

Iron fortification of infant formula*

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Abstract

The purpose of this review is to examine the need for and appropriate level of Fe fortification of infant formula, and to assess any adverse effects of Fe fortification. The appropriate level of Fe fortification of infant formula has been established through studies of Fe absorption or erythrocyte incorporation of Fe, and through clinical trials of formulas with varying levels of Fe that were aimed at preventing the development of Fe deficiency in participating infants. In addition, the effects of varying levels of Fe fortification on the absorption of other minerals and trace elements, and on the incidence of infection and immune function have been studied, as has the effect of adding bovine lactoferrin to formula. Studies of Fe absorption have shown that increasing the level of Fe fortification in formula does not significantly increase the amount absorbed, and that the addition of bovine lactoferrin is unlikely to further increase absorption of Fe. Quite different recommendations for the level of Fe fortification of formula are made in the USA and in Europe. The higher level (12 mg/l) commonly used in the USA is not well supported by the evidence from clinical trials that suggest that lower levels (4 mg/l or less) may be adequate to prevent the development of Fe deficiency. Higher levels of Fe fortification may also interfere with the absorption of other minerals such as Cu and Se. Concerns about potential adverse effects of Fe fortification on immune function and susceptibility to infections have been disproved as have concerns about associated gastrointestinal symptomatology. There are no clearly demonstrated advantages in using 'follow-on' formula with high Fe content (up to 13 mg/l) instead of the standard UK formulas with Fe fortification in the range 4–7 mg/l after the age of 6 months, although they may provide an important 'safety net' for the prevention of Fe deficiency in communities with weaning diets low in Fe.

Infant feeding: Infant formulas: Iron

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Introduction

This review examines the need for Fe fortification of infant formula at various ages, its limits and whether there are any adverse effects on health. Whilst Fe fortification of infant formula effectively eliminates Fe-deficiency anaemia in young children (Vazquez-Seoane *et al.* 1985; Yip *et al.* 1987; Olivares *et al.* 1989; Daly *et al.* 1996), the appropriate level of Fe fortification remains unclear. Considerable variation exists between recommendations in Europe and in the USA where the American Academy of Pediatrics has set a much higher level for Fe fortification of standard formula (American Academy of Pediatrics Committee on Nutrition, 1989). It has also condemned the use of formula with low levels of Fe, which account for up to 30 % of formula sales in the USA and which continue to be prescribed in response to a range of symptomatology in the infant erroneously thought to be due to adverse effects of Fe fortification.

Iron status during early infancy

During pregnancy, Fe is efficiently transported across the placenta so that healthy babies born at term will have accumulated adequate Fe stores mainly in circulating erythrocytes, and also in the liver and reticuloendothelial tissues (Harris, 1992). It has generally been considered that maternal Fe deficiency during pregnancy has little effect on fetal, neonatal and infant Fe status because of preferential transfer of Fe from the mother to the fetus (Rios *et al.* 1975; Morton *et al.* 1988; Hussain *et al.* 1997). Extreme maternal Fe deficiency as occurs in developing countries may be an exception (Singla *et al.* 1996). This view is now challenged by two prospective studies from Spain (Colomer *et al.* 1990) and Jordan (Kilbride *et al.* 1999), that have demonstrated a clear relationship between anaemia in pregnancy and anaemia in the infant at 1 year old. These observations may therefore have a bearing on recommendations about the Fe content of infant formula offered to babies of anaemic mothers.

The high haemoglobin level at birth of about 170 g/l falls in the first 6–8 weeks of life to 125 g/l and the liberated Fe is stored in the liver and reticuloendothelial system. After 2 months of age erythropoiesis increases to supply an increase in total haemoglobin as the infant grows bigger. Stored Fe begins to decrease to 30 mg as compared with 60 mg at birth but total body Fe remains the same. Between birth and the age of 4 months, there is little need for additional Fe to support the synthesis of haemoglobin, myoglobin and Fe-bound enzymes (Dallman, 1986). Consequently, Fe deficiency is uncommon during the early months unless the baby has been born prematurely with low accumulated Fe stores or has lost excessive amounts of blood in the perinatal or neonatal period.

After 4 months of age, extra Fe will be required for incorporation into haemoglobin to fill the expanding blood volume consequent upon rapid growth. An average of 0.7 mg/d bio-available elemental Fe is required for growth and a further 0.2 mg/d to balance basal losses. Unless adequate exogenous Fe is provided in the diet at this stage, liver Fe stores will be depleted by the age of 6 months. Fe deficiency will ensue in the latter half of the first year or early in the second year as indicated by reduced levels of serum ferritin and then falling haemoglobin.

Iron absorption from breast milk

Despite the relatively low level of Fe in breast milk (0.6–0.9 mg/l) compared with that in formula, Fe is well absorbed from breast milk (Garry *et al.* 1981). Fe-absorption studies performed by whole-body counting after the administration of a trace dose of ⁵⁹Fe to 6-month-old

Table 1. Iron content of infant and follow-on formulas

	Fe		
	mg/MJ	mg/100 kcal	mg/l
Cows' milk	0.22	0.09	0.6
UK whey-based formula	1.79–2.51	0.75–1.05	5.0–7.0
UK casein-based formula	1.43–2.34	0.60–0.98	4.0–6.5
UK soya-based formula	0.98–2.87	0.98–1.20	6.5–8.0
UK follow-on formula	2.51–4.66	1.05–1.95	7.0–13.0
USA infant formula	4.30	1.80	12.0
USA formula without added iron	0.29–0.36	0.12–0.15	0.8–1.0
Breast milk	0.22–0.33	0.09–0.14	0.6–0.9

Data from Lawson (1995) and American Academy of Pediatrics Committee on Nutrition (1999).

infants indicated that 49% of the dose was absorbed from breast milk compared with 19% of the dose in cows' milk-fed infants (Saarinen & Siimes, 1977). A more recent study of erythrocyte incorporation of the radioisotope ^{58}Fe by 2-month-old infants demonstrated incorporation of 20% of the dose by breast-fed infants compared with 6.9% by formula-fed infants (Fomon *et al.* 1993). The full reasons why Fe in breast milk is so well absorbed remain unclear but may be explained by the difference in content of factors enhancing Fe binding and Fe absorption. There is a much higher level of binding of Fe in breast milk to fat globules compared with that in cows' milk whereas a higher proportion of Fe is associated with casein in cows' milk. Furthermore the higher Ca content in cows' milk may account for lower absorption of Fe (Fairweather-Tait, 1989). Subsequently, exclusively breast-fed infants rarely become anaemic or develop depleted Fe stores before 6 months of age (Duncan *et al.* 1985). By 9 months of age only a small proportion of breast-fed infants develop Fe deficiency (Siimes *et al.* 1984; Haschke *et al.* 1993) indicating that most breast-fed infants should not require additional Fe provided that there is adequate Fe in their weaning food. A group of Italian infants exclusively breast-fed beyond 7 months were not at risk of anaemia at 12 months whilst 43% of infants who were exclusively breast-fed for a shorter time became anaemic by this age (Pisacane *et al.* 1995).

Iron absorption from infant formula

The lower Fe content of infant formula (see Table 1) and the lesser degree of its absorption make it necessary to fortify infant formula with Fe especially after 4 months of age if Fe deficiency is to be avoided. But does increasing the amount of Fe in infant formula necessarily increase the amount of Fe absorbed?

Absorption studies conducted on young infants using formula with isotopically labelled FeSO_4 have found that as the amount of Fe in the formula is increased, the proportion absorbed is reduced so that the absolute amount absorbed increases only by a modest amount. Rios *et al.* (1975) found that when milk and soya-based formulas with an Fe content in the range 16–18 mg/l were fed to Fe-replete infants in the age range 4–7 months, mean absorption was only 4.2%. Another study of Fe absorption in 1-year-old infants with normal Fe status fed on either formula with no added Fe (0.8 mg/l) or formulas containing 6.8 mg/l and 12.8 mg/l, found absorption rates of 12% in those with no added Fe, 9% with the 6.8 mg/l formula and 7% with the 12.8 mg/l formula (Saarinen & Siimes, 1977). As a consequence the total amount of Fe absorbed from a 50 ml feed of the these formulas was 5 μg from the no added iron, 32 μg from the formula with 6.8 mg/l and 43 μg from the 12.8 mg/l formula, i.e. increasing the Fe content

by 90 % increased the amount of Fe absorbed by only 35 %. The subjects in that study were all Fe replete but in a further Fe-absorption study in a population of young children aged 5–18 months in Chile, where 27 % had a haemoglobin level of less than 110 g/l, Fe fortification of various formulas in the range 10–19 mg/l made little difference to Fe absorption which remained in the range 2.9–5.1 % (Steckel *et al.* 1986). This view is further supported by a recent study of erythrocyte incorporation of Fe in infants fed on formula fortified either with 8 or 12 mg Fe/l (Fomon *et al.* 1997). There was no difference in the quantity of Fe incorporated into erythrocytes in the two groups indicating that Fe absorption was no greater from the formula containing more Fe.

The bioavailability of Fe from different Fe salts added to infant formula has been determined in animal studies (Pabon & Lonnerdal, 1992). Fe from formula fortified with ferric citrate was more available than from formula fortified with the commonly used FeSO₄, and ferric ammonium citrate was significantly less available. Regardless of the Fe salt added, Fe was more available from a low-casein formula than from cows' milk. The addition of vitamin C to infant formula enhances Fe absorption. One study has demonstrated increased absorption up to 11.3 % with the addition of 100 mg or more of vitamin C (Steckel *et al.* 1986). Cows' milk contains only 10 mg vitamin C/l whilst standard infant formula has 69 mg/l and follow-on formula 100 mg/l. On the other hand there are various factors that might reduce the absorption of Fe. Animal experiments have demonstrated an inhibitory effect of a high Ca diet (as in cows' milk) on Fe absorption (Barton *et al.* 1983). A high phytate content in soya formula can also reduce Fe bioavailability (Hurrell *et al.* 1992).

Role of lactoferrin in iron absorption

Lactoferrin is an Fe-binding glycoprotein found in human milk in a much greater concentration than in cows' milk (7 g/l in colostrum, 1 g/l in mature breast-milk compared with only 0.1 g/l in cows' milk) (Sanchez *et al.* 1992). It is not routinely added to infant formula. Its exact biological function has not been fully established but it is generally considered to act as a bacteriostatic agent by sequestering Fe from Fe-requiring bacteria (Brock, 1980; Chierici & Vigi, 1994). The greater bioavailability of Fe and the much higher concentration of lactoferrin in breast milk compared with cows' milk also suggests that it might promote Fe absorption. However, there is no evidence that the Fe in lactoferrin has a higher bioavailability or that lactoferrin mediates uptake of Fe across the gut mucosa. In a study of ⁵⁸Fe absorption and erythrocyte incorporation by infants where the lactoferrin had been removed from their breast milk, the geometric mean Fe absorption was 11.8 % which was actually lower than the 19.8 % absorption from lactoferrin-containing breast milk (Davidsson *et al.* 1994). It has therefore been speculated that lactoferrin may regulate Fe transport rather than act as an Fe-transport protein (Sanchez *et al.* 1992). It may also act as an Fe-scavenging protein that renders harmless free Fe that might otherwise cause free radical-mediated damage to sensitive tissues, reduce absorption of unwanted Fe in the immediate postnatal period, and decrease the availability of Fe to micro-organisms.

Trials of bovine-lactoferrin-supplemented formula have failed to demonstrate any significant improvement in Fe absorption in short-term balance studies conducted in the neonatal period and in early infancy. Infants (7-d-old) fed on formula supplemented with ⁵⁸Fe-labelled bovine lactoferrin were entered into 3 d Fe balance studies. There was a very wide variation in Fe retention amongst the infants but no overall difference between those receiving the lacto-

ferrin and control formula-fed infants without lactoferrin (Fairweather-Tait *et al.* 1987). In a second study several 24 h balance studies were performed on infants (born at term) between 3 and 17 weeks of age who received formula supplemented with 1 g bovine lactoferrin/l. The mean retention of Fe was slightly better (36 % compared with 28 % in control infants fed on an unsupplemented formula) but this did not reach statistical significance (Schulz-Lell *et al.* 1991). However, a more recent longer-term study monitored Fe status variables from birth to 5 months of age in infants fed on a formula supplemented with either 100 or 1000 mg bovine lactoferrin/l (Chierici *et al.* 1992). There were no differences in haemoglobin and serum Fe levels between the supplemented infants and control non-supplemented or breast-fed infants, but serum ferritin levels were significantly higher in those supplemented with 1000 mg lactoferrin/l at 150 d of age, although not at younger ages. It is not clear, however, from these data whether formula should be supplemented routinely with bovine lactoferrin.

Adverse effects of iron deficiency in infancy

Fe deficiency causes a diverse array of symptoms and signs including pallor, anorexia, fatigue, irritability, susceptibility to infection and delayed cognitive development. Fe deficiency of sufficient severity to cause anaemia, defined for children between 6 months and 6 years as a haemoglobin concentration of less than 110 g/l (World Health Organization, 1972), has been associated with impairment of psychomotor and cognitive development in toddlers (for review see Lansdown & Wharton, 1995). This adverse effect may be reversed in some children if Fe levels are repleted by timely Fe therapy (Aukett *et al.* 1986; Lozoff *et al.* 1987; Idjradinata *et al.* 1993). Nevertheless, there is still concern that Fe deficiency during a critical period of early child development may have a permanent adverse effect on cognitive performance (Lozoff *et al.* 1991).

The data on the relationship between Fe deficiency and infection are conflicting. Fe deficiency impairs immune function and so increases the risk of infection (Brock, 1993). Impaired cell-mediated immunity due to reduced T-lymphocyte proliferation is the main effect, with possible impaired macrophage and neutrophil function. B-cell function is not impaired in Fe deficiency. On the other hand, since Fe deprivation in bacterial cultures is associated with inhibition of bacterial growth, it has been suggested that Fe deficiency may offer 'nutritional immunity' and be an important defence mechanism against infection (Weinburg, 1974). Provision of Fe supplements in formula could thereby precipitate infection.

Potential adverse effects of iron fortification of infant formula

Concerns have been expressed about the safety of Fe fortification of infant formula. Oral Fe supplements given as prophylaxis against anaemia or in therapeutic doses may theoretically increase susceptibility to infection by providing the exogenous Fe required for the multiplication of micro-organisms (Weinburg, 1974). This concern initially led the National Supplementary Food Program in Chile to provide milk formula without added Fe. However, several prospective studies of Fe-fortified formula containing 15 mg Fe/l have since found no excess of diarrhoea or respiratory infections (Heresi *et al.* 1987, 1995). There was instead a trend towards reduced diarrhoea morbidity. Furthermore, another study in South Africa found no significant difference in laboratory measures of immune function or incidence of infection when the Fe content of a formula was increased by a factor of 4.8 from 83 mg Fe/kg to 400 mg Fe/kg dry formula (Power *et al.* 1991).

Fe fortification of infant formula has been thought to be associated with the onset of gastrointestinal problems such as colic, constipation, diarrhoea and regurgitation in young children (Grant *et al.* 1972). However, this impression, which appears to be widely held by health professionals and parents in the USA, is not supported by controlled comparisons. Oski (1980) found no difference in stool frequency or the incidence of colic, regurgitation or vomiting in two groups of infants fed on either Fe-fortified or low-Fe formula. A double-blind crossover study comparing formulas with Fe contents of either 1.5 mg/l or 12 mg/l demonstrated no difference in the prevalence of these complaints except for stool colour which was darker in those receiving the higher Fe formula (Nelson *et al.* 1988). The lack of adverse reaction to Fe fortification of formula is further supported by the fact that even therapeutic doses of Fe are usually well tolerated by infants.

Another concern is whether formulas with a high Fe content would competitively inhibit the absorption of other minerals, particularly Zn and Cu, because of a shared absorption pathway (Solomons & Jacob, 1981; Solomons, 1986). Metabolic balance studies were performed on infants receiving either a high-Fe formula (10.2 mg/l) or a low-Fe formula (2.5 mg/l) (Haschke *et al.* 1986). No effects on the absorption of Zn, Ca and Mg were found. However the absorption of Cu was reduced from 27.5% to 13.4% with the higher Fe formula. In another study the trace element status of infants, who had received either a formula containing 4 or 7 mg Fe/l from the age of 6 weeks or who had been breast-fed, was examined at 6 months of age (Lonnerdal & Hernell, 1994). Serum Cu and caeruloplasmin concentrations were similar in all groups except in those who had received the higher level of Fe fortification. As the magnitude of the effect was relatively small, however, the clinical relevance of this finding was thought to be doubtful. Nevertheless the majority of 'follow-on formulas' on the UK market contain additional Cu to compensate for this reduction in absorption due to their higher Fe content.

In the same study (Lonnerdal & Hernell, 1994) plasma Zn levels were similar in the two groups but Se status, as assessed by serum glutathione peroxidase activity, was lower in those fed on the higher Fe formula and much lower than those who had been breast-fed. This may make the infants fed on the higher Fe formula more susceptible to free radical-mediated reactions (Burk, 1989). Whilst the metabolic manifestations and clinical signs of Se deficiency are not well established, it may therefore be prudent to supplement formula with extra Se. As there was no difference or abnormality in haematological status at 6 months in the two groups of infants fed on formula fortified with either 4 or 7 mg Fe/l, the lower level of Fe fortification might then be preferable.

Criteria for adequacy of iron fortification

The adequacy of Fe fortification of infant formula has been established by the documentation of the development of Fe deficiency, measured by haemoglobin concentration, serum ferritin and other measures of Fe status, in cohorts of infants of varying ages fed on formulas of different Fe concentration.

Clinical trials of different levels of iron fortification of infant formula

The physiological evidence that increasing the Fe content of infant formula has only a limited effect on increasing the total amount of Fe absorbed is supported by several clinical trials of

formulas with various levels of Fe fortification including formula with no added Fe (results summarized in Table 2).

Healthy full-term infants from a private practice paediatric population in the USA were fed on either high-Fe formula (12.3 mg/l) or a low-Fe formula (1.2 mg/l) and followed for 1 year (Picciano & Deering, 1980). There was no difference in Fe status at 4 months of age and then throughout the first year of life and none had a significantly abnormal Fe status. A further study from the USA (Bradley *et al.* 1993) comparing the haematological response to two formulas started at 1 week of age containing either 7.4 or 12.7 mg Fe/l, found no difference in haematological status throughout the first year of life. In Vienna, the response to a lower-Fe-containing formula (3 mg/l) started from birth, was compared with that of a 6 mg Fe/l formula. It was found that the formula providing 3 mg Fe/l was still able to effectively prevent depletion of Fe stores during the first 6 months of life (Haschke *et al.* 1993). Similar results are reported from a trial of formulas containing either 2 or 4 mg Fe/l in Sweden (Hernell & Lonnerdal, 1996). The most recent reported trial from Chile (Walter *et al.* 1998) comparing a 12.7 mg Fe/l formula with one containing 2.3 mg Fe/l started from 6 months of age found both to be equally effective in preventing Fe deficiency up to 12 months of age. There would therefore seem to be few haematological benefits for infants from increasing the Fe content of infant formula beyond 3–7 mg Fe/l.

The basis of recommendations for iron fortification of infant formula during early infancy

Few data exist on whether formula-fed infants require additional Fe during the first 4–6 months of life. Studies of lower levels of Fe fortification (2, 3 or 4 mg Fe/l) of formula fed from birth instead of the more usual 6 or 7 mg Fe/l concluded that these formulas were sufficient to prevent the development of Fe deficiency during the first 6 months of life and, if combined with adequate Fe-containing weaning foods, up to the age of 9 months (Haschke *et al.* 1993; Lonnerdal & Hernell, 1994; Hernell & Lonnerdal, 1996). The question remains concerning longer-term follow-up for those infants fed on low-Fe formula. Inadequately repleted liver Fe stores may predispose these infants to Fe deficiency in the latter part of the first year or in the second year. The American Academy of Pediatrics has strongly recommended the discontinuation of the manufacture and use of formulas with Fe concentrations less than 4 mg/l (American Academy of Pediatrics Committee on Nutrition, 1999), highlighting a study of high-risk Canadian infants fed from birth on a 'standard' formula with only 1.1 mg Fe/l. The rate of Fe-deficiency anaemia at 6, 9, 12 and 15 months was 28%, 19%, 12% and 10% respectively in these infants, whilst the rate was 8%, 8%, 2% and 3% respectively in those consuming a formula with 12 mg Fe/l (Moffatt *et al.* 1994). In another study from Chile the prevalence of anaemia at 9 months in infants who had been fed on a cows' milk formula with no added Fe was 20% whilst it was only 0.6% in those fed on an Fe-fortified formula with 150 mg/kg milk powder (Pizarro *et al.* 1991). However these infants may have been at high risk of Fe deficiency for reasons other than the low Fe content of their formula feed. They may have had low body Fe stores from birth consequent on maternal Fe deficiency in pregnancy or have received inappropriate weaning foods of low Fe content from an early age. Nevertheless it would be prudent to recommend that infants in the first 4 months of life should receive a formula with some additional Fe so that iron balance at 4–6-months-old is not stressed by increasing demands for erythropoiesis.

After the age of 6 months, moderate Fe fortification of a standard infant formula should be recommended in case the provision and absorption of Fe from weaning foods is inadequate.

Table 2. Summary of recent trials of iron fortification of formula milks and the prevention of iron deficiency

Trial	Age at intervention	Milk	Fe (mg/l)	Duration (months)	Age at assessment (months)	Mean Hb (g/l)	Hb < 110 g/l (%)	Mean serum ferritin (µg/l)	Serum ferritin < 10 µg/l (%)	Transferrin saturation (%)
Picciano & Deering (1980)	Birth	bm	0.6	> 3	12	133	4			19
		f	12.3	4		123	12			18
		f	12.3	12		131	4			22
Bradley <i>et al.</i> (1993)	1 week	f	1.2	4		124	10			18
		bm	0.6		6	118		31		
		f	7.4			120		39		
		f	12.7			118		45		
Haschke <i>et al.</i> (1993)	Birth	bm	0.6		12	121		23		
		f	7.4			122		18		
		f	12.7			122		31		
		bm	0.6		3	118		136		
		f	3.0			121		86		
		f	6.0			118		102		
		bm	0.6		6	123		86		
Moffat <i>et al.</i> (1994)	Birth	f	3.0		9	124		42		
		f	6.0			124		21		
		bm	0.6			121		16		
		f	3.0			125		21		
		f	6.0			126		29		
		f	1.1		6	108	28	16		
		f	12.8			114	8	27		
		f	1.1		9	112	17	11		
		f	12.8			116	8	33		
		f	1.1		12	112	12	11		
Stevens & Nelson (1995)	6 months	f	12.8		15	118	2	24		
		f	1.1			115	10	11		
		f	12.8			119	3	26		
		f	1.0		12	121	6	15		
		f	12.0			117	7	24		
		f	1.0		18	120	4	15		
		f	12.0			122	0	16		
Daly <i>et al.</i> (1996)	6 months	pcm	0.5	18	12	116	31	23	5	
		f	12.0			124	3	31	3	
		pcm	0.5		18	123	33	16	38	
		f	12.0			115	2	31	0	
Gill <i>et al.</i> (1997)	6 months	pcm	0.5		24	118	26	15	36	
		f	12.0			124	0	32	4	
		pcm	0.5		15	111	33	11	43	
		f	1.4			118	11	15	22	
Walter <i>et al.</i> (1998)	6 months	f	12.3		12	123	13	25	6	
		f	2.3			122	4	11	65	
		f	12.7			125	3	15	49	

Hb, haemoglobin; bm, breast milk; f, formula; pcm, pasteurized cows' milk.

Formulas in common use in North America contain 12 mg Fe/l following the recommendations of the American Academy of Pediatrics Committee on Nutrition (1976, 1989) in which a standard infant formula containing 12.7 mg Fe/l was considered to be well suited for both young and older infants (Fomon *et al.* 1990). An even higher upper limit of fortification of 20 mg Fe/l was proposed by Dallman (1989) whilst acknowledging that lower levels might be equally effective in preventing Fe deficiency. On the other hand, the European Society for Paediatric Gastroenterology and Nutrition (1977) currently recommends a lower level of Fe fortification in the range 6–12 mg Fe/l. European Commission directives, now confirmed in UK law, state that infant formulas fortified with Fe should contain 1.20–3.59 mg Fe/MJ (0.5–1.5 mg Fe/100 kcal; 3–10 mg Fe/l), although no-added Fe formula is permitted providing that the labelling states that if the product is given to infants over the age of 4 months, their total Fe requirements must be met from other additional sources (European Economic Community, 1991; Statutory Instrument, 1995).

The high level of Fe fortification recommended in the USA is probably unnecessary for most infants and appears to be based historically around a public health strategy to effectively reduce the prevalence of Fe-deficiency anaemia in the early 1970s by encouraging the use of high-Fe-fortified formula, and on warnings from a few studies of largely high-risk infants fed on low-Fe formula. Clinical trials would suggest that a maximum level of Fe fortification of up to 4 mg Fe/l should be quite adequate (if not desirable from the point of view of reduced Cu and Se absorption with high-Fe formula) for the first 6 months of life.

The basis for recommendations for iron fortification of formula for the child who has started solids

The UK Committee on Medical Aspects of Food Policy (1994) recommends that solids be introduced into the diet no sooner than 4 months but no later than 6 months. Many commercially produced early weaning cereals are fortified with Fe. A few are fortified with meat extracts. Is there adequate absorption of Fe from fortified weaning foods to allow the 6-month-old infant to switch from infant formula to unmodified cows' milk after 6 months of age? The poor bioavailability of Fe from cereals supplemented with iron pyrophosphate or ferric orthophosphate makes the weaning diet at this age unlikely to compensate for the low Fe content of cows' milk (Fomon *et al.* 1990; Fuchs *et al.* 1993). Absorbed Fe from infant cereal only accounts for 0.12 mg of the 0.7 mg of absorbed Fe that infants require each day (Fomon & Zeigler, 1989). Furthermore some carers of infants offer inappropriate weaning foods of low Fe content through a combination of traditional and cultural choice, lack of availability or affordability of more appropriate foods and lack of knowledge (Daly *et al.* 1999).

When meat-containing baby foods fortified with FeSO₄ were fed to two groups of infants aged 4 months who were also receiving either an Fe-fortified formula (10 mg Fe/l) or a non-fortified formula (3 mg Fe/l), Fe intake in the group fed on the non-fortified formula was significantly lower and less than 10% met the recommended Fe intake of 1 mg/kg per d (Haschke *et al.* 1988). This group had lower mean ferritin levels at the age of 1 year and 4.7% had a haemoglobin level less than 110 g/l. Therefore even in the presence of Fe-fortified weaning foods with a highly bioavailable source of Fe, additional Fe from fortified formula was still required. However, in another study there was no difference in the mean haemoglobin level at 6, 9, 12, 15 and 18 months of age in infants who were changed from a standard formula to a no-added-Fe formula (1 mg Fe/l) compared with others switched to a fortified formula (12 mg Fe/l) (Stevens & Nelson, 1995). These infants must have been able to obtain adequate

Fe from the standard formula before the intervention and from other food sources after the onset of weaning which occurred around 12 weeks of age.

'Follow-on' formulas with a higher protein and Fe content have been advocated by their manufacturers for use from 6 months onwards and into the second year of life as a liquid part of a progressively diversifying weaning diet. The European Society for Paediatric Gastroenterology and Nutrition (1990) recommended that these formulas should contain between 2.39–4.06 mg Fe/MJ (1.0–1.7 mg Fe/100 kcal; 7–12 mg Fe/l) and the European Economic Community (1991) directive 2.39–4.78 mg Fe/MJ (1–2 mg Fe/100 kcal; 7–13 mg Fe/l) i.e. a similar Fe content to the standard infant formula used in the USA. However, there are few data to support their use as being superior to standard formula (Bradley *et al.* 1993). Nevertheless, these milks have been vigorously promoted as a preventer of Fe deficiency and as a necessary stepping stone between infant formula and cows' milk. 'Follow-on' formulas are more expensive than infant formulas and their prolonged use as an alternative food source might have an adverse effect on the maturation of feeding behaviour if fed from a feeding bottle. There are no clearly demonstrated advantages in using 'follow-on' formulas instead of a standard formula during the second 6 months (Walter *et al.* 1998; Wharton, 1992), but what about their longer-term use?

In a study in inner city Birmingham, children who had already started cows' milk by 6 months of age were randomly allocated to receive either a follow-on formula or to continue on cows' milk into the second year of life (Daly *et al.* 1996). The provision of the follow-on formula was effective in preventing anaemia at 18 months of age whilst 33 % of those fed on cows' milk became anaemic. Furthermore, those children who had received the Fe-fortified formula were at an advantage in their psychomotor development (Williams *et al.* 1999). The weaning diet of both groups was similar and contained insufficient Fe to meet the reference nutrient intake, consisting mainly of convenience foods such as soups and spaghetti, biscuits, potato crisps and sweet puddings with little in the way of fresh meat, fruit or vegetables (Daly *et al.* 1999). However, provision of the follow-on formula effectively raised the mean Fe intake of this group above the reference nutrient intake; this did not occur in the cows' milk group. Similar findings are reported from a multi-centre study of haematological status in groups of children fed on either cows' milk, a non-fortified formula (1.4 mg Fe/l) or a 12.3 mg Fe/l formula from 6 months (Gill *et al.* 1997). At the age of 15 months, 33 % of those fed on cows' milk had a haemoglobin level less than 110 g/l compared with 13 % and 11 % in those receiving the non-fortified and Fe-fortified formula respectively. Whilst there was little difference in the proportion who were sufficiently Fe deficient to become anaemic in the latter two groups, 22 % of those with the non-fortified milk had a serum ferritin below 10 mg/l compared with only 6 % of those who had received the Fe-fortified formula (43 % of those on cows' milk had a serum ferritin < 10 mg/l). The follow-on formula had acted as an important safety net in the prevention of Fe deficiency for the socio-economically deprived children in the Birmingham study as their solid diet was so poor in Fe content. If the same volume of standard formula had been consumed instead of the follow-on formula, it was calculated that many of the children would then have not achieved the reference nutrient intake for Fe. However, for children of parents able to provide a better solid diet, breast-feeding or standard formula may be recommended up to the age of 1 year. Cows' milk may then be safely introduced during the second year as long as the child has no feeding behavioural problems leading to reduced intake of solids.

Conclusions

The growing infant requires an on-going exogenous source of Fe after the age of 4 months. Fe is poorly absorbed from unmodified cows' milk and so fortification of infant formula is

necessary to prevent the development of Fe deficiency. However, increasing the Fe content beyond the typical level in UK products of 7 mg Fe/l has only a limited effect on increasing the net amount of Fe absorbed. Clinical trials of formulas with different levels of Fe fortification indicate that lower levels of 4 mg/l or less are probably quite adequate for the majority of infants in the first 6 months of life. Nevertheless infant formula in the USA commonly contain 12 mg Fe/l which is an unnecessarily high level of fortification. After weaning, Fe-fortified formula still needs to be continued until at least the age of 1 year. There are no clearly demonstrated advantages in using 'follow-on' formulas with high Fe content over standard formula after the age of 6 months, although they may provide an important 'safety net' for the prevention of Fe deficiency in deprived communities with diets low in Fe. Current data do not support the routine supplementation of formula with bovine lactoferrin. Iron fortification of infant formula has been shown to be quite safe with no adverse gastrointestinal side-effects, no increased susceptibility to infection and no significant impairment of the absorption of other minerals.

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