

Special Micronutrient Concerns in Premature Infants: Implications for Enteral and Parenteral Feeding

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There are a number of features specific to the infant born prematurely that challenge the caregiver to achieve appropriate goals for growth, nutrient accretion and mental and physiologic development. These features emphasize the differences in nutrient requirements between the infant born at full term versus the infant born before term. These features include: metabolic and gastrointestinal immaturity; physiologic immaturity; minimal nutrient stores, and complicated medical/surgical conditions (table 1). Each of these features, individually and collectively, complicates and impedes attempts to define and meet the nutrient requirements of the premature infant. There may also be gender differences and racial differences that complicate the picture even further.

As difficult as it is to define (and meet) the macronutrient needs of the preterm infant, even less is known about the requirements for micronutrients in this population. Most research has focussed on a combination of accretion rates and organ development to calculate factorial estimates of nutrient accretion. These estimates, in combination with supplemental feeding studies have provided the science behind current estimates of micronutrient requirements. But, for most of the micronutrients, the amount of science is minimal.

Although in this chapter on 'special micronutrient concerns in premature infants' I will not discuss macronutrient requirements for premature infants, both macronutrient and micronutrient metabolism, including requirements, have recently been summarized in a supplement to the *Journal of Nutrition* [1]. This supplement provides a summary of recommendations for energy and 45 nutrient components of enteral formulas for preterm and low birth weight

Table 1. Factors that increase the risk of micronutrient deficiencies in infants born prematurely

Low micronutrient stores at birth
Accretion of trace minerals takes place during the last trimester of pregnancy
Rapid postnatal growth
Unknown requirements for many micronutrients
Variable intake of trace minerals

infants. In this chapter, I have focussed on the micronutrients for which there is some evidence to make recommendations for nutrient intakes. These nutrients include iron, zinc, copper, manganese, selenium and iodine. For the other ultra-micronutrients, like molybdenum, cobalt, etc., there simply is not enough science to provide a critical appraisal or a nutrient recommendation.

For the full-term infant, the provision of human milk at an appropriate volume is the 'gold standard' for determining appropriate nutrient recommendations, with the possible exception of iron and vitamin D. For the preterm infant, a number of factors confound its use as the sole source of essential nutrients for premature infants [2]. Perhaps the most important feature is the variability in the composition of preterm milk. In fact, in clinical practice, the nutrient composition of the specific human milk being fed is unknown. Preterm milk varies in nutrient composition from the milk of mothers of infants born at term (lower content of protein, minerals and some vitamins), and indeed, for many micronutrients there are limited data on the composition of preterm milk. To ensure that preterm infants fed mother's milk receive an appropriate intake of nutrients according to estimated needs, human milk 'fortifiers' containing protein, minerals and vitamins have been commercially developed. The human milk fortifiers (powder or liquid) may be added to expressed mother's milk that is fed by tube or bottle to the preterm infant.

Thus, an important differentiating factor between full-term and preterm micronutrient requirements is the lack of a 'gold standard' as an acceptable starting point.

Typical 'preterm formulas' are designed to serve as the sole source of nutrition, as are 'total' parenteral nutrition (TPN) formulations specifically designed for preterm infants [3]. Both enteral formulas and TPN formulations can promote average rates of macronutrient assimilation and growth that approximate the rates typical for an in utero fetus, but this is not always the case for micronutrients. Good examples of this include iron and probably iodine and manganese, whereas it is possible to duplicate intrauterine accretion rates for copper and zinc [4].

Although there are no 'gold standards' for micronutrient intakes of preterm infants, I would like to put forward the notion that there are three acceptable

Table 2. Factors affecting iron status at birth

Iron status of mother
Placental insufficiency
Gestational diabetes
Fetal blood loss through fetal-maternal or twin-twin hemorrhage
Timing of cord-clamping

objectives for micronutrient intakes that would have direct and important implications for enteral and parenteral intake. These are: (a) the intake should be high enough to prevent overt micronutrient deficiencies; (b) it should be an amount that will allow for accretion of stores that would have been deposited in the developing fetus had the infant stayed in the womb until term, and (c) the intake should not be excessive to the point of toxicity [5]. These three guiding principles should always be taken into consideration when addressing special micronutrient concerns in the preterm infant.

The following micronutrients are nutritionally essential for the human: iron, zinc, copper, selenium, chromium, manganese and iodine. Clinical deficiencies have been described for all of them.

Iron

Iron deficiency during development adversely affects erythropoiesis, neurodevelopment, cardiac and skeletal muscle function as well as gastrointestinal function [6]. Conversely, it is also one of the most toxic elements to humans. In its free form (non-protein bound) state, iron reacts with oxygen to create reactive oxygen species that disrupt cell membranes and result in cell death. Several investigators have expressed concern that large doses of enteral or parenteral iron may overwhelm the iron-binding capacity of preterm infant serum, resulting in oxidative stress of cell membranes [7]. Because preterm infants have a limited iron-binding capacity, iron delivery to the body and trafficking within the body must be tightly regulated [8, 9]. The therapeutic:toxic ratio for iron is more narrow than for most nutrients as the human does not tolerate iron overload or iron deficiency states for long periods of time.

In order to determine the iron needs of the preterm infant, one must take into consideration the iron endowment of the preterm infant at birth. Factors impacting iron status at birth are shown in table 2. Each of these factors either individually or collectively can influence the amount of iron that is transferred to the infant either prior to or at birth. The amount of iron actually stored by the infant during gestation depends on the gestational maturity of the infant at birth. Infants born prior to term therefore have less total iron than full-term

infants. The earlier the birth (i.e. the more premature the infant), the less iron will have been stored. The major iron reserve of the premature infant at birth is in the hemoglobin mass itself, with little storage iron in the liver or spleen. Iron accretion by the fetus is greatest during the last trimester of pregnancy [10].

It is estimated that, during the third trimester, the fetus accumulates iron at a rate of 1.6–2.0 mg/kg/day [10, 11]. Fetal need rather than maternal supply primarily regulates iron transfer.

The infant's hemoglobin concentration (once equilibrated after birth) and the cord serum ferritin concentration combine to give the best estimate of total body iron status. Normal hemoglobin concentrations at birth are a function of gestational age but generally range from 145 to 180 g/l [12]. The 5th percentile for the cord serum ferritin concentration is between 55 and 60 μ g/l at birth [13]. The 24-week gestational age infant weighing 500 g only has an endowment of 37.5 mg, while a term 3-kg infant has closer to 225 mg of iron. Thus, the extremely premature infant has only 17% of the iron that will be needed by full term (40 weeks post-conception age), assuming extrauterine growth at the intrauterine rate. In summary, the infant's birth weight, initial hemoglobin and ferritin concentrations, rate of growth, and balance between blood withdrawn by phlebotomy and blood replaced by red cell transfusion will determine the postnatal iron requirements.

Postnatal Iron Requirements

In the absence of perinatal blood loss or unusually large amounts of blood having been removed for laboratory tests, and not replaced with red blood cell transfusions, the preterm infant has enough iron stores to last 2 months (half as long as a term infant). Postnatal erythropoiesis occurs in three stages [14]. In the first stage, which lasts from birth to 8 weeks, erythropoietic activity is minimal and the preterm infant exhibits a similar early anemia compared to the full-term infant, but the hemoglobin concentration at the nadir is 20–30 g/l lower than in the term infant for, as yet, undetermined reasons. Because of the breakdown of red blood cells during the first 5–7 weeks, iron is released but is not lost from the body. During this first stage, more iron exists in the body than is utilized for hemoglobin synthesis. Prophylactic use of either iron supplements or iron-fortified formula during the first 2 months of life will have no effect on preventing the fall in hemoglobin concentration during the first 2 months of life [15]. Once active erythropoiesis begins, however, all premature infants require supplemental iron to maintain optimal rates of hemoglobin production [16]. Thus, in the second stage that lasts from 1.5 to 4 months, infants who receive sufficient dietary iron to maintain body iron stores are able to support the increased erythropoiesis started in this stage and will maintain a relatively constant hemoglobin concentration during the remainder of the 1st year. Finally, in the

third and final stage, the dose of dietary iron required to sustain adequate erythropoiesis will be directly related to the rate of growth and inversely related to the fetal iron stores [17].

Previous recommendations for iron intake in preterm infants have ranged from 2 to 6 mg/kg/day. The wide range of recommendations is because of differences in the degree of prematurity and whether the infant had been treated with recombinant human erythropoietin. Once preterm low-birth weight infants double their birth weight or reach 2 months of age, the current recommendations for iron supplementation is 2–4 mg/kg/day up to a maximum of 15 mg of total iron [17]. A further recommendation is to supplement preterm infants with elemental iron for the entire 1st year of life [18]. This can be achieved with iron supplements in the breast-fed infant, or with a combination of supplements and iron-fortified formula in the formula-fed infant.

Parenteral Iron

The concern with intravenous iron administration is the potential for exceeding the total iron-binding capacity, which is lower in the preterm infant compared with the term infant, placing the infant at risk for oxidant injury. Supplemental iron is not usually required during TPN unless it is the sole source of nutrition for over 2 months or if iron deficiency develops. A dose of 0.1–0.2 mg/kg/day of intravenous iron (as iron dextran) has been recommended [19].

Zinc

Zinc is an essential micronutrient that participates in carbohydrate and protein metabolism, nucleic acid synthesis, heme synthesis and other vital functions [20]. For example, carbonic anhydrase, alkaline phosphatase, and DNA and RNA polymerase are some of the over 300 zinc-containing enzymes that have been discovered. Zinc is required for cellular division and differentiation. In addition to DNA synthesis, zinc regulates gene expression of transcription factors and nuclear hormonal receptors through its role in determining the configuration of the zinc finger motif. Growth-stimulating hormones such as insulin and insulin-like growth factors need zinc for their activity. Zinc is also involved in the regulation of apoptosis (programmed cell death).

Zinc is an essential nutrient for 'normal' embryogenesis, but the most significant fetal accretion occurs during the last trimester of gestation. Between 24 and 34 weeks of gestation, average daily accretion is in the range of 850 μ g/kg [21]. Zinc is stored in the liver as zinc-metallothionein. This

Growth failure
Diminished food intake
Skin lesions
Poor wound healing
Hair loss
Decreased protein synthesis
Depressed host defense

Table 3. The effects of severe zinc deficiency

zinc-binding protein is the major source of zinc stores for the fetus and may protect the infant from the development of zinc deficiency in the immediate postnatal period [22]. Zinc homeostasis is maintained over a wide range through regulation of fractional absorption and endogenous excretion in the gastrointestinal tract. Generally, the fractional rate of zinc absorption is inversely related to the amount of zinc present in the lumen of the intestine. However, even though the fractional rate is lower with larger amounts of zinc present (in food or supplements), the absolute amount of zinc absorbed and retained is proportionally higher [23].

The concentration of zinc in colostrum is high (5.4 mg/l) and lower in transitional preterm human milk (4.8 mg/l), decreasing to 2.2 mg/l after 1 month of lactation and to 1.1 mg/l after 3 months [24]. If one compares the estimated zinc needs of the preterm infant (based on rates of intrauterine accretion) to that provided by human milk, it is apparent that unfortified human milk is unlikely to provide the daily needs to preterm infants. Currently available human milk fortifiers in the US and Canada provide an additional 7–10 mg Zn/l. These levels are comparable to preterm formulas whose zinc content varies between 8 and 12 mg/l (compared to full-term formulas that contain 5–7 mg/l).

Table 3 shows the clinical effects of severe zinc deficiency. Typically infants start off with a combination of the distinctive skin lesions (acrodermatitis) and diarrhea, and then go on to growth failure including behavioral changes [20]. While such zinc and fluoride deficiency states have been described in preterm infants, they are fortunately rare [25]. The true incidence of subclinical zinc deficiency is unknown because of the difficulty of accurate diagnosis, however the following groups appear to be at highest risk: extremely low-birth weight infants receiving TPN with inadequate zinc content; preterm small-for-gestational age (SGA) infants, and rapidly growing preterm infants fed unfortified human milk. Perhaps most importantly, there is documentation from a randomized controlled trial that demonstrates increased plasma zinc concentrations, improved linear growth and scores for motor development with zinc supplementation after hospital discharge [26].

The most recent recommendations for zinc intake are 0.5–1.0 mg/kg/day during the stable and post-discharge periods for enterally fed infants [27–28]. For infants receiving parenteral nutrition, it is recommended to include

400 $\mu\text{g}/\text{kg}/\text{day}$ in the formulation [27]. However, infants born very prematurely with extremely low birth weights and those with excessive gastrointestinal losses (e.g. severe diarrhea or ileostomy losses) may need additional supplementation. In summary, a sufficient zinc intake is critical for adequate growth and development. Since subclinical zinc deficiency is very difficult to identify, erring on the side of early and adequate zinc supplementation is prudent.

Copper, Selenium, Chromium, Iodine and Manganese

Much more research has been completed on iron and zinc requirements in preterm infants than on other microminerals, although deficiencies have been described for all of them (although very rarely). Like zinc, copper stores accumulate during the last trimester of gestation, thus theoretically infants born very prematurely are at risk of copper deficiency. Again, like zinc, copper deficiency is difficult to reliably diagnose in preterm infants as it is probably very rare. Therefore, it is appropriate to include an adequate source of copper in enteral and parenteral formulations from birth in the preterm infant. The current recommendation suggests 120–150 $\mu\text{g}/\text{kg}/\text{day}$ for enteral formulations and 16–20 $\mu\text{g}/\text{kg}/\text{day}$ for those infants fed parenterally [27]. Both human milk and preterm formulas meet the estimated daily requirement when consumed at the recommended rate of around 150 ml/kg/day. Since copper is excreted in bile, with neonatal hepatic cholestasis, parenteral copper should be withheld.

Clinical selenium deficiency has not been described in preterm infants, although biochemical evidence of selenium deficiency (low serum concentrations and decreased glutathione peroxidase activity) has been observed. Similar to zinc and copper, selenium stores are low at birth, so if the preterm infant is provided with selenium-free TPN, there is a risk of the development of a selenium deficiency [29]. Since selenium, like vitamin E, is an antioxidant, neonatologists have speculated that selenium supplementation may protect infants from diseases associated with oxygen free radical damage. Two recent prospective studies addressed whether selenium supplementation reduces the prevalence of bronchopulmonary dysplasia or retinopathy of prematurity in high-risk infants born in selenium-deficient endemic areas (New Zealand) [30, 31]. Neither demonstrated any protective effect. The current recommended dose of selenium for enteral and parenteral feeding of preterm infants is 1.3–3.0 $\mu\text{g}/\text{kg}/\text{day}$ [27].

Chromium is an essential micronutrient in humans (it is involved in glucose homeostasis), but a chromium deficiency syndrome has not been described in preterm infants [27]. Because infants fed their own mother's milk have not become obviously chromium deficient, this intake is likely adequate for the preterm infant. Infants fed formula with a significantly higher amount of chromium have not developed overt deficiency, thus there is likely a wide safe

range of intake. Similarly manganese deficiency has not been identified in a preterm infant, although there is the potential for manganese toxicity which has been well described in the literature.

The major concern regarding iodine nutrition in infants is endemic cretinism due to maternal iodine deficiency. Excessive iodine can also cause hypothyroidism, especially in the 4% of the population who are sensitive to excess iodine [32]. Infants born prematurely are particularly sensitive to iodine excess and deficiency because of the immaturity of homeostatic mechanisms to deal with perturbations in iodine status. Similar to selenium, the iodine status of the infant at birth is to some degree dependent upon where the infant was born. For example, infants born in low iodine areas (especially those that have limited supplementation programs) will be at greater risk of iodine deficiency.

In summary, all essential micronutrients, including the microminerals are needed to support optimal physiological growth and development. Infants born prematurely are an 'at risk' population for the development of deficiencies primarily because they are born with low stores and they manifest rapid growth (thus increased requirements). Primary prevention is the key to optimal nutritional management of this fragile population group.

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Discussion

Dr. Beard: I am sitting here trying to draw a graph for myself on different stages of processes that come on line during fetal growth. It seems to me that your calculation, I was starting to do this when you were talking about iron but I think it is appropriate for the other microminerals that you talked about, you went from a 500-gram fetus to a 3-kilogram fetus, took the iron content of 37.5 mg and multiplied by 6, I believe, to come up with 225 mg iron content in the 3 kg for term infants. I think that is what you did.

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Dr. Zlotkin: Actually not really. There have been one or two studies looking at the composition of infants who died at various times during gestation. Most of this work was done by Widdowson et al. [1, 2] a long time ago, so in fact these numbers are based on the body composition of infants who actually died prematurely. Again one could argue that that may not be an appropriate population to base nutrient requirements on, but these are based on body composition studies as opposed to mathematical calculations.

Dr. Beard: It is interesting that if you simply multiply by 6 you get the same number. But my real question is, at what stage of fetal growth do antioxidant systems or other micronutrient-dependent systems come on line, if you will, and then determine what influences requirements? It seems to me that probably a 24-week infant would perhaps have a birth weight of 700 g.

Dr. Zlotkin: Even lower perhaps, closer to 500 g.

Dr. Beard: Clearly the liver is probably not very competent at producing transferrin at that point. I would doubt that it is very competent at generating glutathione peroxidase dependent antioxidant systems. Can you give us some sense in fetal growth for these 7 micronutrients that you have talked about? At what stage of fetal growth may they really come on line?

Dr. Zlotkin: My answer to this question is going to be the same as my answer to many questions that were asked this morning and that is, there simply are no good data to answer that question. Perhaps I can say what no good data are and then answer the question to a certain extent. When I was working with the preterm infants, which was 20 years ago, the typical size of the infant born in the nursery at the Hospital for Sick Children in Toronto was about 1,800 g. That was the size of the infants who were included in my studies looking at the amino acid and the protein needs of the infant born prematurely. With an infant weighing 1,800 g there is the possibility of attaching a bag to collect urine. There is also the possibility of taking blood samples, although again the blood volume that one can take is relatively small, about 100–120 μ l of blood in an 1,800-gram infant. In the year 2002 an 1,800-gram infant is considered to be a large infant. Those infants might be in the nursery for a relatively short period of time, so the typical population we are talking about now in the nursery at the Hospital for Sick Children is between 500 g and 1 kg, and in that population it is extremely difficult to collect samples. It is extremely difficult to do appropriate studies because these infants are complex infants with multiple medical and surgical problems. So it is extremely difficult to do proper research in this population. The first answer is that we have little to no information available on all the questions you asked. Having said that I can only imagine that what you said is true, that at 24 or 28 weeks of gestation the antioxidant systems are poorly developed. The ability of the infant to respond to a need for protein synthesis is present but again the development is likely to be limited. I believe that the premature infant will not manifest an appropriate antioxidant response to potential environmental oxidants and thus is markedly at risk. In addition the blood brain barrier in infants of this age is very poorly developed. If the blood brain barrier is an important component in the protection of the developing central nervous system, it is not well developed in this population. So again I would emphasize that these infants are at high risk for the potential effects of oxidants.

Dr. Delange: Regarding iodine, of course I would like to mention that your first sentence has to be slightly enlarged. I think that the reason for iodine supplementation is no longer to prevent endemic cretinism, we are much further than that. If so, iodine supplementation should be required only in a few places in the world, so we have to enlarge this group to borderline impairment of intellectual development. Now regarding the doses, the thyroid system is relatively easy to cope with in terms of dosage. What we want to do is to restore, to fuel the thyroid residue and to reach what

is a normal iodine content in the thyroid gland. In adults this content is some 15,000 μg , the requirement of iodine of an adult is 150 $\mu\text{g}/\text{day}$ which means that the turnover rate of thyroidal iodine is about 1%. In the full-term neonate the content is 300 μg and the requirement is 75 $\mu\text{g}/\text{day}$, which makes a turnover rate of 17% that is markedly accelerated. This explains why neonates, and especially preterm neonates, are of course particularly sensitive to iodine deficiency. I think you are perfectly right by saying that the dose should be adapted to the baseline iodine intake of the population and I fully agree with your proposal, except for parenteral nutrition which is certainly perfectly adequate in areas with a normal baseline iodine supply like in the United States. For Europe and most of the countries in Asia and Africa I would recommend higher doses, coming to the conclusion that when the infants are fed milk I think that 10 $\mu\text{g}/\text{kg}/\text{day}$ from milk for full-term neonates is adequate and for preterm neonates it should be 30 $\mu\text{g}/\text{kg}/\text{day}$. Extrapolating from that I recommend higher doses for parenteral nutrition in the range of 5–10 $\mu\text{g}/\text{kg}/\text{day}$ instead of the 1 $\mu\text{g}/\text{kg}/\text{day}$ you have been showing. I am sure that 1 $\mu\text{g}/\text{kg}/\text{day}$ is perfectly all right in the States, but I am not sure it will be right in a country like mine with borderline iodine deficiency.

Dr. Zlotkin: Let me ask you a question. The reason that the 1- $\mu\text{g}/\text{kg}/\text{day}$ recommendation for parenteral iodine is sufficient is related to the fact that, at least in Canada, the disinfectants that are used to clean the infants often contain large amounts of iodine, and the concern that we have is not for iodine deficiency in the infants born prematurely but indeed iodine excess from the absorption of the iodophores from the skin. So I think one of the reasons why we recommended a relatively low amount is the assumption that the infants will get their skin cleaned with iodine and therefore be at risk for excessive iodine intake.

Dr. Delange: Sorry to say that I would like to recommend excluding the use of iodine solutions in any neonatal unit. I would like to add this as a formal recommendation because as you say the danger of excess is more visible for preterm infants than iodine deficiency.

Dr. Zlotkin: May I just make a comment on your first point, and that is that the goal of course should be the prevention of mild-to-moderate developmental delay. I think the problem in the preterm infant once again is identifying that condition. Very often the very small premature infant may have an intracranial bleed or may have other reasons for developmental delay in addition to nutrient or micronutrient deficiencies. The real problem in this population is identifying unique effects from unique interventions. So although I certainly agree that we want to prevent mild-to-moderate developmental delay, we want these children to develop up to their genetic potential. I think the minimum expectation is that they meet their minimum iodine needs.

Dr. Al Saied: Probably at the Hospital for Sick Children in Toronto you are lucky, you can deal with a population of children weighing 500 g to 1 kg but in other parts of the world, especially in Third World countries, small-for-gestational age (SGA) babies are probably more frequent and they create a lot of problems. I don't know what you mentioned in terms of guidelines applying to SGA babies in terms of requirements. When I say SGA babies, babies who are born near term but they are small for their birth date.

Dr. Zlotkin: I think your question is particularly appropriate and I did want to make the same point. My second slide shows that there is a marked difference between the nutrient requirements of an infant born prematurely at an appropriate size. So a baby at 24 weeks of gestation should probably weight 500 g. That infant is not an SGA baby. An infant born at term weighing 2,400 g is a full-term infant but is of course SGA or has intrauterine growth retardation, and the nutrient endowment in these two populations I think is quite different. Therefore the nutrient needs of these two populations are indeed very different. It is my sense that we know more about the

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needs of the infant born prematurely than the needs of the infant who was born with intrauterine growth retardation, no matter what the gestational age is. I do want to emphasize that the comments in my lecture were directed specifically to the infant born prematurely, as opposed to the needs of the infant who is intrauterine growth retarded or born at a low weight for gestational age. I think those infants' needs will be markedly different and the research studies needed to define those needs are markedly deficient. If I gave another lecture on that population (i.e. SGA infants) the numbers would be quite different. I totally agree with you that in the developing world the real issue is not how do we cope with the infants born prematurely, although that still is probably 10–15% of all infants born which of course numerically is a large population, but an even larger population are those who are born SGA. They are not identical populations, their needs are certainly not identical.

Dr. Young: You indicated that the accretion rate of iron during the last trimester approximated about 1.6–2 mg of iron/kg/day, and then as an indication of an appropriate dose of iron for the premature baby, depending upon the degree of prematurity, you presented us a dose of about 2–4 mg/kg/day, which implies a relatively high bioavailability of iron, much higher than 10%. Would you comment in this context and also to what extent the regulation of iron absorption is developed at this stage in the early part of the life cycle?

Dr. Zlotkin: Let me make a few general points first. The first general point is that when giving a lecture one is forced to give a number which is neither in this particular context the estimated average requirement nor is it the recommended daily allowance, nor in fact is it even an adequate intake because for the preterm infant we really do not have the luxury of the equivalent Institute of Medicine Committee that came up with a standard nomenclature for the needs of the preterm infant. So I am not even sure whether I should call the numbers I showed on this board average requirements. They are really based on a few studies on a limited number of infants. So I am not sure whether I am talking about a population requirement or an individual requirement. Either way those numbers are estimates. So I don't want anyone to stick specifically to those numbers and say that it is exactly what the requirement is. When we are talking about the amount of iron that is needed during that first year of life, it really is meant to be a combination of the iron that is provided by the typical foods eaten by infants and that would be human milk, formula, fortified cereals and the other typical foods in the Western world. There is an understanding that in the preterm infants it is probably not possible to meet the iron needs by food alone. Thus for preterm infants there is a recommendation that supplements are needed. The absorption of iron from supplements (e.g. ferrous sulfate) given as drops between meals is as high as maybe 30 or 40%. So I think if one were to go back and do some of the estimated number crunching they would come to relatively the right numbers. The second question was about the development of absorption in the preterm infants. There have actually been about probably 5 or 6 studies [3, 4] using stable isotopes in preterm infants, and I think the general conclusion is that the ability of the infant to respond to iron needs is not as developed as in the full-term infant or the young adult or the adult. In fact the infant goes through a stage where the absorption of iron is not directly related to the infant's need for iron. Thus gut development in the preterm infant is immature.

Dr. Endres: You said that iron could be the source of free radicals which could be detrimental for the development of bronchopulmonary dysplasia, and then you cited two studies which correlated selenium intake to the rate of bronchopulmonary dysplasia and also of retinopathy of prematurity, and these studies failed. In this selenium study have they used oral iron or parenteral iron? I'm asking because you said only parenteral iron has this capacity to be toxic.

Dr. Zlotkin: If I said parenteral iron has the only potential to be toxic I was wrong. I think there is the potential in the preterm infant for iron in general to be toxic and, again as we well know, if iron is not bound to a protein it can have very toxic effects. The problem with the preterm infant is that it may have limited ability to synthesize transferrin, which of course is the major iron-binding protein to meet the incoming amount of iron. That can occur both with parenteral and enteral or supplemental iron. I apologize I am not aware of the studies well enough to say whether or not they used an iron-fortified preterm formula or a non-iron-fortified preterm formula in those two studies where they looked at the antioxidant effects of selenium. I can look at the references for you but I apologize I can't remember.

Dr. Allen: When I was working on recommendations to meet the nutrient needs of infants during their first 6 months of life, I worried about how to deal with the fact that we don't know how many infants are preterm or even somewhat underweight at birth. In some regions of the world there may be large numbers of preterm infants. The WHO recommendation is for low birth weight infants to get supplemental iron after 2 months of age. This should probably apply to the need for other supplemental micronutrients as well. If it were up to you to make a recommendation for what infants should get in the first 6 months of life, in terms of direct supplementation, in developing countries in situations where one does not know if the infant was born low birth weight or preterm, what would this recommendation be?

Dr. Zlotkin: I hesitate to answer because I really don't know the question. On the one hand I would be tempted to say that we should be on the side of providing more iron than we would otherwise provide to the full-term infants. On the other hand I do have a fear of giving too much iron in terms of its toxic effects, and I simply don't know enough about the endowment of iron in the infants who were born at 2,200, 2,300, 2,400 g to say whether or not they have increased needs. If you provide an adequate amount of all the other nutrients so that the growth rate of the intrauterine growth-retarded infant is very rapid, and the infant is manifesting catch-up growth, then one could imagine that the increase in growth includes a markedly elevated increase in blood volume. In that case I would say that the infant probably does need a significant amount of iron to meet the needs to prevent anemia. On the other hand, if the infant is not manifesting catch-up growth because it is not getting enough protein, energy and all the other micronutrients, it is quite likely that the amount of iron those infants would need would be relatively low because they simply aren't increasing their blood volume at a rapid rate. So I think the minimum expectation should be that we provide the amount of iron that we would want to provide to the typical rapidly growing full-term infant.

Dr. Allen: I was also interested in what to do about zinc and other nutrients for those infants who were possibly born preterm and/or had a lower birth weight.

Dr. Zlotkin: Again I would probably use the same argument that we should provide the nutrients in amounts that we know are needed in the rapidly growing full-term infant (i.e. that amount is based on 780 ml of human milk at the mean concentration of micronutrients in human milk). If we can provide that amount, I think we will be doing no harm to the infants and likely coming close to meeting their needs. Up to this point the real issue of course is that we have not been able to do that adequately. But that would be my starting point.

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