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DO INFANTS UNDER SIX MONTHS OF AGE NEED EXTRA IRON?: A PROBE

WORKING PAPER: 12

March, 1992

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GLOSSARY

AAP	American Academy of Pediatrics
ACC/SCN	(United Nations) Administrative Committee on Coordination/Subcommittee on Nutrition
CDC	Centers for Disease Control
FFe	Formula fortified with iron
Hb	Hemoglobin
IMI	Intramuscular injection
INACG	International Nutritional Anemia Consultative Group
IOM	Institute of Medicine
LBW	Low birth weight
LSRO	Life Science Research Office
NHANES	National Health and Nutrition Examination Survey(s) (United States)
RDA	Recommended dietary allowance
VLBW	Very low birth weight
WCM	Whole cow's milk
WHO	World Health Organization
WIC	Women, Infants, and Children Program

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DO INFANTS UNDER SIX MONTHS OF AGE NEED EXTRA IRON?: A PROBE

Naomi Baumslag, MD, MPH

I. INTRODUCTION

Breast milk is a lifesaving, inimitable biological fluid. Exclusive breastfeeding is recognized as superior to feeding artificial breast milk substitutes during the first four to six months of an infant's life by such expert scientific bodies as the American Academy of Pediatrics (AAP) and the World Health Organization (Committee on Nutrition 1976, WHO 1970).

Methodologically sound studies have provided evidence of the benefits of breastfeeding in communities with either good or poor hygiene.

- Victora and coworkers in Brazil (1987) calculated the relative risk of diarrhea at 14.2 and of pneumonia at 3.6 for bottle-fed infants, compared to exclusively breastfed infants.

- In Scotland, Howie found that infants breastfed for 13 weeks or more had a reduced risk of diarrhea and respiratory disease during their first year of life (Howie et al. 1990).

- Other researchers have noted that if infants are exclusively breastfed for 6 months, their prevalence of diarrhea could by reduced by nearly 60% (Brown et al. 1989).

- Early administration of colostrum to low birth weight infants reduces their risk of infections (Narayanan et al. 1983).

- Exclusive breastfeeding helps prevent a number of non-infective conditions such as allergic and atopic disorders (Chandra 1989), juvenile diabetes (Mayer et al. 1988), childhood cancer (Davis et al. 1988), and malocclusion (Labbok and Hendershot 1987). It also enhances intelligence (according to a new study by Lucas et al. 1992), bonding (Klaus and Kannel 1983), and child spacing (Labbok 1989, Consensus Statement 1988, Short et al. 1990).

Besides its overall immunological and nutritional superiority, breast milk is an important source of iron. Research has shown that:

- Infants absorb iron from breast milk more efficiently than from formula (Committee on Nutrition 1976, Dallman 1980, Dallman 1986, Riordan and Countryman 1980, Davidson et al. 1990, International Nutritional Anemia Consultative Group 1979, Saarinen et al. 1977);

- Exclusively breastfed infants maintain adequate iron status for six months or more (Coulson et al. 1977, Duncan et al. 1985, Good 1977, McMillan et al. 1976, Owen et al. 1981, Pastel et al. 1980, Saarinen et al. 1977, Siimes et al. 1984, Siimes et al. 1979).

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Anemia in exclusively breastfed infants is rare in the first year of life. Iron in breast milk comes packaged with vitamin E, ascorbic acid, vitamin A, and lactose. The combination of iron and vitamin E is ideal for premature infants and could guard against hemolytic anemia. Colostrum has even higher vitamin E and iron levels than mature breast milk.

Despite all of the positive attributes of breast milk, the superiority of exclusive breastfeeding is continually undermined by aggressive marketing of formula producers and by the lack of effective actions to promote breast-feeding. Chemists continue to try to design formula that surpasses the nutritional content of breast milk, including its iron content. The more that is added to formula, however, the higher the cost. At present, infant formula, in essence modified cow's milk, is six times as expensive as cow's milk itself.

Currently, iron supplementation of infants is recommended in the United States by the Food and Nutrition Board of the National Research Council in the recommended dietary allowances (Food and Nutrition Board 1989) and by the AAP (Table 1) at the following levels:

- 1 mg./kg./day for exclusively breastfed infants after three months of age,
- 1 mg./kg./day for artificially fed full-term infants from birth, and
- 2 mgs./kg./day of iron starting by two months of life for all low birth weight (1000-2000 grams) and those infants with a substantial reduction in hemoglobin mass. For infants of normal or low birth weight, iron intake should not exceed 15 mgs./day.

Other national and international pediatric and health organizations have different iron supplementation and fortification recommendations (see Table 1).

This paper will examine and challenge many of the assumptions and studies that are the basis for such recommendations.

II. ISSUES

The problem of whether to fortify or supplement infants' diets with iron is not simple. There are a number of key issues that experimental studies have not yet resolved.

- How adequate is the iron status of exclusively breastfed, full-term, and premature/low birth weight infants? With regard to iron needs, when should solids be introduced?

- If iron supplements are given to premature infants, should vitamin E routinely be given with the iron? In what form should vitamin E be given, and how much? What is its interaction with other micronutrients? Are there any adverse effects? What are the proven health effects?

- Is there any difference in iron status of female or male infants?

- (i) Are the recommended dietary allowances (RDA) and other iron intake recommendations (AAP, United Nations/ACC/SCN) appropriate, and have these requirements been adequately proven?
  (ii) Is the International Nutritional Anemia Consultative Group (INACG) justified in recommending that "countries having a high prevalence of iron deficiency should require the mandatory iron fortification of country specific foods," given that there are other causes of anemia besides iron deficiency?
  (iii) Are the recommendations of other organizations (AAP, United Nations/ACC/SCN, etc.) and researchers for iron supplementation for breastfed infants justified? What studies are they based on? Should findings be applied to all infants regardless of sex, socioeconomic status, diet, birth weight, and geographic location?

- How are iron deficiency, iron depletion, and anemia defined, and which of the biochemical and hematological tests are adequate measures of iron status? Are they standardized to be representative of both full-term normal and low birth weight/premature infants? Should recommendations be the same or distinct for full-term low birth weight and premature infants?

- What are the functional effects of iron deficiency, iron depletion, and anemia? Are there harmful effects of blanket iron administration? What are the benefits of iron administration to infants? What, if any, is the relationship between iron and vitamin A?

- What are the effects of adding solids to the diets of infants on breast milk, formula, and iron-fortified formula? Studies have shown that this practice decreases iron absorption, especially in breastfed infants (Saarinen and Siimes 1979, Oski and Landaw 1980). Does this apply equally to all solids?

- Does maternal iron status and iron supplementation in pregnancy affect fetal iron stores and iron content of breast milk? Does infection in the mother affect maternal breast milk content, or does maternal iron status affect mothers' ability to breastfeed or even the frequency of feeds?

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- What are appropriate population reference data for hematological and biochemical indicators to diagnose iron deficiency, iron depletion, and anemia in infants?

- What formulas/milks have been used in the studies upon which iron fortification recommendations are based, and does protein type or composition of the formula have any effect on iron absorption.

Some of these issues have been raised by Pereira and Barbosa (1986, p. 65) who state that "controversy connotes prolonged argument and dispute because of inaccurate research methodology, faulty interpretation of study results and multifactorial etiology of disease."

III. RATIONALE FOR IRON FORTIFICATION OR SUPPLEMENTATION

The rationale for iron fortification or supplementation for infants is based on a number of assumptions which are either false or only partially valid. These are listed in the box below and are discussed in this and subsequent sections of this paper.

Assumptions

1. Calculated iron requirements are correct and generalizable.
2. The definition of iron deficiency is precise.
3. All anemia is due to iron deficiency.
4. There is a complete correlation between iron deficiency and health effects.
5. Full-term low birth weight and premature infants are the same regarding iron status and needs.
6. Exclusive breastfeeding is the same as breastfeeding.
7. Body iron is proportional to infants' weight.
8. Iron is harmless.
9. Cord blood is inconsequential.

A. Anemia

A number of authorities consider anemia to be one of the most common infant diseases worldwide (Dallman and Siimes 1979, Oski 1985, Rees et al. 1955, Yip 1989b). Anemia in infants (as measured by hemoglobin) has been associated with decreased psychomotor development, tachycardia (an abnormally fast heart beat), evidence of high cardiac output, upper respiratory infections, gastroenteritis, increased susceptibility to infection because of defects in cellular immunity, retarded growth and development, and learning and emotional problems (Committee on Nutrition 1976, Walter et al. 1989, Oski 1985, Oski and Naiman 1972, Fuerth 1972, Scientific Advisory Council 1987, United Nations/ACC/SCN 1990, Dallman 1986, Chandra 1991). The causal relationship between iron deficiency and these conditions, however, is not well established.

Moreover, there is no standard definition of anemia in infants (LSRO 1984, Food and Nutrition Board 1989, Yip 1989a, Lonnerdal 1989), no population-based reference standard for iron levels in infants, and no single, perfect test for diagnosing iron deficiency (Yip 1989a, Lonnerdal 1989). According to the AAP, WHO, and United Nations Subcommittee on Nutrition, any infant who has not met designated standards is considered iron deficient.

Dallman and Siimes (1979) stated that iron deficiency occurs when iron supply is inadequate for the normal synthesis of essential iron-containing compounds (e.g., hemoglobin concentration). Thus, the ideal iron status is one which provides for the normal production of hemoglobin (Dallman 1986).

Classification of iron status from laboratory tests is based neither on national population reference standards nor on proven functional health outcomes. The cutoff points used also vary (LSRO 1984, Yip 1989a). The iron status of infants is divided into subcategories using various biochemical measures or combinations thereof. Iron depletion is based on the serum ferritin level; iron deficiency without anemia is based on the transferrin saturation or erythrocyte protoporphyrin test, and iron deficiency anemia is based on hemoglobin and or the mean corpuscular volume. Some of the indicators used such as the transferrin saturation and erythrocyte protoporphyrin are affected by inflammatory disease. The tests used may thus overestimate the contribution of iron deficiency (LSRO 1984, p. 13). Standards have been developed to prevent iron deficiency, which is believed to be detrimental to infants and children (Oski 1985) because it can result in anemia (Lonnerdal 1989, Yip 1989b, Committee on Nutrition 1976, Dallman 1979 and 1986, Food and Nutrition Board 1989, United Nations/ACC/SCN 1990).

WHO defines anemia in children aged 6 months to 5 years as a hemoglobin level below 11 g./dl. (United Nations/ACC/SCN 1990, WHO 1968). In a study conducted by the Centers for Disease Control (CDC) Pediatric Nutrition Surveillance System, the criteria used to define anemia were hemoglobin < 10.3 g./dl. or hematocrit < 31% for children aged 6 to 23 months, and hemoglobin < 10.6 g./dl. or hematocrit < 32% for children aged 24 to 60 months (Yip 1989b). In determining the prevalence of anemia for infants and children in the United States, NHANES used a hemoglobin level of <10.7 g./dl. for children 1-2 years of age, which is 0.3 g./dl. of hemoglobin lower than the < 11.0 g./dl. cut-off point commonly designated by the AAP (Yip 1989a). In a New Haven anemia prevalence study in children, anemia was diagnosed when the hemoglobin level was below 9.8 g./dl. (Yip 1989b). Dallman (1986) states that in clinical settings, anemia is defined as a hemoglobin value below 11.0 g./dl. for children aged 6 months to 10 years.

The use of laboratory values, particularly for small children, is problematic; e.g., low birth weight infants can develop anemia even though their serum ferritin is normal (Siimes 1984). Furthermore, methods used for testing iron deficiency are prone to error. Both "technical anemia," identified by laboratory testing methods, and "statistical anemia," defined by hemoglobin and hematocrit distribution of a healthy population, can skew results (Yip 1989b). All of these factors should be considered in decisions to recommend iron supplements.

B. Iron Status of Infants

Iron status at birth depends on in utero transfer, placental transfusion, and cord blood loss at delivery. After birth, iron is obtained from the infant's diet -- from colostrum and breast milk, or from formula or breast milk substitutes, foods, and then cereals and food.

- In utero, fetal iron stores acquired from the mother are largely in the form of hemoglobin. These do not appear to be related to her dietary intake, unless she is extremely anemic (Singla et al. 1978, Nhonoli et al. 1975, IOM 1991). Even here the evidence is debatable (see Table 10).

- After birth, dietary intake is the main source of iron for the infant. The iron content of mother's milk is commonly stated as 0.5 mg./L., but some scientists believe that the mean breastmilk iron content is higher, namely 0.8 mg.L. (see Table 11). Iron from breastmilk is absorbed very efficiently (49%). Iron supplementation of the mother does not appear to affect the breastmilk iron content (Table 10). It has been suggested that the iron content in human milk decreases as the period of lactation increases, but this too is debatable (see Table 11).

- Iron loss is generally small except in the case of hemorrhage or possibly parasitic infestations (in particular, malaria, hookworm, and whipworm). Frequent blood sampling may further deplete the infant's iron stores (1 gm. of hemoglobin contains 3.4 mg. of iron). Iron loss from sweat, body fluids, and stools is almost negligible (Saarinen and Siimes 1979, Schultz-Lell et al. 1987, Tunnessen and Oski 1987, Ziegler et al. 1990).

It has been estimated that a normal infant weighing 3.5 kg. at birth has a total body iron content of 250 mg., of which 175 mg. is associated with hemoglobin, 15 mg. with myoglobin and enzymes, and 60 mg. with stored iron (Dallman 1986). It is assumed that the total body iron level of a four-month old is the same, i.e., 250 mg. and that 190 mg. of the iron is in hemoglobin, with only 30 mg. in stores and 30 mg. in myoglobin and enzymes. In a 10 kg. infant (approximately 12 months of age), the total body iron level has risen to 420 mg., of which 320 mg. is in hemoglobin, 50 mg. in iron stores, and 50 mg. in myoglobin and enzymes (Dallman 1986).

It should be noted that hemoglobin iron calculations assume a hemoglobin concentration of 16.8 g./dl. and a blood volume of 90 ml./kg. at birth, and respective values of 12.5 g./dl. and 75 ml./kg. at both 4 and 12 months (Dallman 1986). The infant, it is calculated, has 8 months to accumulate the additional 170 mg. of body iron needed to maintain its normal iron status of 420 mg. at 12 months of age.

Another, significantly different, estimate is that the newborn's total body iron level is 500 mg. and the amount of total body iron in adults is 5 g. To reach the adult level, the infant must absorb an average of 0.8 mg. of iron/day for 15 years, i.e., 4.5 g. of iron over 15 years. Another assumption is that since only 10% of dietary iron is absorbed, the diet must contain 8-15 mg. of iron per day. Furthermore, it is accepted that as the hemoglobin concentration of the newborn drops during the first 2-3 months, iron is reclaimed and stored and that this is usually sufficient for the breastfed infant for the first 6-9 months. The calculations assume that transplacental stores are usually depleted by the time the infant triples its birth weight at around one year of age.

C. Iron Absorption and Storage

Iron stores that accumulate during the fetal period are difficult to measure. The amount of iron stored is influenced by the amount required for hemoglobin production (Dallman 1986). Widdowson and Spray (1959) concluded that iron in the fetus increases with development. Dahro, in a postmortem study of 33 cases ranging from 2 weeks to 7 years (9 were SIDS deaths), implied that the overall iron stores are adequate for the normal-term infant to maintain hemoglobin levels for the first three months of life (Dahro et al. 1983). This appears to be the basis for the RDA recommendation that the infant has enough stores to last three

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months (Food and Nutrition Board 1989) without adding any iron through breastmilk or other foods.

Neonates' iron content can be raised significantly by keeping the umbilical cord intact after delivery of the placenta, waiting for the cord to stop pulsating, and letting the blood drain back into the infant by gravitational effect before severing the cord (Table 6). Studies suggest that 100 ml. of blood or more can be conserved if the birth attendant waits until after pulsations have stopped to tie the cord (Wilson et al. 1941, DeMarsh et al. 1942, Duckmann et al. 1953). As much as 45 mg. of iron can be obtained from 100 ml. of blood (Lanzkowsky 1980, Oski and Naiman 1972, Niccum et al. 1953, Wilson 1941). The practice of placing the baby on the mother's abdomen before tying the cord may result in reverse flow of blood from the infant back to the placenta (Whipple et al. 1957).

Exclusively breastfed infants have a high iron bioavailability (49%), especially when they are breastfed from birth. Colostrum appears to be especially high in iron (see Table 5). The range of iron values from breastmilk are shown in Table 11.

Infants fed formula absorb much less iron (4%) (see Table 7). As a result, the quantity of iron in fortified formula is substantial, 12-22 times higher than in mother's milk or cow's milk. The vast differences in the composition of formula (see Table 9) affect iron absorption: the higher the content the less complete the absorption (Saarinen 1979, Garry et al. 1981).

Infants absorb 10 to 12% of iron in cow's milk. Cow's milk inhibits iron absorption to different degrees depending on the age of the infant. Whole cow's milk untreated (unheated) has been associated with gastrointestinal bleeding, with resultant intestinal blood loss leading to anemia. Because of this occult blood loss from stools, together with the low iron content and poor bioavailability of iron from whole cow's milk, it is necessary to fortify or supplement unheated cow's milk.

The absorption of iron from heme (animal) foods is greater than that from non-heme foods, such as vegetables, by a factor of 10-20 times. There have not been an adequate number of absorption studies carried out on non-commercial weaning foods. Fortified cereals have been suggested as a good source of iron (Table 8); however, it appears "there is considerable doubt about the bioavailability of the electrolytic iron powder used to fortify most of the dry infant cereals" (Fomon 1987). An iron EDTA product is apparently better absorbed than other forms of iron used in cereals (see Table 8); however, the iron is still not absorbed as efficiently as from breastmilk.

Iron absorption is facilitated by a number of factors, e.g. ascorbic acid (Food and Nutrition Board 1989, Dallman and Siimes 1979, Steckel et al. 1985, Steckel et al. 1986), which converts ferric ions to ferrous, or by the addition of lactose. On the other hand, iron absorption has been reported to be decreased by a number of substances such as phytates, calcium, phosphates (especially pyrophospates) (Rios et al. 1975), tea, and coffee (Munoz 1988). Higher absorption of iron occurs in infants fed whey protein formula than those fed casein-based protein formula.

Iron stores are contingent on the body weight of the infant (Rees et al. 1985, Aggett et al. 1989, Dallman 1986). It is assumed that the higher the infant's birth weight, the larger the infant's iron stores. Although the amount of iron is thought to be proportional to total weight, this is not confirmed by data from Widdowson and Spray which are widely quoted.

Anemic and premature infants absorb iron at higher rates. (Bothwell and Charlton 1982). But because the administration of iron can also cause vitamin E deficiency in premature infants with resultant hemolytic anemia (Dallman 1986, Steichen et al. 1987, Dallman 1974, Stockman 1975), it is necessary to administer vitamin E to premature infants on iron-fortified formula (Dallman 1974).

The early introduction of solids has been found to inhibit iron absorption to various degrees, depending on the time of introduction of solids and cereals, the types of solids and cereals given, and the infant's existing iron stores (Food and Nutrition Board 1989, Dallman and Siimes 1979, Lanzkowsky 1980, Lonnerdal 1989, Oski 1985). Early introduction of solids is particularly not recommended for breastfed infants (Saarinen and Siimes 1979, Oski and Landaw 1980), as iron absorption from breastmilk is decreased. Giving solids such as pears to breastfed infants reduces their absorption of iron from breastmilk through chelation (Oski 1980).

Contamination of foods with iron and iron cooking vessels or containers can add significantly to iron intake. Teff, a dietary staple in Ethiopia, was shown to contribute 300 mg./day to dietary iron intake. Later studies revealed, however, that animals used for threshing contaminated the teff with iron-rich dirt. In South Africa, it was found that weakly acidic alcohol standing in iron tins could add from 15-100 mg. of iron per day to the dietary intake of iron (Hercberg et al. 1987). Weakly acidic contents in iron containers can add to the iron content of food or water, so sources of contamination should be examined.

Iron requirements are assumed to be affected by high altitudes. This assumption is based on work done in the early 1940's which suggested that hemoglobin values should be corrected by increasing the hemoglobin value by 4% for every 1000 feet above sea level. This too has been challenged (Hercberg et al. 1987. Owen et al. (1981) in New Mexico (over 5000 feet above sea level) found that breastfed infants had enough iron until they reached 5 or 6 months. A study in Peru also suggests that ferritin stores were adequate in breastfed infants at 6 months even at high altitude (Pastel et al. 1980).

Because sex-specific data are not documented, it is impossible to rule out gender differences in the first six months of infancy in the experimental studies reviewed. Underwood (1972) states that female rats had higher total body iron than males and accumulated more iron in their livers on the same diet. Gross (1968) found that when protein in formula was low, the weight gain of girls receiving iron was lower than in girls not receiving iron. No difference was found in boys. None of these differences were statistically significant. In a study by Burman (1972), birth weight was significantly related to hemoglobin level in infant boys who were given iron supplements at three months. However, the overall trend of hemoglobin through the period from 3 months to 24 months was higher than that of males. The reason for this is not known but may be related to weight gain or birth weight, both of which are lower in females. Oski and Landaw (1980) used adult men in their study of breast milk absorption. Underwood suggests that lower values would be expected in females because of their lower blood hemoglobin and muscle myoglobin. Data on possible sex differences in total body iron are not available. The experimental studies reviewed made no attempt to control for infants' weight (girls are normally 150 gm. lighter than boys at birth). Studies should collect sex-specific data to learn if girls have higher iron needs than boys.

D. Maternal Iron Status

The infant with an iron-depleted mother has surprisingly little evidence of anemia or depletion of iron stores. Where serum ferritin was used to compare neonatal stores of infants from iron deficient mothers with iron sufficient or iron-supplemented mothers, relatively little difference in iron nutriture was found (IOM 1991). Maternal iron stores have been found to influence iron stores in the infant only in cases where mother's anemia is severe (Dallman and Siimes 1979, Aggett et al. 1989, Dallman 1986, Oski 1985).

Available data suggest that blanket distribution of iron to women during pregnancy does not affect the iron status of infants, nor does it affect the iron levels in breast milk (Mbofung and Atinmo 1985, Murray et al. 1978, Sturgeon 1959). In most studies, hemoglobin in most newborns was unaffected. Two studies from developing countries concluded that newborns of anemic mothers were anemic, although to a far lesser degree than their mothers (Singla et al. 1978, Nhonoli 1975). Severe maternal anemia was a hemoglobin of under 6g./dl. (Singla et al. 1978).

Agarwal et al. (1983) found that there was a direct relationship between maternal hemoglobin, cord serum iron, and transferrin saturation. The authors concluded that cord hemoglobin is affected if significant anemia exists from early pregnancy. However, a comparable study by Murray et al. (1978) did not confirm these findings. Geographic variation, nutritional deficiencies, infection (malaria) or definition of anemia could explain the differences. Overall, there is little or no laboratory evidence that infants of iron deficient mothers are more likely to be iron deficient, but it is possible that the risk of low birth weight, prematurity, and perinatal mortality may be increased. The data, however, are far from conclusive (IOM 1990).

IV. RECOMMENDATIONS ON INFANTS' IRON INTAKE

Because of the documented concern for the high prevalence of anemia in infancy, the U.S. Food and Nutrition Board developed recommended dietary allowances of iron for infants and children. Different iron levels are required for full-term infants and for low birth weight infants during their first year of life (Dallman and Siimes 1979, Committee on Nutrition 1976, Dallman 1986, Lanzkowsky 1980, Food and Nutrition Board 1989, Oski 1990, Lundstrom et al. 1977, Dallman 1974). These estimates of requirements (Table 1) have been used as guidelines for the fortification of infant formulas and other infant foods (Dallman 1986, Minchin 1987, Chandra 1991).

According to Dallman, a leading pediatric expert on iron, the accepted rationale for iron requirements is based on the fact that:

> ...the weanling is vulnerable to iron deficiency. At birth the infant's hemoglobin concentration is higher than at any other time and the reserves are relatively generous [no references cited]. Between birth and 4 months there is little change in total body iron and there is no need for exogenous iron. During this period because of a substantial rise in blood volume the concentration of hemoglobin declines from a mean 17 gms/dl to 12.5g/dl [some studies show that iron supplementation does not alter this "physiological iron deficiency"]. In the first 2 months iron deficiency is rare except where there has been an unusual degree of perinatal blood loss.
>
> Between 4 and 12 months a large amount of iron must be absorbed from the diet: an average of 0.7 mg/day to provide for growth and 0.2 mg/day to balance basal losses. The rate and extent to which storage iron becomes depleted during this period can be estimated from changes of serum ferritin and depends on the magnitude of iron stores at birth and the postnatal diet. Iron stores are roughly proportional to body weight. Thus low birth weight infants start off with less iron than term infants, even though their needs will be greater to sustain a more rapid rate of growth. As a result low birth weight infants deplete their stores between 2 and 4 months of age (Lundstrom, Siimes and Dallman 1977) unless they receive iron formula or an iron supplement.
>
> Depletion of iron stores is more gradual in term infants. Infants on unfortified cow's milk formula may develop subnormal concentrations of ferritin after 6 months. However, this rarely exists in breastfed infants until after 6 months of age. Breast milk is associated with slower depletion of iron stores during early infancy due to the fact that iron is better absorbed from breast milk than from cow's milk formula. Nevertheless, in the absence of iron fortification, iron stores eventually become depleted when weaning foods begin to play an important role in the infant's diet. The selection of weaning foods therefore determines in large part whether an infant will progress from the harmless condition of low stores to the physiologic handicaps associated with iron deficiency. Most of these problems do not become evident with mild iron deficiency." (Dallman 1986)

It is this reasoning that has resulted in the iron supplementation and fortification regimes currently in vogue.

In the past decade, the RDAs have changed with the acceptance of new scientific evidence. For example, in 1976, the Committee on Nutrition of the AAP recommended 10 mg. of iron per day for full-term infants 0 to 6 months of age (Food and Nutrition Board 1989). Currently, the daily iron RDA for infants aged 1-3 months is 1 mg./kg./day and 10 mg./day for infants 6 months to 3 years old (Dallman and Siimes 1979, Committee on Nutrition 1976).

The RDA for low birth weight/preterm infants, however, has remained the same, namely, 2 mg./kg./day. Iron intake for low birth weight and full-term infants, however, is not to exceed 15 mg. per day. Avoidance of increased dosage is recommended because of vitamin E depletion which results from iron excess (Dallman 1974, Stockman 1975). Iron given to preterm infants before two months of age not only interferes with vitamin E absorption and causes hemolysis, but also interferes with zinc and copper absorption (Picciano 1976).

The Committee on Nutrition of the AAP (Dallman and Siimes 1979, Committee on Nutrition 1976) recommends 1 mg. of iron/kg. of body weight for full-term infants 3 months to 3 years of age; and 2 mg./kg. of body weight for low birth weight infants from 2 months to 3 years of age. It also recommends that the iron intake not exceed 15 mg. per day.

In 1970, the World Health Organization (Dallman and Siimes 1979) established iron requirements based on the percent of calories obtained from animal foods (Table 1). For infants from 6 months to 3 years of age who receive less than 10% of calories from animal food, 10 mg. of iron per day was recommended. For infants with an intake of less than 25% of calories from animal foods, a lower daily intake of 5 mg. of iron was recommended.

Generally, recommendations for iron intake by various organizations "have been partially derived from estimates of the increase in total body iron with age, with the assumption that the average iron absorption is 10%" (Dallman and Siimes 1979). As noted above, iron absorption from formula depends on a number of factors, such as the type of protein, the amount and form of iron, and the presence of vitamin C, which oxidizes ferric iron to the more absorbable ferrous form. It is important to recognize that these recommendations, specifically those of the Food and Nutrition Committee and the Committee on Nutrition, are only guidelines, "because iron absorption varies considerably according to the iron compound and food with which it is eaten" (Committee on Nutrition 1976). Set high (mean plus two standard deviations) in order to cover the distribution of needs in almost the entire population, the RDA values overestimate average nutrient requirements. The iron intake of infants fed iron-fortified formula exceeds the RDA by a factor of two (Filer 1990). While this would not be problematic with some nutrients, it may be with iron (see below).

The reference standard used to assess iron status in infants less than one year old is based on biochemical and hematological tests for infants one year or older (NHANES II and NHANES III). Since there were no available samples for infants younger than 12 months of age, Yip has stated, "the laboratory values of the 1 to 2 year age group can probably be used for infants 6-12 months of age" (Yip 1989a).

V. DISCUSSION: NEED FOR IRON SUPPLEMENTATION

Underlying many of the recommendations for iron supplementation of infant diets are a number of assumptions which are based on evidence that is either scientifically weak or that has been extrapolated to a questionable extent.

A. Benefits of Supplementation

Although certain negative effects on health have been found in infants with anemia, there is no consistent evidence that iron fortification or supplementation improves infant health or child growth and development, or that it reduces morbidity (Hemminki et al. 1988).

- Studies have not found growth differences in iron supplemented and unsupplemented full-term infants (Hemminki and Rimpela 1991, McMillan et al. 1976, Fuerth 1972, Garry et al. 1981) nor in premature infants (Gorten and Cross 1964).

- One study that has received considerable attention (Walter et al. 1989) found that in Chile anemic children (12-15 months old) had deficient language capabilities and body balance skills. The children were supplemented at 12 months for 10 days or 3 months. Anemia was defined as a hemoglobin of under 10.5 gms./dl. The effects were not reversed by supplementation, and the authors suggested that the only time to prevent iron deficiency is in early infancy. Others, however, more skeptical of the contribution of iron alone to these types of abnormalities, point to "their multifactorial determinism" (Hercberg et al. 1987).

B. Possible Harmful Effects

Although it is currently fashionable to fortify milk regardless of the lack of proven health consequences and available national iron nutriture of the reference population, few studies examine the adverse effects of iron. The Committee on Nutrition cites two studies (Oski 1980 and Nelson et al. 1988) as evidence that iron fortification has no adverse effects.

Iron is a toxic substance, especially in infants, and cases of accidental iron poisoning are not infrequent. Because iron is known to be harmful when given in excess, special precautions are taken when therapeutic iron is given to infants.

- Of note is the fact that iron supplementation is not recommended for infants with thalassemia (United Nations/ACC/SCN 1990, Chandra 1991). Excessive iron intake can cause iron storage disease over time, as the iron accumulates in the tissues.

- Oppenheimer et al. (1986b) found that infants on iron supplementation not only had higher iron stores and higher hemoglobin levels but also a higher incidence of malaria and other infections. Intramuscular injections (IMI) of iron dextran were administered. The authors recommend that iron supplementation not be used in endemic malaria areas, as there is some evidence that malaria plasmodia "grab" iron (Jelliffe 1991).

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- Chandra (1991) has also stated that excess iron may increase an infant's susceptibility to infections.

- Iron fortification in high amounts can interfere with lactoferrin by saturating this iron-carrying compound. It interferes with lactoferrin's antibacteriocidal effect and results in an increased incidence of gastrointestinal infections (Steichen et al. 1987, Chandra 1991). Increased iron intake also can cause stomach cramps (Oski 1980).

The long-term effects of iron overload are well known in adults, but there have been no long-term follow-up studies in children on high iron intake.

The absorption of iron from a typical formula is only 4% (Rios, cited by Walter et al. 1990) and decreases with the amount of iron added. While the AAP's Committee on Nutrition (1989), citing Yip (1985) and Haschke et al. (1986), argues that more iron does not impair the absorption of zinc and copper, others such as Chandra (1991) and Lonnerdal (1989) are concerned not only with the effect of iron fortification on zinc but also with the negative effect of excess iron on the antibacteriocidal action of lactoferrin, which results in an increased incidence in gastrointestinal infections. In the United States, the concentration of iron in formula can be as much as 22 times higher than in breast milk, although the need for such high supplementation has not been established (Minchin 1987, Hemminki et al. 1988).

C. Experimental Fortification/Supplementation Studies

While the AAP's Committee on Nutrition (1989) has stated categorically that the feeding of iron-fortified formula to infants has been shown to "practically eliminate overt iron deficiency," the external validity (generalizability) of the studies cited (Marsh et al. 1959, Andelman and Bered 1966, and Hertrampf et al. 1986) needs to be examined.

The studies of Marsh and Andelman compared infants on formula (iron supplemented and non-iron supplemented) with infants on evaporated milk (Table 3). Not only were these formulations vastly different in composition with regard to protein, fat, and phosphorus, but there are also problems with the study designs, such as small sample size and selection bias. Also, because all of the studies cited by AAP were conducted in low socioeconomic populations, it is not certain that findings can be generalized to the population at large.

Comparisons have been made between breastfed infants and infants fed cow's milk or formulations of cow's milk or soymilk. The outcome measures used were hematological and biochemical tests -- usually low hemoglobin (between 8 and 11 gms. per 100 ml. or a serum iron level of less than 50 ugs./1000 ml.), and in some studies three or four of a battery of tests (Hb, Hct, serum iron, transferrin saturation, ferritin). However, in most studies, breastfeeding was not defined precisely, and few studies compared iron status of breastfed to formula-fed infants. In most of the comparative studies examined, solids were added at or shortly after 3 months (Saarinen and Siimes 1977, Saarinen and Siimes 1979, Steckel et al. 1986, Hertrampf et al. 1986, Walter et al. 1990, Pizarro et al. 1990, Garry et al. 1981, Woodruff et al. 1977, Coulson et al. 1977, Saarinen et al. 1977, Dallman and Siimes 1979, Good 1977, Siimes et al. 1984). The chemical formula of dietary iron and iron quality both have important effects on iron absorption (Dallman and Siimes 1979, Committee on Nutrition 1976, Committee on Nutrition 1989, Dallman 1986). The wide variety of formulas used in experimental clinical studies, with varying protein, lipid, and iron content, makes it difficult to compare study findings.

The few randomized controlled clinical trials available have many methodological problems (Gross 1968, Oski and Landaw 1980, Oppenheimer et al. 1986, Lundstrom et al. 1977, James and Combes 1960, Gorten and Cross 1964). The results of several studies are compromised and cannot be generalized because of the large number of dropouts (Andelman et al. 1966, Fuerth 1972, Saarinen and Siimes 1979, Stekel et al. 1985, Munoz et al 1988, Siimes 1979, James and Combes 1960). In most of the studies, it is hard to determine a cause and effect relationship. Mahomed and Hytten (1989) point out that "...generally, with an illiterate population and a high rate of non-cooperation, and because of the complexity of the clinical background, few trials of treatment have been undertaken and all suffered subject losses which makes interpretation difficult." Furthermore, capillary blood samples were collected more often than venipuncture samples. "Capillary specimens have a higher and generally wider range of hemoglobin values than samples obtained from the umbilical or peripheral vein" (Oski 1990).

It is difficult to compare fortification studies due to a wide range of confounding variables. A wide variety of milk formulas were used, containing different protein, fat, mineral and vitamins, as well as amounts and types of iron. The formulas also varied as to whey and casein protein content. A high casein content reduced iron absorption. In some studies, milk was fortified with iron, and in others the infant was supplemented with varying amounts of iron drops. Some infants were even given intramuscular injections of iron dextran before or after the milk feed (see Table 3).

According to Lonnerdal (1991), "the level of [iron in] infant formula varies considerably; label claims range from a high level of 12 mg/liter in iron supplemented U.S. formulas to 6-7 mg/liter in most European formulas to 1 mg/liter in unfortified formula. When the actual iron level of formula is analyzed, even greater variation is found." (Table 9 illustrates some of the iron levels claimed by formula manufacturers.)

Investigations of premature infants show that iron fortification/ supplementation before two months does not raise the hemoglobin concentration. Higher hemoglobin values in these infants at older ages had no effect on health outcomes, and hence the benefit or iron fortification and supplementation has not been well substantiated. In the experimental studies surveyed, other causes of iron deficiency were not excluded.

The few experimental iron fortification studies in premature or low birth weight infants (Table 4) have no reference standards for full-term, low birth weight, or premature infants to assess iron nutrition status accurately, nor enough information on premature infants as distinct from full-term low birth weight infants (intrauterine growth retardation). The evidence of specific health effects of the different categories of iron deficiency, iron depletion, and anemia in this group is lacking.

Iron absorption from fortification or supplementation is affected by a number of factors, including the type of iron (ferrous is better absorbed than the ferric form), particle size, dose, composition of diet or type of formula, time given in relation to meals; presence of vitamin C, and amount of solids in the diet. Because of the great number of variables involved that affect iron absorption, there is controversy as to how much iron should be given, in what form, and when. The exact mechanism that controls absorption is unknown.

The measurement of iron absorption and iron content (according to Lonnerdal 1991, p. 155) must be interpreted with caution, as the iron content of an infant varies for a number of reasons, including the "high variability in iron absorption...the method of isotopic labeling of the diet, the dose size used and finally, the diet tested."

D. Value of Iron Supplementation of Infants

Iron-fortified formula use increased from 40% of all U.S. formula sales in 1971 to approximately 80% in 1985 (Miller et al. 1985). The AAP's Committee on Nutrition credits the major decline in the prevalence of anemia in the U.S. infants in low income (Miller et al. 1985, Vazquez-Seoane et al. 1985, and Yip 1987) and middle-class populations (Yip 1989) to the fortification of formula with iron and its subsidized distribution to low income groups through the national Women, Infants and Children (WIC) Program.

However, a number of other factors, which have not been considered, may well have contributed to this stated decline. Among these are the change in the composition of formula (heat-treated milk formula, decrease in the use of evaporated milk and of fresh cow's milk); decrease in parasitic infestations (especially hookworm); improved health care; revised selection criteria for WIC recipients; changes in maternal iron status; and the decrease in the incidence of lead poisoning. Also at issue is whether the incidence of anemia has in fact changed because of newer definitions of anemia and more sensitive indicators used to measure iron deficiency. More importantly, what are the established functional health effects of the numerous laboratory tests for iron status?

It is controversial whether to give iron supplements to all breastfed infants at the time of birth, at the time of initiation of solid foods (generally at 4-6 months of age), or at all. Some researchers have recommended iron for all breastfed infants because of the low iron content of human milk (0.5 mg./L.), but this does not take into account the studies of Saarinen, who documented the high bioavailability of iron in breast milk (49%). The studies on which the recommendation to fortify is based do not separate exclusive from nonexclusive breastfeeding, nor do they define exclusive breastfeeding precisely (see Table 2) (Baumslag and Putney 1989, Labbok and Krasovec 1990). Little recognition has been given to the finding that if young infants on breast milk are given solids, this reduces iron absorption (Saarinen et al. 1979, Oski 1980).

Iron deficiency has not been noted in infants exclusively breastfed for 6 months (Saarinen 1979), nor in infants breastfed for 9 months (Pastel et al. 1980), 18 months (McMillan et al. 1976), or 24 months (Coulson et al. 1977). After 6 months, it is generally recommended that infants be weaned gradually onto solids and that complementary breastfeeding continue for up to two years or beyond. The risk of developing iron deficiency, although relatively small at age 9 months, increases as exclusive breastfeeding is prolonged (Siimes 1984).

It may be more important to provide colostrum to the newborn and to ensure cord blood conservation than to fortify breast milk substitutes or supplement with iron. Underwood (1972) stated that the level of iron in colostrum is 3-5 times higher than in human breast milk, but offered no references. Of 116 articles on human colostrum that Jelliffe reviewed (personal communication), none examined the iron content of colostrum. Only a few studies were found after extensive research (Table 5). Available data from 230 samples worldwide indicate a range of mean iron levels from 1.30 mg./L. (Castellanos 1943, cited in Macy 1953) and 1.23 mg./L. (Donangelo et al. 1988) to 0.4 mg./L (Macy 1953). It should be noted that methods of collection and measurement as well as the specific lactation time (hours or days postpartum) of sample collection varied.

The mother's own fresh milk is the first choice for the premature infant weighing less than 1500 gms. (3.3 lbs.), because it contains live cells and other protective factors that ward off infections (Committee on Nutrition 1985). Human milk is easy to digest because

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it contains lipase -- an enzyme that helps digest milk fat more efficiently. Infants fed human milk do not develop the serious condition of necrotizing enterocolitis. In a study of premature infants (average weight of 1300 gms.), breastfed infants had less hypothermia and less oxygen depletion than bottle-fed infants (Meier 1988).

Premature infants weighing more than 1500 gms. grow well on their mothers' milk (Gross 1983, James 1966, Gorten and Cross 1964, Committee on Nutrition 1985). Unfortunately, current weight gain recommendations are based on infants' growth rates in utero, a standard whose validity has not yet been tested or proved (Pereira and Barbosa 1986). The desired weight gain can sometimes be achieved by human milk alone or by supplementing with special formulas or fortifiers. Routine lab testing will tell if the baby needs other nutrients.

A 1 kg. fetus has 64 mg. of iron. The iron stores of infants weighing less than 1.4 kg. would be exhausted after 6-8 weeks, whereas heavier LBW infants' iron stores would last about 12 weeks postnatally. Preterm infants experience a fall in hemoglobin concentration during the first two months more marked than in full-term infants. According to Siimes (1984), the so-called anemia of prematurity cannot be prevented by iron supplementation and should be regarded as physiological. Others argue that premature infants are at risk for iron deficiency anemia because of the fall in hemoglobin in the first two months of life. This is hard to establish, as there are no national reference data for laboratory values of iron in infants under one year old, for full-term newborns, nor for low birth weight and premature infants. Still, Atkinson, Gross and Mendelson consider human milk to be insufficient for preterm infants (Pereira and Barbosa 1986) and therefore advocate "fortifiers for preterm milk." The absorption of iron from milk is higher in preterm infants than in full-term infants (Dauncy et al. 1978). The small LBW infant absorbs iron better when fed on human milk than on formula (Siimes 1984). But some studies show that the premature infant cannot maintain optimal iron nutrition, without supplementation, after the age of two months (Siimes 1984). It is difficult to indicate what the optimal dose of iron as supplement is because individual needs for iron may vary with birth weight, neonatal sickness, and blood loss (Akre 1989).

As mentioned above, the data on iron levels from NHANES II children one to two years of age are extrapolated to infants under one year of age (Yip 1989a). Without reference data on iron levels in infants (under one year), the clinical significance of fortification or supplementation is difficult to determine. While iron deficiency is extremely rare in normal-weight infants who are exclusively breastfed for 6-8 months, it is frequent in infants on formula. Yet merely lowering the concentration of protein in formula to that of breast milk can decrease the incidence of anemia in full-term infants (Gross 1968).

In numerous reports, the consumption of excessive amounts of whole cow's milk (WCM) in infancy has been associated with iron deficiency anemia (Woodruff and Clark 1972, Wilson et al. 1974, Anyon and Clarkson 1971). This is partly due to the low content and poor bioavailability of iron in cow's milk. Whole cow's milk can cause occult bleeding from the gastrointestinal tract. The mechanism is unknown, but enzymatic, toxic, and immunologic reasons have been examined (Eastham and Walker, 1977). The appropriate age at which unheated WCM can be introduced in the infant's diet is unknown and remains controversial. There is no evidence that feeding WCM after 6 months is harmful if adequate supplementary feedings are given (Committee on Nutrition 1983).

Experimental studies show a small increase in hemoglobin levels and less "anemia" in iron-fortified or supplemented groups than in unsupplemented controls; however, the medical significance is difficult to interpret (see Tables 3 and 4). The questions of whether and how much iron should be added to formulas for preterm infants still have to be answered.

The majority of fortification/supplementation studies in full-term infants reviewed were conducted in the U.S. and Chile, mainly among low socioeconomic populations (see Table 3) (Marsh et al. 1959, Andelman and Sered 1966, Gross 1968, Fuerth 1972, Rios et al. 1975, Sadowitz and Oski 1983, Stekel et al. 1985, Pizarro et al. 1990). It appears, however, that baseline hemoglobin levels in the low socioeconomic groups are lower, and cut-off points for hemoglobin used in these studies were also lower for upper income groups. For example, Marsh et al. (1959) used a hemoglobin of 8 g. per 100 ml. or a serum iron of less than 50 micrograms per 100 ml. for a diagnosis of iron deficiency anemia. Pizarro, however, who used a hemoglobin cut-off of 11 g./100 ml., not surprisingly found a higher prevalence of anemia.

The lack of uniformity in the classification of anemia in infants (usually by hemoglobin levels) makes the results hard to interpret. Farquhar et al. (1963) produced higher hemoglobin levels by administering iron to infants from above-average socioeconomic status but concluded that there was no evidence that the difference had any real medical significance. Burman concluded from his study that unless it can be clearly shown that maximal hemoglobin is beneficial to infants, efforts to raise the hemoglobin should not be made, and levels above 9.5 or 10 g./100 ml. should be considered nonpathological, not only at 6-8 weeks but also for the remainder of the first two years of life. Regardless of their type of feeding, nutritional iron deficiency is uncommon in healthy full-term infants under 6 months of age.

VI. CONCLUSIONS

Until age and sex norms are established for the reference population and more precise measures of iron deficiency are developed, there is no justification for the indiscriminate iron fortification of formula and iron supplementation of breastfed infants in the first six months of life.

Exclusive breastfeeding is an excellent source of iron in infancy. Available data indicate that exclusive breastfeeding through six months will prevent iron deficiency anemia. Even in studies where exclusive breastfeeding was not well defined, iron deficiency does not appear to have occurred. Given the current data, it is hard to see why it is recommended that full-term, breastfed infants receive supplemental iron before six months.

With regard to fortification of formula, there remain many unanswered questions. Because of selection biases, differences in formulas used, and lack of randomized controlled trials, past studies do not provide a firm basis for recommending iron fortification of formula or supplementation for infants. Also, physiological anemia (the drop in hemoglobin from 2-4 months of age) has not been adequately studied. Nonetheless, there is some evidence that although far inferior to breast milk fed exclusively for the first 4-6 months, iron-fortified formula can raise hemoglobin levels.

Recommendations for fortifying or supplementing the diet of premature or low birth weight infants with iron still cannot be made with confidence. Studies on premature infants use infants of various weights, so consistent conclusions cannot be drawn. Many more careful, clinically controlled trials are required to establish recommendations for iron supplementation for low birth weight and premature infants. The singular approach that applies limited indicators and does not measure functional effects is a real cause for concern where iron supplements are recommended.

Studies on maternal/fetal iron status yield few correlations between iron transmitted from mothers based on measures of iron status currently available to infants. Although low maternal iron status may result in an increased incidence of lower birth weight infants, iron supplements for pregnant and lactating women have not been shown clearly to be beneficial to infant health. There are no carefully executed studies in which health outcomes have been used to determine optimal iron intake (Hemminki et al. 1988).

Finally, four areas worth exploring are the following:

- Placental iron transfusion or conservation of placental iron. A six-month supply of iron can be conserved if the cord blood is milked or gravitated after the cord has stopped pulsating and before it is tied.

- Colostrum is probably an excellent source of iron. More data are needed to examine this and to promote its consumption by infants, commencing within one hour of delivery.

- More systematic longitudinal absorption studies need to be conducted on the effectiveness of common food sources high in iron on the infant's health (days sick, infections, diarrhea incidence, malaria).

- Finally, exclusive breastfeeding appears to be an excellent source of iron through six months of age. The early introduction of solids, especially types of food used to complement breast milk, needs to be examined carefully.

Working groups should be established to examine more creative and appropriate measures to conserve iron intake, maximize iron intake from local foodstuffs, and explore some of the research avenues suggested.

Table 1

IRON RECOMMENDATIONS FOR INFANTS BIRTH TO ONE YEAR

RDA 1989

	AGE	IRON
Breastfed	After 3 months	1mg/k/day
Non-breastfed	birth - 6 months 6 months - 3 years	1mg/k/day 10mg/day
Low Birth Weight (1,000 - 2,000)*	after 2 months	2mg/k/day

UNITED NATIONS SUBCOMMITTEE
ON NUTRITION 1990

	AGE	IRON
Normal birth weight	0 - 6 months 6 months - 1 year	No supplement 1mg/k/day
Low birth weight (<2.5k)	2 months onwards supplement with iron	No amount given

FAO/WHO (1970)a

	AGE	IRON
<10% calories from animal foods	0.5 - 3 years	10mgs/day
>25% calories from animal foods	0.5 - 3 years	5mgs/day

*Not to exceed 15mgs/day
a WHO Technical report series #452
Requirements of ascorbic acid Vitamin D,
Vitamin B12, Folate and Iron. Geneva 1970

TABLE 2

EXCLUSIVE* BREASTFEEDING AND IRON SUPPLEMENTATION

AUTHOR	STUDY DESIGN	AGE (Follow-up)	N ST/FI	SOLIDS	TEST	COMMENTS/CONCLUSIONS
McWilliam USA, 1976	Excl. bf. (Av.bi.wt 2.8Kg.)	10.9m	4	-	HB, SI	Indicators (HB, SI) at all ages were normal and growth sufficient. Excl. bf. can remain on bm till triples bi wt or at I year.
Woodruff 1977 USA	1. Excl. bf. 2. Similac (Fe 1.5mg/1)	9m	19	-	Hb, Hct, SI	Excl. bf used iron more efficiently. At 9m half of both groups had biochemical Fe deficiency defined as (transferrin < 16%)
Coulson 1977 USA	Healthy breastfed (Exl. for 4m)	3-24m	66	4m	Hct	Breastfed sufficient. Majority had Hct above 33% up to 24m.
Saarinen 1977 Finalnd	Breastfed infants and on cow's milk formula given tracer dose of Fe.	5 - 9m	45	3.5m	Hct, SF	Infants fed breastmilk attained greater iron stores through first 6/7m of life than infants fed cow's milk formula. Absorption highest in breastfed (49%).
Good 1977 USA	1. Excl.bf 2. Bm + Solids	4m 6m	105 42	4m	Hb	Hb same in both groups. No iron supplements needed for bf infants up to 4 - 6m.
Pastel 1980 Peru	1. Excl. bf 2. U.S. contols fed variety of milks.	7.5 - 12m 9 - 12m	7 40	ns	SF, EP	Excl. bf received all the iron they needed for the first 9m Ferritin adequate for most of the first year.
Owen 1981 USA (NM)	1. Excl. bf c and without 10mgs Fe/day 2. Cows milk formula heat treated + lactose	6 - 7m 7 - 12m	90	5m	Hb, SI, SF	Bf infants do not have sufficient iron after 5 - 6m (high altitude > 5000ft)

TABLE 2

EXCLUSIVE* BREASTFEEDING AND IRON SUPPLEMENTATION

AUTHOR	STUDY DESIGN	AGE (Follow-up)	N ST/FI	SOLIDS	TEST	COMMENTS/CONCLUSIONS
Siimes 1984 Finland	1. Excl. bf 2. Controls formula 6mgs/FE/L and cereal Iron Fortified 40 mgs/kilo.	Bi-9m	198	3m	Hb, SF	No anemia in excl. bf infants before 6m infants excl. bf till 9m. Maternal iron supplementation during bf had no effect on infant Iron.
Duncan 1985 USA	Excl. breastfed	2w - 6m	33	-	Hb,SF	Ft. Excl. bf for first 6 months not at risk for Fe deficiency anemia or depleted stroes (used Siimes data as reference population).

Ft - full term; Excl. - Exclusive; m - months; bi - birth; w - weeks; bf - breastfed; st - start; fi - finish; bi wt - birth weight

*Most infants were exclusively breastfed only for 3 - 6 months and then solids were added while breastfeeding continued.

TABLE 3
EXPERIMENTAL STUDIES IN FULL-TERM INFANTS ON IRON FORTIFICATION AND SUPPLEMENTS

Author	FF/S	Study Design	Treatment	Age St/Fn	No.	Solids	Tests	Results/Conclusions	Comments
Marsh 1959 USA	FF	CC	1. F Fe + 12mg/32 oz 2. Formula (Control) 3. Evap. milk + sucrose - (control)	Bi-9m	74	-	Hb/SI Hb<8g	Mean Hb, Hct SF higher for all infants on iron FF. No diff. in growth and development	Comparison between formula with evaporated milk not valid. Race, sex difference in groups
Andelman 1966 USA	FF	-	1. Evap. milk formula + vit 2. Formula 12mg Fe/qt	<4w - 18m	445 603	3m	Hb, SI Hct	Growth rate same. Fe + grp had decreased respiratory infections. Fe fortified formula can control anemia in low SES.	Large numbers of dropouts Not clear how randomized
Gross 1968 USA	FF	DB	4 different formulas with low & high protein (24g/L or 15g/L) & Fe 8-8.5mg/L	Birth - 18m	144	2m	Hb	Hb levels varied by Fe and protein content. Average infant does not need iron supplements	Infants with higher protein intake had lower Hb levels
Burman 1972 UK	S	CC	1. Collodial ferric oxide 10mg/d drops 2. Placebo	3m - 24m	217	-	Hb	Fe(+) birth wt was significantly related to Hb in males at 3m only. No effect on infections	High dropout/rate excluded infants with Hb <9g/100ml
Fuerth 1972 USA	S	DB	1. Formula FES04 drops 30 mg/d 2. Placebo	1m - 18m	329	-	Hb, Hct SI	Supplements no benefit to fullterm healthy infants. No. diff in Hb, Hct, wt. gain or growth	High dropout rate. Self selected. No. info. on feeds
Lammi 1975 Australia	FF	DB	1. FF Fe 9.4mg/l 2. Control Fe 1.2mg/l	4 - 10w to 4 - 7m	327	-	Hb, SI	No difference in wt gain	Not clear how randomized
Saarinen 1979 Finland	FF	-	1. Breastfed (Excl. 4mo) 2. Home-prepared cow's milk formula 3. FF ferrous gluconate '11mg/L	2w - 12m	86 15 31	-	Hb, SF	Breastfed infants maintained Fe status. Dropped when solids added FF maintained total body iron	Results based on TBI calculation
Oski 1980 USA	FF	RCT	1. FF 12mg Fe/qt 2. Formula without iron	3w - 6w	93	-	-	No significance difference in stomach cramps.	
Stekel 1985 Chile	FF	-	1. FF + Fe 15mg/L + 100mg AA/L 2. Controls no Fe formula	3m - 15m	- -	4m	Hb, SI	Milk formula Fe + AA decreased iron deficiency in Chilean infants.	Selection? Dropout?
	FF	-	1. FF Fe 15mg + AA 100mg/L 2. Unfortified full fat *		280				

TABLE 3

EXPERIMENTAL STUDIES IN FULL-TERM INFANTS ON IRON FORTIFICATION AND SUPPLEMENTS

Author	FF/S	Study Design	Treatment	Age St/Fn	No.	Solids	Tests	Results/Conclusions	Comments
Hertrampf 1986 Chile	FF	-	1. Prosbee + Fe 12mg/L +AA 54mg/L 2. Powdered full fat 100mg AA + 15mg Fe/L 3. Breastmilk	3m - 9m	47 45 90	3m	Hb, SF	Soy formula (despite low Fe availability) as effective as Fe fortified cow's milk. Bf group had most anemic infants at 9 mo	Anemia (Hb<11g/100ml Not exclusively bf
Oppenheimer 1986 Papua New Guinea	S	RCT	1. imi Fe dextran (150mgs Fe) 2. Placebo	3m - 12m	236 250		Hb, SI SF	Fe deficiency has protective role against malaria and argues against injudicious use of Fe replacement where malaria is endemic. Fe+ deleterious effect on respiratory infections	Not clear how randomized
Pizzaro 1987 Chile	FF	-	1. FF AA 100mg + Fe 15mg/L 2. Non-fortified dry full fat milk	3m - 15m	167 143	-	Hb, SF	High Fe formula less Fe deficiency	Separated groups on stool Stool as measure of complainc Not clear how randomized
Schultz-Lell 1987 Sweden	FF	-	1. Breastfed 2. Adapted Formula Fe 1.1 mg/L 3. FF Fe 10.35mg/L	3w - 17w	10 3 4	-	urine faeces breastmil	Exclusive breastfed retained Fe for first 6 m. FF Fe retained 12 - 40 times more iron	All subjects male Iron balance study
Palti 1987 Israel	S	QE	1. Cow's milk + Fe carbonate syrup + vit C 2. Control cow's milk*	3m-12m	467	-	Hb, MCV	Fe supplements reduced no. of infants with Hb <11mg but did not eliminate anemia	Compliance - no cross check
Pizzaro 1975 Chile	FF S	RCT	1. Unfortified formula 2. Fe fortified formula 3. Breastfed + IMI dextran (150mg Fe)	Birth - 9m	151 138 77	3m	Hb, SI SF	Anemia most common in unfortified formula group. Least in Fe Dextran group	Not exclusively breastfed
1980			1. Unfortified milk formula 2. Fe fortified formula	152 85	- -			Supplement diets of unfortified formula w/ iron on or before 9 months to prevent Fe deficiency and Fe deficiency anemia.	

TABLE 3

EXPERIMENTAL STUDIES IN FULL-TERM INFANTS ON IRON FORTIFICATION AND SUPPLEMENTS

Author	FF/S	Study Design	Treatment	Age St/Fn	No.	Solids	Tests	Results/Conclusions	Comments
1985			1. Unfortified milk formula	102	-				
			2. Fe fortified formula	85	-				
			3. Breastfed for at least 9 months	102	-				
Garry 1981	FF S	RCT	1. Breastfed w/o Fe	Birth	42	5m	Hb, SF	Exclusively breastfed need Fe supplementation to prevent Fe deficiency at 4-6 months.	Not clear how randomized Used TBI calculation for results
			2. Breastfed w/Fe 10mg/Fe/L	S	48		SI		
			3. F Similac Fe 0.5mg/L		69				
			4. FFe 12mg/l		73				

* Studies breastfed for 3 months before assigned to groups. Not clear if exclusive or mixed feeding.

Age St/Fn= Age at start and at finish

AA = Ascorbic acid
DB = Double Blind
CC = Case Control
RCt = Randomized clinical trial
QE = Quasi experimental
d = day
m = month

FF = Fortified Formula iron
S = Supplement drops/tablets
IMI = intramuscular injection
Hbl = Hemogloblin iron
BSI = Body storage iron (calculated from log of serum ferritin and body weight)

TBI = Total body iron (calculated from the =sum of HBI and BSI)
oz = ounce
evap = evaporated
vit = vitamin
bm = breastmilk

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TABLE 4

EXPERIMENTAL STUDIES IN PREMATURE INFANTS ON IRON FORTIFICATION

Author	Study Type	FF/S	Study Design	Av. Wt	Age St/Fn	No. Start	Drop out	Solids	Test	Conclusions/Results	Comments
Lundstrom 1977 Finland	RCT	S	1. FsSO4 drops 2mg/k/d 2. No supplements	1650 gms	2w - 6m	117	+	3m	Hb, SI SF	Low mean Hb at 2m Supplementation started at 2w, prevents iron deficiency	Paucity of normal values in 3 - 6m infants
James 1966 USA	RCT	S	1. 1 ml Fe dextram/d 2. No supplements	<2000 gms	Birth-11m	205	+++	-	Hb	No significant difference in weight or respiratory infections No Fe deficiency in IMI dextran group	High dropout rate
Gorten 1964 USA	RCT	FF	1. Fortified formula Fe 12mg/qt 2. formula with no Fe	<1900 gms	1w -18m	69	+++	3m	Hb, Hct	Growth equal in both groups Prevents iron deficiency	High dropout rate Iron deficiency Hb<9g/100ml
Rios * Chile	_	S	1. Fe drops 2.5mg/k/d 2. Milk fortified w/ Fe 15mg+AA 100mg/ 100milk powder	-	3m -12m	65 65	-	-	Hb	With Fe and ascorbic acid, higher Hb and lower rate of anemia	Field trial over longer period 10 years. Selection? Anemic = <11gHb/100ml

*FROM: Walter, T., Olivares, M., Hertrampf, E., Field Trials of Food Fortification with Iron: The Experience of Chile, CRC Press, pp.127-155, 1990

FF = fortified formula
S = supplement
FM = fortified milk
AA = ascorbic acid
m = month

Av. Wt = Average weight
Age St/Fn = Age at start and finish
RCT = Randomized clinical trial
w =week

TABLE 5

COLOSTRUM AS A SOURCE OF INFANT IRON

Source	Number in Sample	When Collected	How Collected	Type of Analysis	Iron (mgs/L)	Mean or Median
Vega-Franco et al- 1987 Mexico	99	First 42 hrs. post-partum	Manually	Atomic absorption spectrophoto-metry	0.85	Mean
Garg et al- 1988 India	wn[1] 20 un[2] 15	-	-	Atomic absorption spectrophoto-metry	wn[1] 0.45 un[2] 0.38	Mean
Castellanos et al- 1943 Argentina[3]	-	-	-	-	1.30	Mean
Escudero et al- 1943 Argentina[3]	-	-	-	-	1.00	Mean
Macy before 1953[3]	-	-	-	-	0.40	Mean
Fransson et al- 1980 Sweden	15	3 days	Handpump	Atomic absorption spectrophoto-metry	0.50	Mean
Donangelo et al- 1988 Brazil	83	1-5 days	Manually	Atomic absorption spectrophoto-metry	1.23 1.05	Mean Median

[1]Well-nourished
[2]Undernourished

[3]FROM: Macy IG, The composition of milks; a compilation of the comparative composition and properties of human, cow, and goat milk, colostrum and transitional milk. Washington, National Academy of Sciences-National Research Council, 1953.

TABLE 6
IRON AVAILABLE THROUGH THE UMBILICAL CORD

Source	No in Sample	Technique	When Clamped	Age	Results	Conclusions	Comments
Grodberg & Carey 1938 USA	235	Placental blood was drained into a flask while milking the cord	-	-	Av. yield = 105cc blood	-	Study was to examine the use of placental blood for transfusions
Wilson et al	15	Immediate clamp	After the placenta had begun to descend into the vagina Time not stated	8m - 10m	Stat. sig diff MCH	Used data from the literature to calculate that 105cc of blood and 56.3mg of iron is lost to the infant through early clamping. Depriving infant of placental blood by early clamping may lead to Fe deficiency during the first year of life.	Infants from a previous study showed that early clamping decreased RBC and Hb during the first week of life
DeMarsh et al 1953 USA	18	Immediate clamp Delayed clamp	After the placenta had begun to descend into the vagina Time not stated	.25h - 3h	Hct diff D&I -9%, TBV diff D&I-61%	Early clamping deprives infant average of 107cc of placental blood.	Uses av. of 2 reading on each to calculate results
Duckman et al 1953 USA	a = 23 b = 24 c = 47	Delayed clamp Infant held in scale 6" above mother Infant held in scale at same level as mother Infant held in scale 6, 12, or more inches below mother	2m - 5m	2m - 5m	Wt gain highest in group c	Infants whose cords were not clamped immediately seem to enjoy better health while in nursery. Infant held below level of mother most likely to receive greatest volume of blood.	Those infants with wt gain >50gms enjoyed the best results
Whipple et al 1957 USA	38	1. Immediate clamp 2. Infant placed on table 15cm below vagina 3. Infant placed on mother's abodmen 4. Infant in lap of OB and cord milked 5 times	 3m 3m	7h - 24h 60h - 104h	Mean RCV first measure: 1-3 = 44.1, 4 = 62.4 Second measure: 1-3 = 40.2, 4 = 58.1	Possible to increase blood vol. newborn 22% and RBC vol. by 45% by milking cord 5 times before clamping. Simple delay in ligation does not significantly influence these measures even with help of gravity	Not clear number in each group Felt that RCV is better measure than TBV for measuring effects of clamping

h - hours
m = minutes
wt - weight

TBV = Total Blood Volume
RCV = Red Cell Volume
RBC = Red Blood Volume

av = average
I = immediate clamp
D = Delayed clamp

OB = obstetrician
Stat = statistics

Table 7

IRON ABSORPTION

Source	Percent absorbed
Breastmilk	49%
Unfortified cow's milk or cow's milk formula	10 - 12%
Fortified formulas (with 11 - 12 mg Fe/Liter)	4%
Wheat, barley maize mixture (with hydrogen-reduced Fe of small particle size)	4%

NOTE: It is believed that the rate of absorption increases as the amount of fortification decreases in formula

Source: International Anemia Consultative Group (INACG) - 1979

TABLE 8

IRON SOURCES USED IN CEREAL FORTIFICATION

Source	% Fe	1990 Cost ($/kg)	Cost ($/kg of Fe)	Bioavailability	Color	Stability
Hydrogen Reduced Iron	98	1.94	2.00	Fair -	Black	Good
Electrolytic Iron	98	4.71	4.80	Fair +	Black	Good
Ferrus Sulfate	32	2.35	7.30	Good	Tan	Fair
Ferric Orthophosphate	28	2.73	9.80	Poor	White	Excellent
Ferrous Fumarate	33	2.94	8.90	Good	Red	Fair ?
Iron EDTA	13	6.60	50.90	Excellent	White	Good ?

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TABLE 9

Nutrient Comparison—Infant Formulas per 100 Calories*

Nutrient	Units	Breast Milk	GOOD START™	Similac®	Enfamil®	SMA®	Gerber®	Isomil®	Pro-Sobee®	Nursoy®
Protein	g	1.5	2.4	2.22	2.2	2.2	2.2	2.66	3	3.1
Fat	g	5.4	5.1	5.37	5.6	5.3	5.4	5.46	5.3	5.3
Carbohydrate	g	10	11	10.7	10.3	10.6	10.7	10.1	10	10.2
Linoleic acid	mg	540	850	1,300	1,300	500	1,300	1,300	1,200	500
Linolenic acid	mg	75	100	NA	56	69	225	NA	56	69
Cholesterol	mg	20	10	1.6	<1.6	6	NA	0	0	2.3
Calorie/liter		730	670	676	680	676	676	676	680	676
Vitamin A	IU	310	300	300	310	300	300	300	310	300
Vitamin D	IU	3.05	60	60	63	60	60	60	63	60
Vitamin E	IU	0.32 (mg)	2.0	3	3.1	1.4	1.4	3	3.1	1.4
Vitamin K	mcg	0.29	8.2	8	8.6	8	8	15	15.6	15
Vitamin B_1	mcg	29	60	100	78	100	100	60	78	100
Vitamin B_2	mcg	49	135	150	150	150	150	90	94	150
Vitamin B_6	mcg	28.5	75	60	63	62.5	60	60	63	63
Vitamin B_{12}	mcg	0.07	0.22	0.25	0.23	0.2	0.25	0.45	0.31	0.3
Niacin	mcg	208	750	1,050	1,250	750	1,050	1,350	1,250	750
Folic acid	mcg	7	9	15	15.6	7.5	15	15	15.6	7.5
Pantothenic acid	mcg	250	450	450	470	315	450	750	470	450
Biotin	mcg	0.6	2.2	4.4	2.3	2.2	4.4	4.5	7.8	5.5
Vitamin C	mg	6	8	9	8.1	8.5	9	9	8.1	8.5
Choline	mg	12.5	12	16	15.6	15	16	8	7.8	13
Inositol	mg	14.9	18	4.7	4.7	4.7	4.7	5	4.7	4.1
Calcium	mg	39	64	75	69	63	75	105	94	90
Phosphorus	mg	19	36	58	47	42	58	75	74	63
Magnesium	mg	4.9	6.7	6	7.8	7	6	7.5	10.9	10
Iron	mg	0.04	1.5	1.8/0.22	1.88/0.16	1.8/0.2	1.8	1.8	1.88	1.7
Zinc	mg	0.17	0.75	0.75	0.78	0.8	0.75	0.75	0.78	0.8
Manganese	mcg	0.08	7	5	15.6	15	5	30	25	30
Copper	mcg	35	80	90	94	70	90	75	94	70
Iodine	mcg	15.3	8	15	6	9	15	15	10.2	9
Sodium	mg	25	24	28	27	22	33	44	36	30
Potassium	mg	73	98	108	108	83	108	108	122	105
Chloride	mg	58	59	66	63	55.5	70	62	83	56
Taurine	mg	5.6	8	6.7	5.9	5.9	NA	6.7	5.9	5.9
Carnitine	mg	0.95	1.6	NA	NA	5.5	NA	NA	1.88	1.3

TABLE 9 (Continued)

Comparison of Macronutrients*

Nutrient	Breast Milk	GOOD START™	Similac®	Enfamil®	SMA®	Gerber®	Isomil®	Pro-Sobee®	Nursoy®
Protein g/100 mL	1.05	1.6	1.5	1.52	1.5	1.5	1.8	2	2.1
% Soy protein							100	100	100
% Casein	20		82	40	40	82			
% Whey protein	80	100	18	60	60	18			
Fat g/100 mL	3.9	3.4	3.6	3.8	3.6	3.6	3.7	3.6	3.6
% Polyunsaturated	16	22.2	31	28	14.5	37.3	32	28	14.5
% Monounsaturated	43	33.2	17	15.5	41.3	17.6	17	15.5	41.3
% Saturated	41	44.6	52	48	44.2	45.1	51	48	44.2
% Polyunsaturated: saturated (source)	0.39 (Mature term human milk)	0.5 (47% palm olein, 26% soybean, 21% coconut, 6% high-oleic safflower)	0.6 (50% corn, 50% coconut)	0.58 (55% coconut, 30% corn, 15% soy)	0.33 (33% oleo, 27% coconut, 25% high-oleic safflower, 15% soy)	0.83 (60% soy, 40% coconut)	0.63 (50% corn, 50% coconut)	0.58 (55% coconut, 30% corn, 15% soy)	0.33 (33% oleo, 27% coconut, 25% high-oleic safflower, 15% soy)
Carbohydrate g/100 mL (source)	7.2 (lactose)	7.4 (lactose and maltodextrin)	7.2 (lactose)	7 (lactose)	7.2 (lactose)	7.2 (lactose)	6.8 (corn syrup solids; sucrose)	6.8 (corn syrup solids)	6.9 (sucrose)
Renal solute load (mOsm/L)	79	99.3	99.7	134	91.4	100.3	115.6	178	122
Osmolality (mOsm/kg water)	300	265	300	300	300	290	240	200	296
Canister size (powder) (oz)		12	16	16	16	16	14	14	16
Total fl oz servings†		87.2	116	120	107	118	102	102	107

*Powder formulations; sources of data available upon request. Information on competitive products derived from figures provided by the manufacturers as of February 1991. Similac and Isomil are registered trademarks of Ross Laboratories. Enfamil and ProSobee are registered trademarks of Mead Johnson & Company. SMA and Nursoy are registered trademarks of Wyeth-Ayerst Laboratories. Gerber is a registered trademark of Gerber Products Company.
†Per canister powder, when mixed to standard dilution.
NA = Not available.

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TABLE 10
MATERNAL IRON STUDIES

Author	Study Type	Study Design	Age St/Fn	No. at Start	Results/Conclusions	Comments
Hemminki 1990 Finland	RCT CC	1. No routine Fe 2. Routine Fe supplements 100mg/d	12 weeks-term	1461 1451	Fe supplements increase Hct but no increase in infants' birth weight.	Compliance self-reported. Exclusions?
Celada 1982 Switzerland	CC	1. Folate and Fe 100mg/d 2. Non-lactating control	Pregnancy-10dPP	46	No correlation between iron concentration in breastmilk and maternal iron stores.	Not clear how cases chosen.
Donangelo 1988 Brazil	-	Pregnant mothers B12 , Fe 25-65mg/d 23% received folate	Birth-9 months	83	Fe, B12 and folate of nursing mothers were adequate.	Exclusive breastfed defined as more than 2x/day.
Mbofung 1985 Nigeria	RCT	1. Lactating 2. Non-pregnant	Birth-3 months	232 100	Maternal Fe status(PCV Hb) did not affect breastmilk Fe.	Selection?
Singla 1978 India	-	1. Hb <11g/l 2. Hb >11g/l	Delivery	69 16	Direct relation between maternal and cord blood. Fetus takes iron proportional to levels available in anemic pregnant women.	Selection of anemia based on a single Hb. Not clear how randomized.
Rios 1975	-	Mothers at the time of admission divided into 2 groups based on Plasma ferritin of <9ngs/ml or >9ngs/ml	Birth-6 months	6 20	Maternal Fe stores did not influence Fe acquired by infants.	Most of the women received supplements in pregnancy.

Age St/Fn = Age at start and at finish
RCT = Randomized clinical trial
CC = Case control
dPP = Days postpartum

Table 11

STUDIES ON BREASTMILK AS A SOURCE OF INFANT IRON

Source	Number of samples	Collected	Analysis	Time	Iron mg/L Term	Iron mg/L Preterm
Celada et al Switzerland 1982	46	Handpump	Colorimetry	10 d	0.40	-
Donangelo et al Brazil 1988	83	Manually	Atomic Absorption Spectrophotometry	6 - 30d	0.84	-
					0.60	-
				21 - 280d	0.42	-
					0.39	-
Siimes et al Finland 1979	27a	-	Atomic Absorption Spectrophotometry	2w	0.56	-
				5m	0.30	-
Murray et al Niger 1978	62	-	Colorimetry	2w	1.19	-
Munoz et al Costa Rica 1988	1w = 21	Manually	Atomic Absorption Spectrophotometry	1w	0.24	-
	1m = 26			1m	0.27	-
Feeley et al USA 1983	102	Handpump & manually	Argon plasma Emmission Spectrophotometry	4 - 7d	0.965	-
				10 - 14d	0.854	-
				30 - 45d	0.761	-
Fransson et al Sweden 1980	15	Handpump	Atomic Absorption Spectrophotometry	3m	0.32	-
				5.5m	0.4	-
				10m	0.52	-
				19m	0.26	-
Karmarkar and Ramkrishnan 1960 b	-	-	-	3 - 6m	1.7 - 2.1	-
Cavell and Widdowson 1964 b	-	-	-	0 - 0.5m	0.59	-
Nassi et al 1974 b	-	-	-	0 - 0.5m	0.36 - 0.41	-
Picciano and Guthrie 1976 b	-	-	-	0.5 - 3m	0.20 - 0.23	-
Anonymous 1977 b	-	-	-	0.5 - 3m	0.49	-

Table 11 (cont'd)

STUDIES ON BREASTMILK AS A SOURCE OF INFANT IRON

Source	Number of samples	Collected	Analysis	Time	Iron mg/L Term	Preterm
Vaughan et al 1979 b	-	-	-	>6m	0.38 -0.42	-
Kirksey et al 1979 b	-	-	-	0 - 0.5m	0.33 - 0.46	-
Dewey and Lonnerdal 1983 b	-	-	-	0.5 - 3m	0.22 - 0.31	-
				3 - 6m	0.20 - 0.22	-
Palma et al 1983 b	-	-	-	0 - 0.5m	0.43 - 0.72	-
				0.5 - 3m	0.30 - 0.50	-
				3 - 6m	0.22 - 0.40	-
				>6m	0.24 - 0.26	-
Fransson et al 1984 b	-	-	-	0 - 0.5m	0.46 - 0.50	-
Finley et al 1985 b	-	-	-	0.5 - 3m	0.19 - 0.34	-
				3 - 6m	0.16 - 0.22	-
				>6m	0.22	-
Saner et al Turkey 1988	21	Manually	Atomic Absorption Spectrophotometry	1w	-	0.64
					0.40	-
				2w	0.50	0.61
				3w	0.42	0.40
				4w	0.30	0.33
Saner et al Turkey 1984 a	6	Manually	Atomic Absorption Spectrophotometry	1m	0.58	-
				3m	0.23	-
Lemon et al USA 1982	PT = 20 T = 7	Electric pumps	Atomic Absorption Spectrophotometry	1w	0.77	1.50
				2w	0.98	1.52
				3w	0.80	1.72
				4w	0.81	1.31
				6w	0.42	1.39
				8w	0.51	1.77

PT - Preterm
T - Term
a - Exclusively breastfed
b - From: Hamosh and Goldman, Human Lactation 2: Maternal and Environmental Factors New York, Plenum Press, 1986

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