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Effects of Iron in Neonates and Young Infants: a Review

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Abstract

Iron is essential to erythrocyte oxygen transport and is a catalyst for oxidative metabolism in all cells. Iron is absorbed by the duodenum and requires an acidic environment for optimal absorption. Iron is found for 70% in erythrocytes, and 30% in storage, and a small amount in myoglobin and cytochromes. Iron supplementation reduces anemia in breastfed infants and increases in significant dose-dependent effects hemoglobin and ferritin levels, transferrin saturation, mean cell volume, and transferrin receptor levels. The prevalence of iron deficiency at 6 months of age is 36% in the placebo, 8.2% after 1 mg/kg per day, and 3.8% after 2 mg/kg per day iron ($P<0.05$).

The prevalence rates of iron deficiency anemia is 9.9%, and 2.7%, respectively ($P<0.05$). Iron supplements are well tolerated. Infants with iron-deficiency anemia test lower in mental and motor development assessment. Low-birth-weight (2,000 to 2,500 grams) infants received 0, 1, or 2 mg/kg iron per day from 6 weeks to 6 months of age. The prevalence of child with Child Behavior Checklist scores were 12.7%, 2.9% and 2.7% in the placebo, 1 mg and 2 mg iron supplementation, respectively ($P<0.05$). Infants lacking iron supplements respond less positively to the physical and social environment and have growth and development retardation. Prenatal alcohol exposure causes an increase in the incidence of iron-deficiency anemia. Iron is used to combat iron deficient anemia in infants. The aim of this study was to review the effects of iron in infants.

Key Words: Anemia, Effects, Infant, Iron, Neonate.

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1-INTRODUCTION

Iron deficiency is the most common cause of anemia. It can result from inadequate iron intake, malabsorption, blood loss, or an increased requirement, as with pregnancy. When severe, it results in a characteristic microcytic, hypochromic anemia (1). Iron also, is an essential component of myoglobin; heme enzymes such as the cytochromes, catalase, and peroxidase, including xanthyne oxidase and the mitochondrial enzyme α-glycerophosphate oxidase. Iron deficiency has been associated with behavioral and learning problems in children, abnormalities in catecholamine metabolism, and possibly, impaired heat production (2).

Iron deficiency anemia is the most common micronutrient deficiency worldwide and infants constitute a risk group due to their iron requirements (3). Iron is critical for brain development, and case control studies have shown a consistent association between iron deficient anemia in infancy and poor neurodevelopment, suggesting that, it is important to prevent iron deficiency anemia in infants. Due to the redistribution of iron from hemoglobin to iron stores, healthy, term, normal birth weight infants are virtually self-sufficient with regard to iron during the first 6 months of life. After that age, iron becomes a critical nutrient. The estimated daily iron, requirements at age of 6 to 12 months of age is between 0.9 to 1.3 mg/kg body weight. Exclusively breast-fed infants normally do not need additional iron until 6 months of life.

Iron deficiency anemia continues to be overwhelmingly the leading cause of anemia in early childhood and a global public health challenge (4). Although there has been a significant decrease in the frequency of iron deficiency anemia and iron deficiency in infants and toddlers in recent years in the United States, iron deficiency and iron deficiency anemia persist and the adverse effects of iron deficiency are long-lasting if not permanent. In developing countries where the nutritional status of many women is poor, the infants clearly benefit, if the mother takes a regular daily supplement (60 mg of iron and 400 µg of folic acid) during pregnancy. All infants need a further 0.4 to 0.7 µg of iron a day to maintain their body stores, because the circulating blood volume triples during the 12 months, and this requires a diet containing 1 to 2 mg/kg of iron a day. Newborn infants normally have substantial iron stores even when born prematurely. These stores start to be depleted unless dietary intake is adequate by the time the child's blood volume has doubled. Fortification of artificial feeds with 0.6 mg iron/100 ml is enough to prevent iron deficiency in infants of normal birth weight. Breastfed infants weighing < 2,000 grams at birthday are, however, at risk of developing iron deficiency anemia 2 to 3 months after birth due to the rapid expansion of their circulating blood volume with growth. These newborns benefit from supplement iron starting within 4 to 6 weeks after birth (5).

The level of iron stores in newborns is related to maternal iron status. The maternal-fetal unit is dependent on exogenous iron, which is necessary to prevent iron deficiency in both mothers and infants. In industrialized countries, iron supplements should be prescribed for pregnant women in the third trimester, when the need for iron is prominent. In developing countries, supplementation should be initiated as soon as possible after conception, because of the prevalence of iron deficiency at the onset of pregnancy (6). Iron deficiency is a common cause of anemia and is usually due to blood loss from the gastrointestinal tract. If inadequate dietary intake of iron occurs, iron storages are depleted followed by impaired synthesis of hemoglobin. Under

these conditions iron absorption can increase to approximately 2 to 4 mg per day (7). Preterm infants are at risk for both iron deficiency and iron overload. The role of iron in multiple organ functions suggests that iron is essential for the preterm infant. Conversely, the potential for iron overload and the poorly developed antioxidant measures in the preterm infant argue against indiscriminate iron supplementation in this population (8).

Infants who experience iron deficiency during the first 6-12 months of life are likely to experience persistent effects of the deficiency that alter functioning in adulthood. A lack of sufficient iron intake may significantly delay the development of the central nervous system as a result of alterations in morphology, neurochemistry, and bioenergetics. The mechanisms of iron accumulation in the brain and perhaps redistribution are beginning to be understood. The data in human infants are consistent with altered myelination of white matter, changes in monoamine metabolism in striatum, and functioning of the hippocampus. Rodent studies also, show effects of iron deficiency during gestation and lactation that persist into adulthood despite restoration of iron status at weaning (9).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and PubMed as search engines; March 2016 was the cut-off point. Key references from extracted papers were also hand-searched. The bibliographic search was performed using PubMed database as search engine.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keyword AND "Iron" keyword AND "Effects iron neonate" keyword AND "Infants" keyword), were used to search for the relevant literature. In addition, the book Neonatal Formulary (5) was consulted.

3-RESULTS

3-1. Prophylaxis and treatment

3-1-1. Healthy term neonates

Breastfed neonates benefit from supplementation, if no other source of iron is introduced into the diet by about 6 months of age. Term neonates fed standard milk formula do not require further supplementation (5).

3-1-2. Preterm neonates

A daily dose of 5 mg elemental iron as prophylactic iron supplementation for neonates of low birth weight, who are solely breastfed is recommended. There is no good evidence that formula-fed preterm neonates benefit from further supplementation after discharge, and excess can have disadvantages (5).

3-1-3. Neonates with anemia at birth (hemoglobin <120 g/l)

Neonates, who have suffered chronic blood loss from Fetomaternal hemorrhage or twin-to-twin transfusion, may benefit once their initial deficit has been corrected by transfusion. Iron supplements are not needed in anemic newborns after acute blood loss at birth or in hemolytic anemia (5).

3-1-4. Neonates on parental nutrition

Neonates, unable to tolerate even partial enteral feeding, by 3 months benefit from 100 µg/kg of iron a day intravenously (most conveniently given iron chloride). Neonates on erythropoietin also, need intravenous supplementation, if they cannot be given oral iron (5).

3-2. Toxicity

Get the stomach empties and organize prompt lavage, if oral ingestion is

suspected. Activated charcoal is of no value, but an attempt should be made to identify the amount ingested, and treatment started by giving 15 mg/kg of desferrioxamine mesylate per hour intravenously for 5 hours, if the ingested dose is thought to exceed 30 mg/kg. No universally agreed treatment exists, and advice should be sought from the local poisons centre. Acute toxicity is likely, if the serum iron exceeds 90 µmol/l 4 hours after ingestion. A leucocytosis (leucocyte count >15 x 10(9)/l), or blood glucose of over 8.3 mmol/l, suggests serious toxicity. Early symptoms include diarrhea and vomiting followed, after 12 to 48 hours, by lethargy, coma, convulsions, intestinal bleeding and multi-organ failure. Intestinal strictures may develop 2 to 5 weeks later (5).

3-3. Iron supplementation reduces anemia in breastfed low-birth-weight infants

Most low-birth-weight infants (2,000 to 2,500 grams) may need iron supplementation. Berglund et al. (10) studied the effects of iron supplementation in marginally-low-birth-weight infants. A total of 285 marginally-low-birth-weight infants received iron supplements at a dose of 0 (placebo), 1 or 2 mg/kg per day between 6 weeks and 6 months of age. Hemoglobin levels, ferritin levels, transferrin saturation, mean cell volume, and transferrin receptor levels were analyzed at 6 months of age. Iron supplementation resulted in significant dose-dependent effects on hemoglobin and all iron status indicators at 6 months of age. The prevalence of iron deficiency at 6 months was 36% in the placebo group, 8.2% in the 1 mg/kg per day group, and 3.8% in the 2 mg/kg per day group ($P<0.001$). The prevalence rates of iron deficiency anemia were 9.9%, 2.7%, and 0%, respectively ($P=0.004$). Among infants who were exclusively breastfed at 6 months of age, the prevalence of iron deficiency anemia was 18% in the placebo group. Marginally-low-birth-weight infants have relatively high risk of iron deficiency and iron deficiency anemia, especially if they were breastfed. Iron supplementation at 2 mg/kg per day from 6 weeks to 6 months of age reduces this risk effectively, with no short-term adverse effects on morbidity or growth.

3-4. Iron supplements causes modest augmentation of iron status, are well tolerated and have no measurable effect on growth

Ziegler et al. (11) tested the hypothesis that iron supplementation enhances iron status. The prospective, placebo-controlled study involved exclusively breastfed infants who were randomly assigned at 1 month of age to iron (n=37) or placebo (n=38). Iron (7 mg per day as multivitamin preparation with ferrous sulfate) or placebo (multivitamin preparation without iron) was given from 1 to 5.5 months of age. Complementary foods were allowed at > 4 months of age. Infants were followed to 18 months. Blood concentrations of ferritin, transferring receptor, hemoglobin, and red cell indexes were determined at bimonthly intervals. Iron supplementation caused modest augmentation of iron status during the intervention at 4 and 5.5 months of age, but not thereafter. Iron supplements were well tolerated and had no measurable effect on growth. Plasma ferritin and hemoglobin were tracked over time. Early iron supplementation of breastfed infants is feasible and transiently increases iron status, but not hematologic status. Iron is tolerated by most infants. The prevalence of iron deficiency anemia is low (3%) among unsupplemented breastfed infants in the first 6 months of life.

3-5. Infants with iron-deficiency anemia test lower in mental and motor development assessments and show affective differences

Iron-deficiency anemia continues to be the most common single nutrient deficiency in the world. Infants are at particular risk due to rapid growth and limited dietary sources of iron (12). An estimated 20% to 25% of the world's infants have iron-deficiency anemia, with at least as many having iron deficiency without anemia. High prevalence is found primarily in developing countries. Infants with iron-deficiency anemia test lower in mental and motor development assessments and show affective differences. After iron therapy, follow-up studies point to long-lasting differences in several domains. Neurofunctional studies showed slower neural transmission in the auditory system despite 1 year of iron therapy in iron-deficiency anemia infants; they still had slower transmission in both the auditory and visual systems at preschool age. Different motor activity pattering in all sleep-waking states and several differences in sleep state organization were reported. Persistent sleep and neurofunctional effects could contribute to reducing the potential for optimal behavioral and cognitive outcomes in children with a history of iron-deficiency anemia.

3-6. Effects of delayed versus early umbilical cord clamping on infant iron status and ferritin concentration

Andersson et al. (13) investigated the effects of delayed umbilical cord clamping (180 seconds after delivery), compared with early umbilical cord clamping (10 seconds after delivery), on infant iron status at 4 months of age. A total of 400 full term infants after a low risk pregnancy were enrolled. At 4 months of age, infants showed no significant differences in hemoglobin concentration between the groups, but infants subjected to delayed cord clamping had 45% higher mean ferritin concentration (117 µg/l versus 81 µg/l, P<0.001) and a lower prevalence of iron deficiency (1 $\pm$ 0.6% versus 10 $\pm$ 5.7%, P=0.01). The delayed cord clamping group had lower prevalence of neonatal anemia at 2 days of age (2$\pm$1.2% versus 10$\pm$6.3%, P=0.02). Delayed cord clamping, compared with early clamping, resulted in improved iron status and reduced prevalence of iron deficiency at 4 months of age, and reduced prevalence of neonatal anemia, without demonstrable adverse effects. As iron deficiency in infants even without anemia has been associated with impaired development, delayed cord clamping seems to benefit full term infants even in regions with a relatively low prevalence of iron deficiency anemia.

3-7. Lack of effects of 13.4 mg iron/l versus 20.7 mg iron/l on hematologic status and cognition outcome in low birth weight formula-fed infants

Friel et al. (14) investigated the effect of increased iron intakes on hematologic status and cognition in low birth weight infants. These authors randomly assigned 58 infants to receive formula with 13.4 mg iron/l (normal iron) or 20.7 mg iron/l (high iron). At baseline, discharged, and 3, 6, 9, and 12 months' corrected age, Friel et al. (14) assessed anthropometry, infections, red blood cell hemoglobin, catalase, glutathione peroxidase, red blood fragility (hydrogen peroxidase test), and superoxide dismutase values, plasma malondialdehyde, ferritin, iron, transferrin, zinc and copper levels, and diet intake. Griffiths' Development Assessment was done at 3, 6, 9, and 12, months of age. No statistical differences were noted for weight, catalase or malondialdehyde levels, red blood cell fragility, or Griffiths' Development Assessment. Iron intakes were greater in the high iron group except at 12 months of age. Hemoglobin (high iron, 123$\pm$9; normal iron, 118$\pm$8 g/l) was not different at 3 months of age. Plasma zinc levels (high iron, 70$\pm$14; normal iron, 89$\pm$27 mg/dl) and copper levels (high iron, 115$\pm$26; normal iron 132$\pm$27 mg/dl) at 12 months of age suggested inhibition of

absorption by high iron formula. Glutathione peroxidase levels were higher in the high iron group. The total number of respiratory tract infections was greater in the high iron group (3.3±0.9) than in normal iron group (2.5±0.9). In terms of cognitive outcome, there was no advantage associated with elevated iron intake for low birth weight infants.

3-8. Effects of nutritional status of preterm infants fed either a term (0.5 mg iron/dl) or preterm (0.9 mg iron/dl) formulas fortified with iron

Griffin et al. (15) evaluated the iron nutritional status of preterm infants fed either a term (0.5 mg iron/dl) or preterm (0.9 mg iron/dl) formula fortified with iron after hospital discharge. Healthy low birth weight preterm infants were randomly assigned into 3 groups at the time of hospital discharge. Group A were fed an iron fortified preterm formula (0.9 mg iron/dl) until 6 months corrected age; group B, a fortified term formula (0.5 mg iron/dl) until 6 months corrected age; group C, the preterm formula between hospital discharge and term, then the term formula until 6 months corrected age. Seventy-eight infants were followed up at 6 months corrected age. Iron intake from formula differed significantly between the groups (A, 1.17±0.32 mg/kg per day, n=29) > C, 0.86±0.40 mg/kg per day (n=15) = B, 0.81±0.23 mg/kg per day (n=34); $p<0.0001$. Hemoglobin concentrations were similar to those of iron sufficient preterm infants of the same postnatal age, and term infants of the same postmenstrual age (after 3 months of age). There were no significant differences in hemoglobin concentrations, plasma ferritin, or in the incidence of iron deficiency. Iron fortified formulas containing between 0.5 and 0.9 mg per day of iron seem to meet the iron nutritional needs of preterm infants after hospital discharge.

3-9. The regular provision of iron led to improved iron status during and for some months after the intervention

Ziegler et al. (16) provided iron (medicinal iron or iron-fortified fruit-cereal combination) to breastfed infants. The study tested the hypothesis that regular provision of iron improves the iron status of breastfed infants without adverse effects. In a prospective, randomized, open-label trial, breastfed infants received on a regular basis either medicinal iron (n=48) or an iron-fortified fruit-cereal combination (n=45) from 4 to 9 months or no intervention (control group, n=59). The interventions provided 7.0 to 7.5 mg ferrous sulfated per day. Infants were enrolled at 1 month of age and were followed to 2 years. Iron-status indicators were determined periodically, stool characteristics were recorded, and growth was monitored. The regular provision of iron led to improved iron status during and for some months after the intervention. Both sources of iron were about equally effective. However, medicinal iron was associated with a small but significant reduction in length gain and a trend toward reduced weight gain. Iron deficiency anemia was observed in 4 infants (2.3%), most of whom had a low birth iron endowment. Mid iron deficiency was common in the second year of life. Regular provision of medicinal iron or iron-fortified fruit-cereal combination improves the iron status of breastfed infants and may prevent iron deficiency. Both modalities are equally effective but medicinal iron leads to somewhat reduced growth.

3-10. Supplementing iron at 2 weeks of age does not improve serum ferritin and/or hematological parameters at 2 months of life in very-low-birth-weight infants

Sankar et al. (17) evaluated if supplementing iron at 2 weeks of age improves serum ferritin and/or

hematological parameters at 2 months of life in very-low-birth-weight infants. Preterm very-low-birth-weight infants who received at least 100 ml/kg per day of oral feeds by day 14 of life were randomized to either 'early iron' (3 to 4 mg/kg per day from 2 weeks) or 'control infants' (no iron until 60 days) groups. Forty-six infants were included in the study; primary outcome was available for 42 infants. There was no difference in either serum ferritin (mean: 50.8 versus 45.3 µg/l; adjusted difference in means: 5.8, 95% confidence interval: -3.0, 14.6; p=0.19) or hematocrit (32±5.3% versus 30.8±6.3%; P=0.35) at 60 days between the early iron and control groups. The magnitude of all in serum ferritin from baseline to the end of study period was also not different between the groups (4.9 versus 13.8 µg/l; difference in means: 8.8; 95% confidence interval: -0.3, 17.9, P=0.06). The requirement of blood transfusions and a composite outcome of common neonatal morbidities were also not different between the two groups. Supplementing iron at 2 weeks of age in very-low-birth-weight infants did not improve either serum ferritin or the hematological parameters at 2 months of age when compared to the standard practice of starting iron from 8 weeks of age.

3-11. Anemia in toddlers in developed countries is more likely to be due to causes other than iron deficiency

White (18) determined if the presence of anemia correctly diagnoses iron deficiency and if the absence of anemia correctly rules out iron deficiency in young children. In the US National Health and Nutrition Examination Survey III, the prevalence of iron deficiency ranged from 6% to 18% in various subpopulations of toddlers. In the general population the positive predictive value of hemoglobin concentration <110 g/l for iron deficiency was 29% (95% confidence interval: 20-38%), and the sensitivity was 30% (95% confidence interval: 20-40%). Changing the diagnostic cutoff point to hemoglobin concentration <107 g/l resulted in a positive predictive value of 38% (95% confidence interval: 24-52%), but lowered the sensitivity to 15% (95% confidence interval: 7-22%). Anemia in toddlers in developed countries is more likely to be due to causes other than iron deficiency. Conversely, most children with iron deficiency are not anemic.

3-12. Among infants <1,500 grams birth weight, iron supplementation, in addition to routine iron intake, does not significantly increase the 36-week hematocrit or decrease the number of transfusions

Taylor and Kennedy (19) determined if iron supplementation of 2 mg/kg per day, in addition to routine iron-fortified formula or mother's milk, increased the hematocrit at 36 weeks postmenstrual age. Infants with a birth weight <1,500 grams who reached 120 ml/kg per day of feedings before 32 weeks' postmenstrual age were randomly assigned to iron (multivitamin with iron) or control (multivitamin). One hundred fifty infants were enrolled (76 iron, 74 controls). One hundred other infants (47 iron, 53 controls) received transfusion(s). There was no significant difference in the primary outcome ranking, in the number of transfusions per subject, or in 36-week hematocrit (iron mean± standard deviation 29.2%±4.0%; control, 28.3%±4.5%). No short-term adverse effects on iron supplementation were observed. Among infants <1,500 grams birth weight, iron supplementation, in addition to routine iron intake, did not significantly increase the 36-week hematocrit or decrease the number of transfusions.

3-13. Unsupplemented infants with iron respond less positively to the physical and social environment

Lozoff et al. (20) determined the behavioral and developmental effects of preventing iron-deficiency anemia in infancy. Healthy full-term chilean infants who were free of iron-deficiency anemia at 6 months were assigned to high- or low-iron groups or to high- or no-added-iron groups. Behavioral/developmental outcomes at 12 months of age included overall mental and motor test scores and specific measures of motor functioning, cognitive processing, and behavior. There were no differences between high- and low-iron groups in the prevalence of iron-deficiency anemia or behavioral/developmental outcome, and they were combined to form an iron-supplemental group (n=1123) for comparison with the no-added-iron group (n=534). At 12 months of age, iron-deficiency anemia was present in 3.1% and 22% of the supplemented and unsupplemented groups, respectively. The groups differed in specific behavioral/developmental outcomes, but not on global test scores. A smaller proportion of them resisted giving up toys and test materials, and more could not be soothed by words or objects when upset. They crawled somewhat later and were more likely to be tremulous. The results suggest that unsupplemented infants responded less positively to the physical and social environment. The observed differences seem to be congruent with current understanding of the effects of iron deficiency on the developmental brain. The study shows that healthy full-term infants may receive developmental and behavioral benefit from iron supplementation in the first year of life.

3-14. Iron deficiency anemia causes growth and developmental retardation in infants

Iron deficiency anemia causes growth and developmental retardation in infants (21). Iron supplementation from the 4th month of age may prevent iron deficiency anemia, but side effects of oral iron supplementation limit its usage. Baykan et al. (21) investigated the effect of maternal supplementation on the iron status of mothers and their exclusively breast-fed infants. In a prospective, placebo-controlled, double-blinded randomized study, healthy mothers (hemoglobin $\geq$ 11 g/dl) and their 10-20-day-old healthy term infants who were admitted to as intensive care neonatal unit were enrolled. The mothers who were intending to exclusively breast-feed at least up to four months were included. Iron supplementation (n=82, 80 mg elementary iron) and placebo (n=86) were given to the mothers randomly for four months. The anthropometrical measurements of infants were recorded monthly. Of all, 69 mothers and their infants in the iron group and 63 in the placebo group completed the study. At the end of the study period, blood samples (complete blood count, serum iron, iron binding capacity and serum ferritin) were drawn from the mothers and their infants. Giving maternal iron supplementation during the first four months of the lactation period had no effect on the serum iron and ferritin levels of mothers and infants. This could be due to the relatively short duration of the follow-up period. A longer follow-up period is recommended to detect the effect of the maternal iron supplementation during lactation.

3-15. The prenatal alcohol exposure is associated with an increased incidence of iron-deficiency anemia in infancy

Carter et al. (22) determined whether prenatal alcohol exposure is associated with an increased incidence of iron-deficiency anemia in infancy and compared effects of fetal alcohol exposure and iron-deficiency anemia on infant growth. A total of 96 infants born to mothers from the Coloured (mixed ancestry) community in Cape Town, South Africa, were recruited prenatally; 42 mothers drank heavily during pregnancy,

and 54 abstained or drank small amounts of alcohol. Growth was assessed at birth and 6.5 and 12 months of age, and iron-deficiency anemia was assessed at 6.5 or 12 months of age. Infants whose mothers binge drank during pregnancy (≥ 4 drinks per occasion) were 3.6 times more likely to be diagnosed with iron-deficiency anemia at 12 months of age than were infants whose mothers did not binge drink. Prenatal alcohol exposure was associated with reduced weight at birth, 6.5 months, and 12 months of age and with shorter length at 6.5 and 12 months of age. Iron-deficiency anemia was related to reduced 12-month weight and head circumference and to slower growth velocity between 6 and 12 months of age. The effects of prenatal alcohol on weight were not mediated by iron-deficiency anemia; however, they were seen primarily in infants with iron-deficiency anemia. The association of maternal binge drinking with an increased incidence of iron-deficiency anemia may reflect disruption of accumulation of fetal iron stores or postnatal deficiencies of iron intake, absorption, or intake. Moreover, iron deficiency seems to exacerbate the prenatal alcohol effects on growth.

3-16. Iron supplementation of 80 mg ferrous sulfate to mothers is associated with a lower risk of low birth weight infants

Palma et al. (23) assessed whether iron and folic acid supplementation reduce the risk of low birth weight in women without anemia. A total of 322 mothers without anemia delivering a term non-small-for-gestational-age infants were enrolled. Agreement between the two sources of information was good (82% for folic acid and 94% for iron). Folic acid only (15 mg per day) was unrelated to low birth weight, whereas iron supplementation (80 mg ferrous sulfate) was associated with a lower risk of low birth weight (odds ratio 0.58, 95% confidence interval 0.34 to 0.98), adjusted for smoking, maternal education, body mass index, obstetric diseases during pregnancy, weight gain during pregnancy, and previous low birth weight. The results of iron plus folic acid were similar to those for iron. There was a significant trend towards a lower risk of low birth weight ($P<0.001$) with the duration of iron supplementation. After stratifying by the type of low birth weight, the trend was also significant for any kind of low birth weight. Iron supplementation is associated with a lower risk of low birth weight in pregnant women without anemia.

3-17. Erythropoietin increases the ferritin index in very-low-birth-weight infants

Kasper et al. (24) assessed the validity of four-quadrant diagnostic plot of iron availability (ferritin index) versus iron demand for erythropoiesis (reticulocyte hemoglobin content) for differentiating iron status in anemic very-low-birth-weight infants. Study subjects were enrolled in a previously reported randomized controlled trial of clinically stable very-low-birth-weight infants < 31 weeks' gestation and < 1,300 grams at birth to receive 18 days of treatment with: group 1: oral iron; group 2: erythropoietin and iron, and group 3: erythropoietin plus intravenous iron plus oral iron. At the end of treatment the ferritin index was significantly higher in both erythropoietin groups compared to the control group. By day 18, reticulocyte hemoglobin content of the control group declined into the quadrant of the diagnostic plot characteristic of functional iron deficiency and anemia of chronic disease. Both erythropoietin groups ended in the quadrants that are characteristic for latent iron deficiency and iron deficiency anemia, respectively. The diagnostic plot for differentiating anemia in very-low-birth-weight infants may be an informative, critically useful tool for iron

status assessment under different physiologic and therapeutic erythropoietic status.

3-18. Maternal iron deficiency during pregnancy may be a risk factor for schizophrenia spectrum among offspring

Insel et al. (25) determined whether maternal iron deficiency, assessed by maternal hemoglobin concentration during pregnancy, increases the susceptibility to schizophrenia spectrum disorders among offspring. Of 6,872 offspring for whom maternal hemoglobin concentrations were available, 57 had schizophrenia spectrum disorders (0.8%) and 6,815 did not (99.2%). A mean maternal hemoglobin concentration of 10.0 g/dl or less was associated with a nearly 4-fold statistically significant increased rate of schizophrenia spectrum disorders (adjusted rate ratio, 3.73; 95% confidence interval, 1.41 to 9.81; P=0.008) compared with a mean maternal hemoglobin concentration of 12.0 g/dl or higher, adjusting for maternal education and ethnicity. For every 1-g/dl increase in mean maternal hemoglobin concentration, a 27% decrease in the rate of schizophrenia spectrum disorders was observed (95% confidence interval, 0.55 to 0.96; P=0.02). These findings suggest that maternal iron deficiency may be a risk factor for schizophrenia spectrum disorders.

3-19. Hepcidin is closely associated with iron status and may be a useful indicator of iron stores and iron deficiency in infants

Berglund et al. (26) studied hepcidin and erythropoietin and their correlation with iron status in iron-replete and iron-deficient low-birth-weight infants, a group at particular risk on iron deficiency. A total of 285 otherwise healthy low-birth-weight infants received 0 (placebo), 1 or 2 mg/kg daily iron. Hepcidin, erythropoietin, hemoglobin, and variables of iron status were analyzed. Serum hepcidin did not change over time in the placebo group, despite a rapid decrease in serum ferritin. In iron-supplemented infants, hepcidin increased significantly, reaching a mean$\pm$ standard deviation concentration of 19.2$\pm$2.5 ng/ml in the 2-mg/kg group compared 13.0$\pm$2.6 ng/ml in the placebo group at age 6 months (P<0.001). The difference was even larger between iron-deficient and iron-replete infants. Hepcidin was independently positively correlated with ferritin at all ages and was negatively correlated with the transferrin receptor concentration at age 6 weeks and with transferrin at age 6 months. Erythropoietin was initially similar between groups but decreased significantly in iron-supplemented infants. In addition to being negatively correlated with hemoglobin, it was also independently negatively correlated with indicators of iron status. Hepcidin is closely associated with iron status and may be a useful indicator of iron stores and iron deficiency in infants. Erythropoietin is negatively correlated with iron status, which suggests a feedback mechanism that needs further study.

3-20. High supplementation of iron to pregnant women had lower percentages of iron depletion at partum, iron deficiency anemia, and preterm deliveries as well as a higher birth weight of the newborn and greater percentage of women at risk of hemoconcentration at partum

Ribot et al. (27) evaluated the effect of different iron supplementation doses (including no supplementation) during pregnancy on the iron status of the mother and on the health of the neonate. A longitudinal study was conducted involving 358 pregnant women and their newborns. Mothers were classified as non-supplemented, low iron supplemented (<60 mg per day), moderate iron supplemented (between 60 and 100 mg per day) or high iron supplemented (>100 mg

per day). General clinical and obstetric histories, hemoglobin, serum ferritin and transferrin saturation were evaluated in the first, second, third trimesters, and at partum. Serum ferritin and hemoglobin decreased less sharply in the iron-supplemented groups compared to the non-supplemented group. The higher the doses of iron supplementation, the lower the percentages of iron depletion at partum (P<0.001), iron deficiency anemia (P<0.001) and preterm deliveries (P=0.009) as well as a higher birth weight of the newborn. However, the group with high supplementation had a greater percentage (27.6%) of women at risk of hemoconcentration at partum. Our Mediterranean women began gestation with iron stores close to deficit (serum ferritin, 28.1 µg/l; 95% confidence interval 27.9 to 28.4). With these iron stores, supplementation with iron at daily doses of between 60 and 100 mg appears to be the most beneficial for the health of mother and child.

3-21. Early iron supplementation of marginally very-low-birth-weight infants significantly reduces the prevalence of behavioral problems

Berglund et al. (28) hypothesized that iron supplementation of very-low-birth-weight infants would improve cognitive scores and reduce behavioral problems. In a randomized controlled trial, 285 marginally very-low-birth-weight infants (2,000 to 2,500 grams) received 0, 1, or 2 mg/kg per day of iron supplements from 6 weeks to 6 months of age. At 3.5 years of age, these infants and 95 normal birth weight controls were assessed with a psychometric test (Wechsler Preschool and Primary Scale of intelligence) and a behavioral problems test (Child Behavior Checklist; CBCL). There were no significant differences in IQ between low-birth-weight groups or low-birth-weight infants versus controls. Mean± standard deviation full-scale Intelligence Quotient (IQ), was 105.2±14.5, 104.2±14.7, and 104.5±12.7 in the placebo, 1 mg, and 2 mg groups, respectively. However, for behavioral problems, there was a significant effect of interaction. The prevalence of children with CBCL scores above the US subclinical cutoff was 12.7%, 2.9% and 2.7% in the placebo, 1 mg, and 2 mg groups, respectively (P=0.027), compared with 3.2% in controls. Relative risk (95% confidence interval) for CBCL score above cutoff in placebo-treated children versus supplemented was 4.5 (1.4 to 14.2). Early iron supplementation of marginally very-low-birth-weight infants does not affect cognitive functions at 3.5 years of age but significantly reduces the prevalence of behavioral problems. The study suggests a causal relation between infant iron deficiency and later behavioral problems.

3-22. The most common nutritional problem of very-low-birth-weight infants is iron deficiency

Very-low-birth-weight infants (<1,500 grams) are at risk of multiple macro- and micronutrient deficiencies, but most very-low-birth-weight infants are larger (1,500 to 2,500 grams), and the most common nutritional problems of these infants is iron deficiency (29). Globally, about 25% of pre-school children have iron deficiency anemia, and there is good evidence that iron deficiency is associated with impaired brain development. However, adverse effects of excessive iron supplementation have been observed. Delayed umbilical cord clamping, which increases infant iron stores, should be recommended for all newborns. There is good evidence that intakes of 2 mg of dietary iron per kg body weight daily prevents iron deficiency anemia in low-birth-weight infants without causing adverse effects. A recent study shows that this dose of iron supplementation also, reduces the risk of behavioral problems at 3 years of age in infants with birth weight of 2,000 to 2,500

grams. Very-low-birth-weight infants need 2 to 3 mg/kg iron per day. To achieve these intakes, breastfed low-birth-weight infants should receive iron supplements, and formula-fed low-birth-weight infants should receive an iron-fortified infant formula.

4-DISCUSSION AND CONCLUSION

Absorption of iron occurs predominantly in the duodenum where an acidic environment enhances solubility. Most iron in food is ferric (Fe^{3+}) hydroxide, ferric protein complexes or haem-protein complexes. Iron is more readily absorbed in the ferrous (Fe^{2+}) state. Proximal small bowel mucosal cells have an important role in iron absorption. Iron released into plasma binds to transferrin. The hormone hepcidin expression is regulated by iron stores, erythropoietic activity, hemoglobin, oxygen content and inflammation, and has an inverse relationship with iron absorption. Hepcidin binds to ferroportin causing cellular internalization and destruction. Increased hepcidin expression reduces intestinal iron absorption and increases iron stores in macrophages and hepatocytes. This occurs in the anemia of chronic disease. Iron is stored in hepatocytes and reticuloendothelial macrophages as ferritin, which is non-toxic and readily mobilized, and has its aggregate, haemosiderin. Small intestinal abnormalities may interfere with iron absorption, e.g. celiac disease and other malabsorption syndromes, or with conversion of iron into the reduced form, e.g. from gastric hypoacidity (30).

Iron is used to combat iron-deficiency anemia. The prevalence rate of iron deficiency anemia is inversely related to the prevalence of iron deficiency. The prevalence rates of iron deficiency anemia are 9.9%, 2.7%, and 0% in the placebo, 1 mg/kg per day, and in 2 mg/kg iron, respectively, in marginally-low-birth-weight infants (10). The prevalence of iron deficiency at 6 months of age is 36% in the placebo, 8.2% in the 1 mg/kg per day, and 3.8% in the 2 mg/kg per day groups (10). Iron supplementation of 7 mg per day, at the age of 1 month, causes modest augmentation of iron status at 4 and 5.5 months in breastfed infants. Iron supplements are well tolerated and have no measurable effect on growth (11). Infants with iron-deficiency anemia test lower in mental and motor assessments. High prevalence of iron-deficiency anemia is found primarily in developing countries (12). Delayed umbilical cord clamping was compared with early clamping at 4 months of age. Delayed cord clamping, results in 45% higher ferritin concentration and a lower prevalence of iron deficiency. The neonatal anemia at 2 days of age is lower in delayed umbilical cord clamping than early umbilical cord clamping (13). At 4 months of age, delayed cord clamping results in improved iron status and reduces prevalence of iron deficiency and prevalence of neonatal anemia. Delayed cord sampling benefits full-term infants.

Griffin et al. (15) evaluated the iron nutritional status of preterm infants fed either term (0.5 mg iron/dl) or preterm (0.9 mg iron/dl) formulas. Iron intake from formula differs significantly between groups. Iron intake is 1.17 ± 0.32 mg/kg per day in the group fed with 0.9 mg iron/dl and 0.86 ± 0.40 mg/kg per day in the group fed with 0.5 mg iron/dl ($P<0.001$).

Ziegler et al. (16) tested the hypothesis that regular provision of iron improves iron status of breastfed infants. Infants received on a regular basis either medicinal iron or an iron-fortified fruit-cereal combination from 4 to 9 months of age. The intervention provided 7.0 to 7.5 mg ferrous sulfated per day. Both sources of iron were equally effective. However, medicinal iron is associated with a small but significant reduction in infant length and weight gain. Regular provision of medicinal iron or

iron-fortified fruit-cereal combination improves the iron status of breastfed infants and may prevent iron deficiency.
Anemia in toddlers in developed countries is more likely to be due to causes other than iron deficiency, most children with iron deficiency are not anemic (18, 19). Taylor and Kennedy (19) observed that a supplement of 2 mg/kg iron per day in addition to routine-fortified formula or breast milk in infants < 1,500 grams does not differ in 36-week hematocrit or decrease the number of transfusions. No short-term adverse effects on iron supplementation were observed.

At 12 months of age, iron-deficiency anemia is present in 3.1% and 22% of the supplemented and unsupplemented groups, respectively. Unsupplemented infants respond less positively to the physical and social environment. These differences seem to be congruent with current understanding of the effects of iron deficiency on brain development (20). Iron deficiency anemia causes growth and developmental retardation.

Iron supplementation (80 mg elementary iron) was given to the mothers for 4 months of lactation (21). At the end of the study period, complete blood count, serum iron, iron binding capacity and serum ferritin were not different from control mothers and their infants. This could be due to the relatively short duration of the follow-up period. Iron deficiency anemia causes growth and development retardation in infants.

Prenatal alcohol exposure is associated with an increased incidence of iron-deficiency anemia in infants at birth, and after 6.5 and 12 months of age. Prenatal alcohol exposure causes reduced weight and shorter length of the infants at 6.5 and 12 months of life compared to infants born to mothers who abstained or drank small amounts of alcohol (22). The association of maternal binge drinking with an increased incidence of iron-deficiency anemia may reflect deficiencies of iron intake. Iron deficiency seems to exacerbate the prenatal alcohol effects on growth. Palma et al. (23) assessed whether iron and folic acid supplementation reduce the risk of low birth weight in infants born to women without anemia. Folic acid only (15 mg per day) was unrelated to low risk of birth weight, whereas iron supplementation (80 mg ferrous sulfate) was associated with a lower risk of low birth weight. There was a significant trend towards a lower risk of low birth weight ($P<0.001$) with the duration of iron supplementation.

Kasper et al. (24) compared the effects of iron, erythropoietin and iron, and erythropoietin plus intravenous iron, plus oral iron on the ferritin index in anemic very-low-birth-weight infants. At the end of treatment the ferritin index was significantly higher in both erythropoietin groups compared with iron only. These data suggest that erythropoietin, but not iron, increases the ferritin index.

A mean maternal hemoglobin concentration of 10.0 g/dl or less is associated with a nearly 4-fold statistically significant increased rate of schizophrenia spectrum disorders compared with a mean maternal hemoglobin concentration of 12.0 g/dl or higher in infants. For every 1-g/dl increase in mean maternal hemoglobin concentration, a 27% decrease in the rate of schizophrenia spectrum disorders was observed in infants (25). In iron-supplemented infants, hepcidin increases significantly reaching a concentration of 19.2 ± 2.5 ng/ml in the 2-mg/kg group compared to 13.0 ± 2.6 ng/ml in the placebo at 6 months of age ($P<0.001$). The difference is even larger between iron-deficient and iron-replete infants (26).

Mothers were classified as control (no iron supplementation), low iron supplementation (<60 mg iron per day), moderate iron supplementation (between 60 and 100 mg per day) or high iron

supplemented (>100 mg per day). Ribot et al. (27) evaluated the effect of different iron supplementation doses during pregnancy on the iron status of the mother and on the health of the neonate. The higher doses of iron supplementation caused lower percentages of iron depletion at partum (P<0.001), iron deficiency anemia (P<0.001) and preterm deliveries (P=0.009) as well as a higher birth weight of the newborn. However, the group with high supplementation had greater percentages (27.6%) of women at risk of hemoconcentration at partum. With these daily supplementations of iron, the supplementation between 60 and 100 mg appears to be the most beneficial for the health of mother and child.

Low-birth-weight (2,000 to 2,500 grams) infants received 0, 1, or 2 mg/kg per day of iron from 6 weeks to 6 months of age. The prevalence of children with Child Behavior Checklist scores were 12.7%, 2.9% and 2.7% in the placebo, 1 mg and 2 mg iron groups, respectively (P=0.027), compared with 3.2% in term infant controls. These data suggest a causal relation between infant iron deficiency and behavioral problems at the age of 3.5 years (28). The most common nutritional problems of very-low-birth-weight infants is iron deficiency (29). About 25% of pre-school children have iron deficiency anemia, and there is good evidence that iron deficiency is associated with impaired brain development. There is good evidence that intakes of 2 mg/kg daily of iron prevents iron deficiency anemia in low-birth-weight infants without causing adverse effects (29). This dose of iron supplementation reduces the risk of behavioral problems at 3 years of age in infants. Very-low-birth weight infants need 2 to 3 mg/kg iron per day. To achieve these intakes, breastfed low-birth-weight infants should receive iron supplements, and formula-fed low-birth-weight infants should receive an iron-fortified infant formula. The present body of knowledge is consistent with the view that iron supplementation to infants or to pregnant women has some beneficial effects on neonates and young infants. The most common nutritional problem of very-low-birth-weight infants is iron deficiency. Iron is important for the synthesis of hemoglobin; it is also present in myoglobin, and in cytochromes. One molecule of hemoglobin requires one atom of iron. The most important effect of iron is the treatment of anemia and iron deficiency causes anemia. Iron deficiency is associated with behavioral and learning problems and is critical for brain development, and causes growth and developmental retardation in infants. Early iron supplementation of low-birth-weight infants significantly reduces the prevalence of behavioral problems. Infants unsupplemented with iron respond less positively to the physical and social environment. The level of iron stores in newborns is related to the maternal iron status. All infants need a further 0.4 to 0.7 µg of iron per day to maintain their body stores, because the circulating blood volume triples during the 12 months of age and this requires a diet containing 1 to 2 mg/kg of iron per day. Iron supplementation reduces anemia in breastfed low-birth-weight infants. Prenatal alcohol exposure is associated with an increased incidence of iron-deficiency anemia in infants. Antenatal alcohol exposure reduces the weight and shortens the length of neonates. Iron supplementation of a daily 80 mg ferrous sulfate supplementation to mothers reduces the risk of low birth weight of infants. Maternal hemoglobin deficiency during pregnancy may be a risk factor for schizophrenia spectrum disorders among offspring. Although there are several studies on the effects of iron in infants more investigations are required for an evidence-based treatment of neonates and young infants with iron.

5-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

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