Bayley Scales Mental Development Index or Psychomotor Development Index. On meta-analysis of these two studies, no statistically significant difference was detected.

Five of the included studies measured bone mineralization. Four of these did not find any significant difference between babies who had received enriched formula compared with those who had received standard term formula. However, one study reported statistically significantly lower bone mass (measured using dual energy X-ray absorptiometry) among infants receiving enriched formula as compared to those who received standard-term formula. In another study, the bone mineral content was statistically significantly higher in the group of infants who had received the nutrient-enriched formula milk (mean difference 20.6, 95% confidence interval 7.8–33.4 mg/cm). The indicator used for bone mineralization differed in these studies and in most of them data were presented in graphs and could not be extracted for calculation of mean differences. Therefore, meta-analysis for bone mineralization could not be performed.

Other secondary outcomes used were frequency of vomiting or possets per day and introduction of weaning food. None of the studies which measured these outcomes, found any statistically significant differences between babies receiving enriched formula compared with standard-term formula.

**4. DISCUSSION**
4.1 Applicability of the results

Data from two trials in which follow-up was done up to 6 months of age suggest that infants fed with nutrient-enriched formula have statistically significantly lower growth indicators (weight, length, and head circumference). Meta-analyses of trials that had followed-up the babies for 12–18 months did not reveal any statistically significant differences in the growth parameters. Thus, the current review is inconclusive with regard to whether nutrient-enriched formulas favour or retard growth in preterm babies. Therefore, no guidance for practice can be provided until further data become available.

4.2 Implementation of the intervention

Based on the findings of this review, the use of nutrient-enriched formula is not recommended for feeding preterm babies.

4.3 Implications for further research

The current review reveals that there is a paucity of trials comparing nutrient-enriched formula with standard term formula for feeding preterm babies. Moreover, the limited number of available studies has used different outcomes measures for making this comparison. Therefore, there is a need to conduct large multicenter randomized controlled trials on this topic. Follow-up of study subjects up to later childhood (e.g. up to 5 years of age) is likely to provide important information on the effects of this intervention. Further research may focus on subgroup of preterm infants who are at high risk for nutritional failure (e.g. very-low-birth-weight babies, those who are not able to feed properly following hospital discharge, and those who have high metabolic demands due to other underlying conditions). A consensus on the outcomes to be measured in future trials on this topic will be helpful.

References
