

Age of Introduction of Complementary Feeding and Iron Deficiency Anemia in Breastfed Infants

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SUMMARY

The objective of this systematic review was to investigate the relationship between timing (4 months vs. 6 months) of introduction of complementary foods to the full-term breastfed infant and iron status. An electronic search of peer-reviewed and gray-literature was conducted for randomized control trials (RCTs) and observational studies related to the timing of introduction of complementary foods. Three RCTs and one observational study met the inclusion criteria. Meta-analysis showed significantly higher hemoglobin levels in infants fed solids at 4 months in comparison to those fed solids at 6 months in developing countries [mean difference (MD) 5.0 g/L; 95 % CI 1.5, 8.5 g/L; $P=0.005$]. Meta-analysis also showed higher serum ferritin levels in the 4-month group in both developed [MD: 26.0 $\mu\text{g/L}$; 95% CI -0.1, 52.1 $\mu\text{g/L}$, $P=0.05$] and developing countries [MD 18.9 $\mu\text{g/L}$; 95% CI 0.7, 37.1 $\mu\text{g/L}$, $P=0.04$]. The authors concluded that the rate of iron deficiency anemia in breastfed infants could be positively altered by introduction of solids at 4 months.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: The benefit of breastfeeding infants has been established across the world; in fact there is general consensus that this is the ideal method of providing nutrition and other healthcare related advantages to newborn babies and young infants. The World Health Organization and UNICEF jointly recommend early initiation (within one hour of birth) and sustained exclusive (at least six months) breastfeeding for all infants [1,2]. It is estimated that optimal breastfeeding could reduce childhood under-five mortality by 800,000 each year [3]. Despite the obvious benefits of breastfeeding, it is noted that only about one-third of infants receive this optimally [2]. Amongst the various social, cultural and economic reasons for sub-optimal breastfeeding in terms of quantity and duration, there is a

perception that exclusive breastfeeding may be inadequate to take care of all the nutritional needs of infants beyond a certain age. In particular, it is felt that delaying the introduction of complementary foods can create greater risk of depleting iron stores, leading to iron deficiency anemia and its consequences. This is the justification for this systematic review [4] of trials comparing the introduction complementary feeding to infants (P=Population) at 4 months (I=Intervention) versus 6 months (C=Comparison) of age, on growth and iron status (O=Outcomes).

Critical appraisal: Considering that (properly conducted) systematic reviews rank the highest in the evidence hierarchy, it is vital to appraise them critically. There are a plethora of tools available [5-9] for the purpose; and there is no consensus on the optimal model. In general, they take into consideration three broad issues viz Validity, Results and Applicability. **Table I** summarize the appraisal of this systematic review using criteria from multiple tools.

There are several additional points worth considering in the critical appraisal of this review. The authors have not factored in several variables that could affect both the growth pattern and iron status of infants. These include birth weight, gestation, timing of umbilical cord clamping, neonatal conditions requiring interventions, presence of co-morbidities during the first few weeks of life *etc.* The baseline maternal nutritional status has also not been considered. These variables need to be carefully evaluated within as well as among studies, to make reasonable conclusions.

Further, the authors did not specify the time-point at which the outcomes would be measured. Ideally this could be done in one of two ways. If the outcomes are measured after a fixed duration of complementary feeding in both groups (say 3 months), then it creates a risk of bias because the growth velocity from 5-8 months is not expected to be the same as the velocity during 7-10

TABLE I CRITICAL APPRAISAL OF THE SYSTEMATIC REVIEW

<i>Validity</i>	
Did the review address a clearly focused issue?	Yes. However, the review question has not been explicitly stated in the standard PICO format. Nevertheless, it is possible to frame a PICO question from the available information.
Was an 'a priori' design provided?	No. There is no mention of a protocol published or developed prior to undertaking this review.
Types of studies included	The abstract states that RCT and observational studies were included in this systematic review. However, the Methods section does not specify this clearly. It is debatable whether a systematic review addressing this question should include only RCTs, or can include other relatively more biased study designs.
Search strategy and criteria for inclusion of studies.	The authors electronically searched MEDLINE and CINAHL. Literature search in two databases is currently considered the bare minimum for a systematic review. However EMBASE has been inexplicably omitted. The impact of this has not been described by the authors. The authors also made an effort to search the 'grey literature' (for unpublished studies) and reported the output. This is noteworthy since it is missing even in many high quality systematic reviews. However, there is no mention of searches through Conference Proceedings. The date range for literature searching has not been mentioned. Included/ Excluded studies have been well presented in Tables. A flow chart summarizes the search output. It is unclear whether the search strategy was restricted to English language publications.
Assessment of methodological quality	The authors used the Cochrane Risk of Bias tool [10] to evaluate methodological quality of RCTs. However, the methodological quality of observational studies was not evaluated [11].
Data extraction and analysis	The authors chose to evaluate only measures related to growth (weight, length, head circumference) and iron status (hemoglobin, ferritin). The precise timing of these measurements has not been stated. Unfortunately, for every included outcome, there was only one trial each from which data could be included. Hence heterogeneity among studies for the selected outcomes could not be evaluated. Only aggregate data were used in the analysis. The authors chose to analyze trials from developed and developing countries separately. The basis for this and the definitions used have not been presented. A comparison Table of included studies and the forest plots suggests that the authors have not undertaken intention to treat analysis. Thus the impact on participants with missing data is unclear.
<i>Results</i>	
What are the results?	Complementary feeding introduced at 4 vs 6 mo Weight gain (g): MD -41.0 (95% CI -174.6, 92.6), 1 trial with 97 participants. Weight z score: MD -0.08 (95% CI -0.49, 0.33), 1 trial with 100 participants. Weight gain z score: MD -0.01 (95% CI -0.15, 0.13), 1 trial with 100 participants. Length gain (cm): MD -0.10 (95% CI -0.56, 0.36), 1 trial with 97 participants. Length z score: MD -0.17 (95% CI -0.52, 0.18), 1 trial with 100 participants. Length gain z score: MD -0.01 (95% CI -0.21, 0.19), 1 trial with 100 participants. Head circumference z score: MD -0.08 (95% CI -0.41, 0.25), 1 trial with 100 participants. Head circumference gain z score: MD 0.00 (95% CI -0.17, 0.17), 1 trial with 100 participants. Hemoglobin (g/L): MD 2.46 (95% CI -2.23, 7.16), 2 trials with 239 participants, I ² 79%, Random effects model. Ferritin (mcg/L) : MD 21.21 (95% CI 6.31, 36.12), 2 trials with 239 participants, I ² 0%, Random effects model.
<i>Applicability</i>	
Can the results be applied to the local population?	The local setting in India is not different from the research settings. However, several outcomes that are relevant in our context have not been addressed in this systematic review.
Are the benefits worth the harms and costs?	This review does not address such issues.

months of age. Similarly, if iron status is measured close(r) to the time coinciding with the physiological nadir of infancy, there will be a falsely lower hemoglobin and iron status, irrespective of the timing of complementary feeding. On the other hand, if outcomes are measured at a fixed chronological age, any observed differences could be simply because of differences in duration (rather than timing) of complementary feeding. Thus either method has limitations that should have been considered prior to undertaking the systematic review. The Table of included studies does not describe the nature of complementary feeding in any of the studies.

In terms of outcomes of interest, this review focused on a narrow aspect *viz* growth and iron status. Several other outcomes that could be relevant to breastfeeding duration and/or sufficiency *viz* incidence of infections, episodes of diarrhea, immune status, costs associated with complementary feeding, infants and/or maternal satisfaction, have not been considered at all. These are especially relevant in resource-constrained settings.

The authors concluded that in developing countries, earlier introduction of complementary feeding (at 4 months) is associated with higher hemoglobin (mean difference 0.5 g/dL) and marginally higher ferritin level (mean difference 19 µg/L). It should be emphasized that this was based on one trial; data from over 15% participants in the trial were not included in analysis, the relative distribution of missing participants in the two arms has not been specified, and the differences appear to be 'magnified' by presenting them as g/L and µg/L rather than the more commonly used g/dL and µg/dL. It is also unclear why the authors chose to separately present data from developed and developing countries; the statistically significant differences disappeared when data were pooled (see **Table I**)

Extendibility: The authors' conclusion that developing countries may benefit from earlier introduction of complementary food in infants, is not supported by robust data from methodologically high-quality studies. Therefore, there is no justification for their conclusions and recommendations that feeding patterns may be individualized to attain the best benefit in terms of iron stores in later infancy. Even if this systematic review had been able to demonstrate statistically significant improvements in growth and/or iron stores with earlier complementary feeding, it would be unwise to opt for such a strategy until all aspects of shortened duration/amount of breastfeeding (as described above) had been thoroughly explored.

Conclusions: This systematic review has several limitations. Therefore its conclusion/recommendation that earlier introduction of complementary feeding among infants living in developing countries could be beneficial, cannot be accepted, until supported by robust data.

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Pediatrician's Viewpoint

Early nutrition plays an important role in long-term health of children. Breastfeeding has been shown to have a protective role in the development of several chronic diseases in later life. While there is complete agreement that exclusive breastfeeding is best for a young infant in the initial months, the timing of introduction of complementary foods is not clear. On one hand, early complementary feeding has been shown to increase the risk of overweight and obesity during childhood and adulthood, and on the other hand late introduction may predispose infants to micronutrient deficiencies, including iron. World Health Organization (WHO) recommends exclusive breastfeeding during the first six months of life, with gradual introduction of complementary foods after this period. European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommend not introducing complimentary foods before 17 weeks and no later than 26 weeks.

With this background, authors of the present article have carried out a systematic review on an important topic related to early infant feeding. The systematic review included studies which investigated the relationship between moderate (4 months) *versus* late (6 months) introduction of complementary foods to full-term breastfed infants. The review concluded that early solids significantly improved hemoglobin levels in developing countries but not in developed countries. There was no effect on the growth of infants. The conclusions have to be accepted with some caution as the number of studies included in the analysis was very small (only 4 studies) and the follow-up was also short. Till the time more data is available, it is prudent to follow the WHO recommendations for introduction of complementary feeding to infants.

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Child Health Viewpoint

It is well known that controversies or discussions in medicine result in newer concepts or developments. However, the controversy regarding age of introduction of complementary feeding in this systematic review or meta-analysis seems unnecessary and unwarranted. It is well accepted fact that exclusive breastfeeding for six months and introduction of proper complementary feeding thereafter has many advantages as far as the child's optimal growth and development (including neuromuscular) is considered [1]. Deviation from this practice may result in many disadvantages and problems for the child morbidity and mortality.

Though we are living in the third Millennium and the age of technical advances, there are numerous misconceptions regarding child nutrition not only in the minds of parents/relatives but also for health workers. The suggestion of introduction of complementary feeding at the age of 4 months seems to be an unpalatable recommendation for the solitary benefit of micronutrient nutriture. In developing countries, this recommendation will attract lots of criticism and discussions as indirectly it recommends iron-rich commercial food. The availability and affordability of such food will raise many eyebrows, more debates and more discussions.

The authors have themselves agreed that the short follow-up and small sample size are the limitations of this study. I feel that such studies are going to create more misconceptions and confusions related to the "Weanling dilemma" rather than having any significant positive impact or outcome as far as child health perspective is concerned.

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