Vitamin E and Iron Deficiency in Preterm Infants

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VITAMIN E

The biological functions attributed to vitamin E are performed by a group of related chemical compounds, namely the tocopherols and the tocotrienols. These compounds are the major source of natural protection against lipid peroxidation of the polyunsaturated fatty acids in biological membranes. The most biologically active of these chemicals is α-tocopherol. The term "vitamin E" will be used to refer to this group of compounds and their collective biological activity.

Prevention of Vitamin E Deficiency

Alpha-tocopherol is present in the body of the fetus throughout gestation at a level of approximately 5 mg per kilogram body weight (1). Infants born prematurely have stores of tocopherol that are reduced in proportion to their body weight, and their plasma tocopherol concentrations at birth are similar to those of term infants, 0.2–0.3 mg/dl (2–4). Tocopherol levels generally rise to 0.5 mg/dl or higher by the end of the first week in infants fed human milk or typical infant formulas.

Gordon and de Metry (5) demonstrated in 1952 that the erythrocytes of preterm infants were susceptible to hemolysis in the presence of hydrogen peroxide and that vitamin E reduced this hemolytic tendency. In the 1960s, infants in North America were fed diets that were low in vitamin E and high in polyunsaturated fatty acids. With such feeding practices, preterm infants were sometimes found to have increased erythrocyte hemolysis (6) and even hemolytic anemia (7) that could be prevented or corrected by the administration of vitamin E. It should be noted that several clinical trials of vitamin E supplementation conducted in that era demonstrated no effect on the incidence of anemia among preterm infants (8–10), although the protective effect of vitamin E was shown in other trials (7,11–13).

The hemolytic anemia of vitamin E deficiency is rarely seen with modern feeding practices (1,14,15)—that is, when preterm infants are fed human milk or vitamin-E-
fortified infant formula without medicinal doses of iron. Infants who are too sick to be fed enterally may continue to have low tocopherol levels unless supplemented, but these infants are also likely to have low intakes of polyunsaturated fatty acids and are therefore at relatively low risk of manifestations of vitamin E deficiency.

The infants at greatest risk of vitamin E deficiency are those with primary fat malabsorption or cholestasis and those who receive intravenous lipid emulsion without adequate supplements of vitamin E. Lipid emulsions contain large amounts of polyunsaturated fatty acids but also contain tocopherol in varying amounts (1,16). In general, the amount of vitamin E delivered in intravenous multivitamins is adequate to protect infants receiving lipid emulsions from vitamin E deficiency. A daily vitamin E intake of 3 IU/kg delivered intravenously as α-tocopheryl acetate will generally provide adequate tocopherol levels in plasma (1–3 mg/dl) without risking toxicity (17,18). Intravenous intakes of 6 IU/kg/day are associated with potentially toxic plasma levels (above 3.5 mg/dl) in approximately one-third of cases (18), and intravenous intakes of 15–30 IU/kg/day were associated with hepatic and renal failure and death (19,20). Oral vitamin E intakes of 1–20 IU/kg/day appear to be both safe and adequate (21). These intakes are provided by human milk or typical infant formulas. The incidence of vitamin E deficiency in preterm infants in the first days of life, before enteral feeding or parenteral vitamin supplementation is begun, is unknown but probably small. Any concern about the possibility of vitamin E deficiency in such infants could presumably be averted by administering a modest dose of vitamin E (20–30 IU/kg, intramuscularly or enterally) soon after birth, although such therapy has not been experimentally tested.

High-Dose Vitamin E for Prevention of Complications of Prematurity

Pharmacological dosing of vitamin E has been proposed for the prevention of several complications that occur among preterm infants: bronchopulmonary dysplasia (BPD), retinopathy of prematurity (ROP), and intracranial hemorrhage (ICH). After an initial promising report (22), subsequent studies (23,24) showed no protective effect against BPD.

Studies of high-dose vitamin E for the prevention of ROP (25–30) are contradictory. Taken together, however, these studies suggest efficacy of high doses of vitamin E in reducing the incidence or severity of ROP (31). It is not clear that the potential benefit, if any, outweighs the risks of giving high-dose vitamin E to all very-low-birth-weight infants in order to protect the few who might otherwise develop significant ROP (31).

Vitamin E has also been proposed as a possible protective factor against intracranial hemorrhage in preterm infants. Six studies (29,32–36) that examined this question are summarized in Table 1. Although the results of these studies varied, meta-analysis of the data indicates a beneficial effect of vitamin E in protecting against ICH. The analysis was conducted using the method of Galbraith (37). The overall odds ratio (of risk in vitamin-E-treated infants to risk in control infants) was
TABLE 1. Vitamin E and intracranial hemorrhage in preterm infants: meta-analysis

<table>
<thead>
<tr>
<th>Author</th>
<th>Vitamin E</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minkowski (32)</td>
<td>1/45</td>
<td>6/45</td>
</tr>
<tr>
<td>Chiswick et al. (33)</td>
<td>9/21</td>
<td>10/23</td>
</tr>
<tr>
<td>Speer et al. (34)</td>
<td>10/64</td>
<td>24/70</td>
</tr>
<tr>
<td>Sinha et al. (35)</td>
<td>31/102</td>
<td>58/108</td>
</tr>
<tr>
<td>Phelps et al. (29)</td>
<td>57/93</td>
<td>60/102</td>
</tr>
<tr>
<td>Fish et al. (36)</td>
<td>24/68</td>
<td>35/69</td>
</tr>
<tr>
<td>Overall:</td>
<td>132/393</td>
<td>193/417</td>
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</tbody>
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FIG. 1. Graphical representation of meta-analysis of effect of vitamin E on the incidence of intracranial hemorrhage in preterm infants. Odds ratios and 95% confidence intervals were computed by the method of Galbraith (37).
0.587, with 95% confidence interval from 0.439 to 0.785. The odds ratios and 95% confidence intervals for the six individual studies are shown in Fig. 1.

IRON

During fetal life, body iron stores increase in proportion to body weight and are approximately 75 mg/kg (38). Thus, the preterm infant is born with the same iron stores per kilogram as is the term infant. Because of his relatively faster growth, however, the preterm infant becomes iron-deficient more rapidly than does his term counterpart once erythropoiesis increases in response to the postnatal decline in hemoglobin concentration and red cell mass (39–41). The iron stores of the preterm infant are depleted at an earlier age than are those of the term infant, as indicated by the more rapid postnatal decrease in serum ferritin concentration in preterm infants (42,43). Even with iron supplementation, the hemoglobin concentrations of preterm infants reach lower levels than those seen in term infants (39,41), indicating the need for earlier initiation of iron supplementation.

The fraction of dietary iron absorbed from the gastrointestinal tract varies with iron stores and iron source. Fractional absorption is inversely proportional to iron stores and is higher from human milk than from infant formula (39). Absorption of iron from formula is higher in preterm than in term infants, presumably because of their lower iron stores (39).

Prevention of Iron Deficiency

The incidence of iron deficiency among preterm infants in the first year of life varies among published reports, presumably as a function of age at testing, infant feeding practices, and maternal diet. Halliday et al. (44) examined preterm infants receiving 1–4 mg of iron/kg/day; they found evidence of iron deficiency (low serum ferritin or transferrin saturation or both) in 26% of infants with gestational age between 28 and 36 weeks, generally occurring after the age of 3 months. Friel et al. (45) found low serum ferritin concentrations in 54% of very-low-birth-weight infants at 12 months of age and in 74% at 15 months. These infants had initially been fed iron-fortified formula (13 mg/l), but by 12 months most were receiving low-iron formula. Iwai et al. (46) found 86% of breast-fed preterm infants to be iron-deficient (low serum ferritin or mean corpuscular volume) at 6 months of age, whereas 33% of infants fed iron-fortified formula (8 mg/l) were iron-deficient at 6 months; neither group received iron supplements unless iron deficiency had been diagnosed.

Rudolph et al. (47) found no effect of iron intake (low-iron formula versus formula fortified with 12 mg/l) on hemoglobin concentration of preterm infants during the first 6 weeks, but more sensitive measures of iron deficiency were not reported. Hågå (42) found no evidence of iron deficiency during the first month of life in preterm infants fed formula containing 5.5 mg of iron per liter. Thereafter ferritin levels fell in infants with the fastest weight gain. Other studies indicate that iron deficiency
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may develop after 2 months (48) or 3 months (43,49) of age in preterm infants if iron intake is inadequate. Iron deficiency may develop earlier with unmodified cow milk feeding (50), a practice that should be avoided in the first year of life in term as well as in preterm infants.

Medicinal doses of iron may increase hemolysis in vitamin-E-deficient infants (11), but iron doses of 2–3 mg/kg/day may be safely begun at 3 weeks of age provided the diet also contains adequate amounts of vitamin E (48,49). It is almost certainly safe to use iron-fortified formulas from the time enteral feeding is initiated in preterm infants. These formulas contain adequate amounts of vitamin E to protect against iron-induced hemolysis. Moreover, the iron intake will be low during the early phase of feeding and will increase only as the tolerated volume of formula increases. With iron-fortified preterm formulas such as those now available in North America (12 mg iron/l), additional iron supplements are not needed. Infants fed human milk should be given iron supplements (2–3 mg/kg/day) beginning when full enteral intake is achieved. Such infants should also be given a multivitamin supplement that contains vitamins A, D, and E, unless they are receiving a vitamin-containing human milk fortifier.

CONCLUSION

Preterm infants are born with relatively low vitamin E stores and suboptimal plasma tocopherol concentrations. However, vitamin E deficiency is rare once enteral feeding with human milk or modern infant formulas can be undertaken. Small intravenous doses of vitamin E delivered in multivitamin preparations are generally sufficient to protect infants receiving parenteral nutrition. All infants receiving intravenous lipid emulsions should be given intravenous multivitamins that contain vitamin E. It seems reasonable to consider administering a single dose of vitamin E, 20–30 IU/kg, on the day of birth to preterm infants who are not likely to receive enteral feedings or intravenous multivitamins for several days; however, this practice is of unproven benefit. The role of high-dose vitamin E in protecting against certain complications of prematurity remains controversial, but available data suggest that there may be a protective effect against intracranial hemorrhage.

Preterm infants are at risk of developing iron deficiency after 2 months of age unless given iron-fortified formula or supplementary iron. Extremely preterm infants are likely to be at risk of developing iron deficiency at an even earlier age, especially in the face of repeated phlebotomy in intensive care. There seems to be little or no risk in initiating iron-fortified formula or iron supplements at an early age, provided that vitamin E intake is also adequate.

REFERENCES

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DISCUSSION

Dr. Doyle: With Dr. Jack Sinclair we did an analysis of the effects of vitamin E supplementation on hemoglobin. Using the available clinical trials, we showed that at about 6 weeks of age the vitamin-E-supplemented babies tended to have a hemoglobin of 6- to 7-g/l higher than nonsupplemented babies. However, by 10 weeks the difference was no longer apparent and the clinical significance of such a small difference is anyway in doubt. I should add that the peroxide hemolysis test is affected by many other variables, including selenium and glutathione peroxidase. I should be reluctant to take it as a sole measure of vitamin E status.

I am confused by the interaction of vitamin E and iron. Trials in premature infants from...
the 1960s showed consistent benefit from iron supplementation. These infants were vitamin-E-deficient. In the early 1970s we began to see evidence of interaction; and in babies who were supplemented with both iron and vitamin E, hemoglobin values were lower than when neither was given. This was documented in clinical trials at the time. In the 1980s, in a setting of vitamin E sufficiency, there is again an apparent benefit from iron. Perhaps Williams (1) got the answer when she studied the effects of different dietary fats and showed that if monounsaturated fats predominated in the feed, hemolysis did not occur when concurrent iron and vitamin E supplementation was given.

Dr. Bell: I agree that the peroxide hemolysis test should not be used alone to diagnose vitamin E deficiency, but I think that a combination of the peroxide hemolysis test and plasma tocopherol concentration is better than tocopherol level alone since this adds a measure of functional vitamin E sufficiency. A new technique has been introduced that involves measurement of the production of ethane and pentane in the body by analyzing the amounts exhaled in the breath. With β-oxidation of long-chain fats in vivo, pentane and ethane are produced as degradation products of ω-6 and ω-3 fatty acids, respectively.

Dr. Doyle's analysis of the varying effect of iron supplementation over the decades is, I think, correct. It can be explained by differences in the fatty acid composition of the feeds. As industry is becoming better at developing and producing infant formulas, we have reached a point where the balance of intakes of iron, vitamin E, and poly- and monounsaturated fatty acids is quite good if we can refrain from tampering with it!

Dr. Shaw: Do you give vitamin E to your patients?

Dr. Bell: Our practice has been to rely on normal nutritional sources of vitamin E and not to use supplements. We consider that the formulas we now use, which are specifically targeted at preterm infants, have adequate amounts of vitamin E. Human milk is also a fairly good source, though we tend to add commercial milk fortifier preparations after several weeks. Babies who are fed intravenously routinely get multivitamins containing small amounts of vitamin E. This still leaves the question of the first few days of life in the preterm infant born with low vitamin E levels. Is there a vulnerable period in the first week when preterm infants have vitamin E deficiency? The answer is not known, but it would almost certainly be safe to give a single intramuscular or even oral dose of vitamin E on the first day of life. There are no data on the efficacy of this practice.

Dr. Koletzko: We measured vitamin E status in healthy enterally fed German preterm infants, mean birth weight 1700 g, and compared it with results from other age groups. We were disturbed to find a mean α-tocopherol level of less than 0.5 mg/dl in these infants in the first few days of life. The tocopherol/lipid ratio was satisfactory, at above 0.8, though it was lower than in older infants; however, in spite of this the total amount of tocopherol available to the tissues was extremely low. Gutcher and coworkers have shown that peroxide-induced hemolysis in preterm infants correlates better with absolute tocopherol concentrations than with the tocopherol/lipid ratio. At the value of 0.5 mg/dl, the mean value for our infants, they found markedly increased hemolysis, which only normalized at values above 1.0 mg/dl.

We also found that tocopherol concentrations did not increase much in the first 3 weeks, the mean value at 3 weeks being about 0.6 mg/dl. This was in spite of full enteral feeding with either breast milk or formulas. The latter were adequate for preterm infants according to the ESPGAN standards. The striking thing is that in spite of the fact that the formula contained 2½ times as much vitamin E as human milk, the plasma tocopherol concentrations were not higher in the formula-fed infants than in those fed breast milk. One explanation for this could be that, in contrast to human milk, formulas usually contain vitamin E esters,
which are split by bile-acid-dependent esterases. Thus in the presence of low intraluminal concentrations of bile acids in the first few weeks of life, there may be a problem of bioavailability. A second potential problem is that most formulas contain dL-α-tocopherol, which has been shown to result in lower tocopherol concentrations in the plasma lipoproteins, and at least in animal experiments in lower tissue concentrations.

_{Dr. Bell:}_ Dr. Zipursky and I have shown that vitamin E is quite well absorbed from the gut under most circumstances in preterm infants, even the ester dL-α-tocopheryl acetate. The question of bile salts is very important and warrants further study. There may well be more difficulty with bioavailability in infants with deficient bile salts, and this is especially likely to be a problem in the very tiny infants we are managing now. However, the epidemic of vitamin E intoxication that occurred in the 1980s in preterm infants given a new intravenous product (2,3) arose in part as a reaction to this concern; it was thought that intravenous vitamin E would circumvent the problem of poor absorption from the gut. Unfortunately there was insufficient knowledge of its potential toxicity, and the gastrointestinal tract remains by far the safest route of administration.

_{Dr. Shaw:}_ For how long do you think iron supplements should be continued in preterm infants?

_{Dr. Bell:}_ In formula-fed infants we use iron-fortified formulas and continue them throughout the first year of life. In breast-fed infants we recommend iron supplements as long as they are exclusively breast-fed and until they are getting significant amounts of iron from other sources, usually at about 6 months.

_{Dr. Shaw:}_ Is there any evidence of vitamin E deficiency in children recovering from malnutrition?

_{Dr. Viteri:}_ We looked for this in the late 1960s in Guatemala but found no evidence for it, though there were several reports of vitamin E deficiency anemia from the Middle East at the time. Michael Golden (4) has been trying to unify the theory of edema and other characteristics of kwashiorkor by relating them to free-radical damage and lipid peroxidation. I don’t know how strongly his data back up his theory.

_{Dr. Adelekan:}_ In our study (5) we looked at vitamin A, β-carotene, and vitamin E in severely malnourished children. Serum vitamin E concentration was significantly lower in the malnourished children than in controls, but when expressed in relation to serum lipids the malnourished children were not vitamin-E-deficient.

_{Dr. Dallman:}_ I am concerned about very-low-birth-weight infants given large amounts of iron. A recent survey of neonatal units in Great Britain showed that many were routinely given more than 10 mg of iron per day (6). In a very-low-birth-weight infant this would be equivalent to the doses that were used when vitamin E deficiency was first recognized as a problem. It is also likely that high doses of iron will be used in conjunction with recombinant erythropoietin in the treatment of anemia of prematurity. Do you see vitamin E deficiency as a potential problem in these situations?

_{Dr. Bell:}_ I think neonatologists have tended to take rather a simplistic approach to vitamin supplementation, namely to give the same dose to every infant regardless of body size. This is partly because of our ignorance about vitamin requirements and partly because the vast majority of premature infants formerly weighed between 1500 and 2000 g. Now that smaller infants are surviving, we need to be more careful about dosing according to body size. If higher intakes of iron are needed with erythropoietin therapy to provide adequate erythropoiesis, it may also be necessary to provide additional vitamin E. The iron doses used with erythropoietin therapy are generally around 6 mg/kg/day. Such intakes are not likely to cause serious problems with hemolysis given modern nutritional practices.
Dr. Zlotkin: Are there any data to show whether preterm infants have the ability to absorb the amount of iron they may get if erythropoietin is successful?

Dr. Bell: Data are presently being collected to answer this using stable isotopes of iron. Our initial impressions are that infants probably absorb enough iron to be able to use it once the marrow starts working.

Dr. Atkinson: It is important to point out that European standard formulas have much lower iron fortification than do North American formulas (6-8 mg versus 12 mg/l). And in Canada, standard formulas are only fortified to a level of 7 mg/l, which will provide about 1.4 mg/kg if the baby is fed at 200 ml formula per kilogram body weight daily. I wonder whether further supplementation with iron is required if such formulas are fed. Another issue is the balance of nutrient supplements for breast-fed preterm infants. Although there are not large numbers of such infants who go home on breast milk exclusively, the situation could arise in which there is a relatively large iron intake (from supplements) and a relatively low copper intake (from breast milk), with inhibition of copper absorption by the high iron intake.

Dr. Bell: There are ongoing studies addressing the issue of the optimum level of iron fortification. All we know at this point is that a level of 12 mg/l is better than no fortification, but exactly how much is needed is still to be determined. The level of 2-3 mg/kg/day has been shown to be helpful; whether 1.4 mg/kg/day would suffice I don’t know. This will depend on the absorption.

With regard to the fully breast-fed preterm infant, we give a multivitamin preparation that contains iron and vitamins A, C, and D but not usually vitamin E. Copper intake is probably lower with exclusive breast feeding than with formula feeding, and we need to know more about this topic.

REFERENCES