

Letters to the Editor

Breastfeeding and iron status

Iron deficiency in infants fully breastfed for 6 months may not be transitory: first observations during the second half of infancy

Madam

The advisable duration of exclusive breastfeeding has been a matter of debate in the field of public health nutrition in recent years. Before 2001, the WHO recommended that infants should be exclusively breastfed for 4–6 months. In 2001, after a systemic review and expert meeting, this advice was changed to recommending exclusive breastfeeding for the first 6 months of life as public health measure⁽¹⁾. At the same time it was recognized that exclusive breastfeeding up to 6 months may impose a risk of marginal Fe status in susceptible infants⁽²⁾. This is one of the reasons why the latest comment by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommends the introduction of complementary food (CF) between 4 and 6 months (17 and 26 weeks) of age⁽³⁾.

Very recently, Yang *et al.*⁽⁴⁾ published a valuable report assessing the prevalence of iron deficiency (ID; ferritin <12 µg/l) and iron-deficiency anaemia (IDA; ferritin <12 µg/l and Hb <105 g/l) among fully breastfed infants with a birth weight >2500 g before 6 months of age. They were able to summarize data from their own six randomized clinical trials conducted in four countries worldwide. They found a percentage of infants with IDA before 6 months of <10% in these six studies. They discuss that IDA in these fully breastfed infants may be transitory, if Fe-rich or Fe-fortified CF are consumed beginning at 6 months. However, they acknowledge that evidence on this question is lacking.

Regarding this question, we re-evaluated data from the Dortmund Intervention Trial for Optimization of Infant Nutrition (DINO). DINO is a double-blinded, randomized, controlled intervention trial that compared primarily the effect of different amounts of meat in CF on the Fe status of infants in the second half of infancy⁽⁵⁾. In addition, fatty acid status was examined⁽⁶⁾. The study cohort was fed according to German and European dietary guidelines including introduction of CF between 4 and 6 months.

Term-born, healthy infants were randomized into a 'high meat' group (HM, *n* 48) receiving commercial baby jars with a meat content of 12% by weight (according to paediatric guidelines) and a 'low meat' group (LM, *n* 49) receiving meals as marketed (meat 8% by weight, the lowest level of EU law). Intervention was from 4 to

10 months of age. Dietary intake was recorded continuously; repeated venous blood samples were collected.

In the primary analysis of the total sample including breastfed and (Fe-fortified) formula-fed infants, Fe status was adequate before (4 months), during (7 months) and after (10 months) the intervention. In a secondary analysis in the subgroup of infants who were fully breastfed for 4–6 months (those infants with the lowest dietary Fe intake during the first half of infancy), there was weak evidence of an increased risk to develop ID and IDA during the second half of infancy⁽⁵⁾.

Actually, using the definitions of Yang *et al.*⁽⁴⁾, we found that eleven out of fifty-three infants fully breastfed for 4–6 months presented with ferritin <12 µg/l, indicating ID, at 10 months of age. One of these showed Hb <105 g/l, indicating development of IDA. On the other hand, none of those infants on Fe-fortified formula during the first 4 months presented with low values of ferritin or with Hb <105 g/l at the age of 10 months.

These findings of the DINO study, representing a population from a developed country, indicate that the potential risk for the development of Fe deficiency in infants fully breastfed in the first 6 months may not be transitory even when CF with highly bioavailable Fe (from meat) is consumed. Our findings are consistent with a recent re-evaluation⁽⁷⁾ of current recommendations for the optimal duration of exclusive breastfeeding. The authors concluded that, although there is a persuasive scientific evidence for exclusive breastfeeding for 6 months rather than 4–6 months for infants in developing countries, this evidence is weaker for infants in developed countries.

In conclusion, the results of this re-evaluation of the DINO study analysis show low values of ferritin and of Hb at 10 months of age in some infants fully breastfed for the first 4–6 months and support the recommendation of an age range of 4–6 months for introduction of Fe-rich CF in infants in developed countries. However, further trials specifically designed to investigate the risk of Fe deficiency during the second half of infancy in healthy infants fully breastfed for the first 4–6 months of age are necessary.

We completely agree that knowledge on the development of Fe metabolism during infancy is still limited in spite of growing awareness that nutrition during infancy may have profound biological effects and important consequences for both short- and long-term health. This is especially true considering the regulation of Fe metabolism in healthy, fully breastfed infants during the period of complementary feeding^(3,7).

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*Exclusive breast-feeding***Response to Drs Kalhoff and Dube**

Madam

Drs Kalhoff and Dube cite our systematic review⁽¹⁾, which contributed to WHO's recommendation of 6 months for the optimal duration of exclusive breast-feeding (EBF)⁽²⁾. The concern we expressed in the systematic review with respect to iron nutriture was focused on developing-country settings in which maternal iron status (and thus newborn iron stores) may be suboptimal⁽¹⁾. The only relevant developed-country study on iron status as a function of EBF duration was a small Italian study that actually showed *superior* haematological status in Italian infants who had been exclusively breast-fed for at least 7 months⁽³⁾.

Of the six randomized trials included in the study by Yang *et al.*⁽⁴⁾, only the two Honduran trials compared different durations of EBF. The purpose of Yang *et al.*'s observational analysis (i.e. not based on the randomized treatment allocation) was to examine risk factors for iron deficiency and iron-deficiency anaemia among infants with birth weight ≥ 2500 g who were 'fully' breast-fed (no source of milk other than breast milk up to the age of 6 months). Male sex, birth weight 2500–2999 g and post-natal weight gain above the median independently increased the risk of iron-deficiency anaemia at 6 months of age. None of the analyses carried out by Yang *et al.* involved variation in the duration of EBF.

The DINO study⁽⁵⁾ involved a secondary (*post hoc*) analysis of a subgroup of infants who were primarily breast-fed (>95% of energy intake) for the first 3 or

References

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4 months and continued to be at least partially breast-fed thereafter. The randomized interventions in the DINO study were low *v.* high meat content of complementary foods provided from 4 to 10 months of age. The method of randomization is not described, and the rate of loss to follow-up was 27%. Unfortunately, those lost to follow-up included post-randomization exclusions from both treatment arms because of poor compliance with the study protocol, thus potentially biasing the treatment comparison. Nevertheless, mean Hb concentrations were nearly identical at 7 months and differed (although not significantly) only at 10 months. It is difficult to understand how a reduction in Hb concentration that develops between 7 and 10 months of age can be attributed to lower iron intake between 4 and 6 months, the relevant period for which Kalhoff and Dube claim (with no evidence) insufficient iron intake among infants who receive EBF for 6 months.

In summary, no data from the DINO trial, the observational analysis by Yang *et al.* nor any other study of which I am aware suggest an increased risk of iron deficiency or iron-deficiency anaemia when healthy, normal-birth-weight infants from developed countries receive EBF for the first 6 months of life. The small Italian study by Pisacane *et al.*⁽³⁾ reporting improved iron nutriture among Italian infants who were exclusively breast-fed for 7 months or more requires replication. Even in low- and middle-income countries, iron deficiency can be prevented with iron supplementation alone starting at 4 months, thereby avoiding the displacement of breast milk and the nutritional inadequacies and risk of contamination of complementary foods in those settings.