ESPGHAN Committee of Nutrition position paper on Enteral Nutrition for Preterm Infants 2022:
Trace elements (February 2022)

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Literature search

1. iron [ti] (preterm OR premature OR "low birth weight") (randomized OR randomised OR meta-analysis) NOT pregnancy
2. zinc [ti] (preterm OR premature OR "low birth weight") (randomized OR randomised OR meta-analysis) NOT pregnancy
3. copper [ti] (preterm OR premature OR "low birth weight") NOT pregnancy
4. selenium [ti] (preterm OR premature OR "low birth weight") NOT pregnancy
5. manganese [ti] (preterm OR premature OR "low birth weight") NOT pregnancy
6. (iodine [ti] OR iodide [ti]) (preterm OR premature OR "low birth weight") (randomized OR randomised OR meta-analysis) NOT pregnancy
7. chromium [ti] (preterm OR premature OR "low birth weight") NOT pregnancy
8. molybdenum [ti] (preterm OR premature OR “low birth weight”) NOT pregnancy

Trace elements

Trace elements, including iron, zinc, copper, selenium, manganese, iodine, chromium and molybdenum are essential for many functions in different organ systems, as well as for normal growth and development. It is important to provide adequate amounts of microminerals in the diet since preterm infants are at increased risk of micromineral deficiencies but also may have adverse effects of excessive intakes.

Iron

Iron is an essential nutrient which is required for heme synthesis, oxygen transport, and many enzyme functions, especially cellular energy metabolism. Preterm infants are at high risk of iron deficiency (ID) due to low iron stores at birth, higher iron requirements due to

rapid growth, and in very preterm infants, iron losses due to frequent blood samplings during neonatal intensive care (1). ID should be avoided since it causes anemia and is associated with impaired brain development (2). However, in contrast to most other nutrients, there is no mechanism for iron excretion from the human body and iron is a highly reactive pro-oxidant as well as an important substrate for pathogens, so excessive iron supplementation of infants should be avoided since it may have adverse effects, including increased oxidative stress, risk of infections, poor growth and even poor neurodevelopment (1).

The main public health problem associated with ID in childhood is the risk of poor neurodevelopment and many studies have shown that infants with iron deficiency anemia have long-lasting poor cognitive and behavioural performance up to adolescence. Prevention of iron deficiency is thus of great importance. A Cochrane systematic review from 2012 investigated the effects of enteral iron supplementation in preterm and LBW infants and concluded that infants who receive iron supplementation, compared to un-supplemented infants, have a lower risk developing iron deficiency anemia but that there is a complete lack of studies investigating long-term benefits in terms of neurodevelopmental outcomes. There was no discernible benefit in exceeding standard doses of iron (i.e. 2-3 mg/kg/day) (3).

Since the Cochrane meta-analysis, there has been only two new published placebo-controlled, randomized clinical trials investigating neurodevelopmental outcomes of iron supplementation of preterm infants. The first was a follow-up of a randomized controlled trial (4) where 385 marginally low birth weight infants (most of which were moderately or late preterm) were randomized to receive 0, 1, or 2 mg/kg/day of iron supplements from 6 weeks to 6 months of age. The infants from the original intervention as well as 95 normal birth weight reference children were assessed at 3½ years and 7 years. At 3½ years, there was no difference in cognitive scores between groups, but children in the placebo group had significantly more behavioral problems: 13% compared to 3% in the two iron supplemented groups ($p = 0.027$) and also compared to 3% in the reference group (5). These effects largely persisted at 7 years and the effects were seen mostly for externalizing behaviour, suggesting that iron supplementation confers long-lasting health benefits for preterm infants (6).

In the second, recently published trial, 66 healthy late preterm infants ($34^{0/7}$-$36^{6/7}$ wk) were randomized to iron supplements (2 mg/kg/day) or placebo from 3 weeks of life to 6 months postconceptial age (7). At 12 months of age, iron supplemented infants had significantly higher developmental quotient as assessed by the Griffiths scale.

A meta-analysis from 2015 including mostly very low birth weight infants, suggests that early start of iron supplementation (2-3 weeks in most studies), vs late (4-8 weeks in most studies) is associated with a lower need for blood transfusions (8). A more recent systematic review in 2019 concluded that iron supplementation with a duration of at least 8 weeks results in reduced risk of iron deficiency and anemia in preterm and low birth weight infants (9). Regarding long-term effects, the review reports a lack of RCTs and suggests further studies. For late or moderately preterm infants with birth weights > 2000 g, iron supplementation lasting until 6 months of life seems to protect from iron deficiency at least up to 12 months of life (10). Iron intakes from 6 months of life is highly dependent on infant diet and iron-rich complementary foods are recommended for all infants from this age (11).

In VLBW infants, the timing of umbilical cord clamping, blood losses and blood transfusions related to neonatal intensive care, as well as erythropoietin treatment, will greatly influence iron status and iron requirements. Delayed umbilical cord clamping increases neonatal iron stores and is associated with a lower mortality, lower risk of intraventricular hemorrhage and lower need for red cell transfusions in preterm infants (12). Phlebotomy losses commonly amount to 6 mg/kg of iron per week (13) and in some cases much more. Each red blood cell transfusion typically adds 8 mg/kg of iron and hepatic iron stores as well as serum ferritin concentrations in preterm infants are highly correlated to the number of blood transfusions received (14). Erythropoietin may reduce the need for red blood cell transfusions in VLBW infants and is used in some centers. However, this treatment greatly increases iron requirements and high doses of oral or parenteral iron are thus recommended as an adjunct to this therapy. Factorial calculations suggest that parenteral iron requirements of VLBW infants would be 0.2-0.37 mg/kg/day (15). However, parenteral iron has been given in much higher doses, up to 3 mg/kg/day, in erythropoietin trials. Some studies have showed that 6 mg/kg/day of enteral iron supplements is as effective as parenteral iron in this context (16). There is insufficient data on safety of high doses of iron in combination with erythropoietin, but a Cochrane meta-analysis has shown that early

erythropoietin treatment, which includes supplemental iron, increases the risk of retinopathy of prematurity (17).

Ferritin is a useful biomarker of iron status also in preterm infants but reference intervals are different from older infants and children. Ferritin concentrations lower than 35-40 µg/L indicate iron deficiency while concentrations > 300-350 µg/L indicate iron overload (1, 14, 18). Ferritin is not useful as a biomarker of iron status in patients with ongoing inflammation or liver disease.

Recommendations

- A daily iron intake of 2-3 mg/kg/day starting at 2 weeks of age is recommended for very low birth weight infants. LOE 1+, RGA
- Infants who receive erythropoietin treatment need a higher dose (up to 6 mg/kg/day) during the treatment period. LOE 1-, RGB
- Since individual iron status in VLBW infants is highly variable, depending on the number of received blood transfusions and blood losses from phlebotomy, it is recommended to follow these infants with repeated measurements of serum ferritin during the hospital stay. LOE 4, RG0
- If ferritin is <35-70 µg/L, the iron dose may be increased up to 3-4 (or maximum 6) mg/kg/day for a limited period. LOE 4, RG0
- Prolonged dietary iron intakes of >3 mg/kg/day should be avoided in most cases because of possible adverse effects. LOE 1-, RGB
- If ferritin is >300 µg/L, which in the absence of ongoing inflammation and liver disease usually is the result of multiple blood transfusions, iron supplementation and fortification should be discontinued until serum ferritin falls below this level. LOE 4, RG0
- Iron supplements or intake of iron-fortified formula in the recommended doses should be continued after discharge, until 6-12 months of age. LOE 4, RG0
- Like all infants, preterm infants should receive iron-rich complementary foods from 6 months of age. LOE 1+, RGA
- Delayed umbilical cord clamping, whenever feasible, is recommended for all preterm infants. LOE 1++, RGA

Zinc

Zinc is an essential trace element which plays an important role in growth and tissue differentiation. Zinc deficiency in children and preterm infants is associated with stunted growth, increased risk for infections, skin rash, and possibly poor neurodevelopment (19). In contrast to iron and copper, zinc does not have a pro-oxidant effect and adverse effects of excess zinc intakes are rarely reported, with the exception of a negative effect on copper absorption with high zinc intakes.

Using a factorial method based on fetal accretion, the requirement for retained zinc has been estimated to be approximately 400 µg/kg/d at 1500-2500 g (30-32 weeks of gestation) (20). Based on data from 14 metabolic balance studies in preterm infants, it has been calculated that an enteral zinc intake of at least 2.0-2.25 mg/kg/d is required to achieve this zinc retention (21). Theoretically, zinc requirements are higher (500-600 µg/kg/day) in extremely preterm infants, due to their faster growth rates (20),and intakes up to 3 mg/kg/d have been suggested (22).

Even though the concentration of zinc in colostrum is high (up to 2.8 mg/L(23)), human milk alone does not cover zinc requirements in infants with a birth weight of less than 1500-2000 g, since it would only correspond to an intake of 0.4 mg/kg/day from 150 ml/kg/day of breast milk.

There have been few clinical trials of different zinc intakes in preterm infants, suggesting that an intake of at least 1.4-2 mg/kg/d is needed in order to achieve optimal growth in preterm infants (24, 25).

In a double-blinded study from 2013, Terrin randomized 193 preterm infants (average 28 weeks) to receive multivitamin drops with or without zinc from 7 days until discharge or 42 weeks of postconceptional age (26). Total zinc intake was 10.3 mg/day in the zinc group and 1.3 mg/day in the placebo group, corresponding to an average of 6.6 and 0.9 mg/kg/day. Neonatal morbidities (composite of sepsis, BPD, PVL and ROP) were significantly lower in the zinc group (27% vs 42%, p=0.03). The occurrence of NEC was significantly higher in the placebo group (6.3% vs 0%, p=0.014), as was mortality (RR 2.37; CI 1.08-5.18, p=0.006) but no growth effects were observed. This study is potentially very interesting and suggests that higher enteral doses of zinc are safe and may confer health benefits. However, as

pointed out in an editorial, (27) it is important to distinguish between supplementation aiming to cover nutritional requirements and supplementation using pharmacological doses. In this case, the dose of zinc supplement used was much higher than the estimated requirements. Further studies are thus needed to ensure that high dose zinc supplementation > 3 mg/kg/d is safe and effective.

Two recent meta-analyses suggests that zinc supplementation improves weight gain and linear growth in preterm infants and may decrease mortality (Staub E, Cochrane Database Syst Rev 2021, Alshaikh B, J Perinatol 2022; 42: 430).

Very preterm infants can develop symptomatic zinc deficiency with acrodermatitis enterohepatica and/or poor growth, especially those infants who have an enterostomy after NEC sugery (Wulf K et al. Klin Pädiatr 2013; 225: 13).

Recommendations

- We recommend an enteral zinc intake of 2-3 mg/kg/d, based on the most recent randomized, controlled trial as well as on factorial calculations. LOE 4, RG0
- Measurement of serum zinc should be considered in preterm infants with dermatitis or poor growth and low alkaline phosphatase level, especially if they have excessive GI fluid losses. LOE 4, RG0

Copper

Copper is an essential nutrient with multiple functions as part of enzymes, including antioxidant enzymes, e.g. copper/zinc superoxide dismutase (CuZn-SOD).

Severe copper deficiency is a rare condition associated with anemia, neutropenia, thrombocytopenia and osteoporosis (28, 29). However little is known about the prevalence and possible health impact of marginal copper deficiency.

Low birth weight is a risk factor for copper deficiency (20, 28). Copper deficiency was reported relatively frequently in preterm infants in the 1970s and 1980s (30). However, most of these case reports were of infants who received copper-free long-term parenteral nutrition and there are no similar recent reports.

The intrauterine accretion rate of copper is approximately 50 µg/kg/d (31). Fractional copper absorption is about 60% from breast milk and generally lower from formula. Copper

homeostasis is maintained by regulation of both intestinal absorption as well as biliary excretion.

Using a factorial method based on fetal accretion, the required net retention of copper in preterm infants has been estimated to 30 µg/kg/d, corresponding to an enteral requirement of 100 µg/kg/d (20).

The copper content of human milk declines from 600 µg/L during the first week of lactation (800 µg/L in preterm milk) to 220 µg/L by 5 months (32).

High doses of copper can damage the liver, kidneys and central nervous system (33).

A calculation, based on nine published studies of copper balance in preterm infants, has suggested that enteral copper requirements are around 210-232 µg/kg/d if zinc intake is 2-2.25 mg/kg/d, in order to achieve a net copper retention of 30 µg/kg/d (21).

There are very few clinical trials of different copper intakes in preterm infants. Enteral feeding of 41-89 µg/kg/d of copper in preterm infants has been associated with copper deficiency (34). Tyrala showed no clear benefit of a copper intake of 294 µg/kg/d compared to 121 µg/kg/d in preterm infants as assessed by copper balance, serum copper and ceruloplasmin (35). However, no adverse effects were observed in the high copper group. Zinc intakes in those infants were 2.0-2.3 mg/kg/d.

The ESPGHAN 2010 recommendations suggest 100-130 mcg/kg/d (36). However, to ensure adequate intestinal absorption, the zinc to copper molar ratio should not exceed 20 (31).Thus, since the zinc intake has been increased (see above), a higher copper intake is needed.

Recommendations

We recommend an enteral copper intake of 120-230 µg/kg/d. The lower value is based on the Tyrala study and the higher is based on the calculation of copper retention noted above. LOE 4, RG0

The zinc to copper molar ratio in infant formulas should not exceed 20. LOE 4, RG0

Selenium

Selenium is an essential trace element which plays an important role as a component of selenoproteins, including glutathione peroxidases, antioxidant enzymes which prevent free radical formation and oxygen toxicity, as well as deiodinases, which are required for the metabolism of thyroid hormones.

Dietary selenium is highly bioavailable. A stable isotope study showed that 60-80% of selenium in formula was absorbed in preterm infants (37). A balance study has shown that net absorption of selenium from breast milk was 77% in extremely low birth weight infants (38).

Selenium status is usually assessed by measuring serum or plasma concentrations of selenium or the activity of glutathione peroxidase in plasma or red blood cells. In preterm infants, glutathione peroxidase activity is not a useful marker of selenium status since it is affected also by immaturity and oxygen exposure (38).

Selenium concentrations in breast milk are significantly associated with maternal selenium intake, and most often range between 6-28 µg/L in the USA and Europe, with an average of around 15-18 µg/L (20, 38). Based on 15 µg/L in breast milk and an intake of 150 ml/kg/d, this corresponds to an intake of 2.3 µg/kg/d.

Children receiving long-term parenteral nutrition without selenium supplementation have been reported to develop low plasma selenium, erythrocyte macrocytosis, loss of hair and skin pigmentation and muscle weakness, which responded to selenium supplementation (39).

Preterm infants are at high risk for oxidative stress related disorders, including bronchopulmonary dysplasia (BPD), retinopathy of prematurity and cerebral white matter injury. Selenium deficiency has been associated with increased susceptibility to oxidative lung injury in rats. Several studies have demonstrated that plasma selenium concentrations decrease during the first weeks of life in preterm infants, suggesting possible selenium insufficiency (38). Furthermore, several studies have shown an association between low plasma selenium levels and BPD in preterm infants (40).

Excessive selenium exposure in adults leads to selenosis, with symptoms including headache, memory difficulties, alopecia and GI symptoms (41). There have been no reports of adverse effects caused by excessive selenium intakes in infancy.

A few studies have shown that selenium intakes of 3-5 µg/kg/d result in improved selenium status in preterms (42).

Darlow et al performed a randomized, controlled, blinded trial of selenium supplementation in 534 VLBW infants in New Zealand, a country in which soil and food are low in selenium (43). The supplemental dose was 5 µg/kg/d enterally (resulting in 7 µg/day when considering selenium from breast milk) or 7 µg/kg/d parenterally. Supplements were given from 4 days of life and continued until 36 weeks postmenstrual age or discharge. A significant effect was observed on plasma selenium concentrations, which reached similar levels as healthy, term infants. However, no significant effect was observed on oxygen dependency at 28 days of age, which was the primary outcome. Among the secondary outcomes, no effects were observed except that, among infants who were exposed to antenatal steroids (n=403), selenium supplementation was associated with significantly fewer sepsis episodes: relative risk 0.66 (95% CI 0.46-0.86). No adverse effects were observed in this study.

Aggarwal et al (2016) performed a blinded RCT of selenium supplementation in 90 very low birth weight and very preterm infants (< 1500 g, < 32 wk, average 1464 g) in India (44). Se (10 µg/day) or placebo was given orally daily from birth to 28 days of life. A large proportion of these infants were Se deficient at birth with mean Se level of 31 µg/L. Se supplementation increased serum Se levels significantly on day 28 (64 vs 41 µg/L, p<.01). Furthermore, the incidence of late onset sepsis was significantly lower in the Se group (15.6% vs 48.9%, p=0.001).

Recommendations

We recommend an enteral selenium intake of 7-10 µg/kg/d, which in the studies by Darlow and Aggarwal (see above) has been shown to result in Se status similar to term infants and possibly a reduced risk of sepsis. LOE 1+, RGA

Manganese

Manganese is an essential trace element which is a cofactor for many enzymes. Manganese dependent superoxide dismutase (SOD2 or Mn-SOD) is important for cellular defense against free oxygen radicals. Reduced activity of this enzyme has been shown in manganese deficient animals, and mice lacking SOD2 die after a few days due to massive oxidative

stress. Manganese dependent enzymes are also important for bone formation and manganese deficiency in animals leads to abnormal skeletal development.

There are very few reports of manganese deficiency in humans. The most comprehensive description is from a paper in which experimental manganese deficiency was induced in seven adult subjects (45). In that study, a manganese deficient diet for 39 days resulted in negative manganese balance, biochemical evidence of bone resorption and clinical scaly dermatitis. There has been only one clinical report of manganese deficiency, in a 4-year-old girl with short bowel syndrome who since the neonatal period had received total parenteral nutrition which was deficient in manganese. She had short stature and brittle bones as well as a low serum manganese concentration. Bone density and longitudinal growth improved after manganese supplementation (46).

In contrast, there have been many reports of possible adverse effects of high manganese intakes. The main adverse effect of manganese is a neurotoxic effect, called manganism, which can occur with excessive occupational exposure to airborne manganese. Several studies have shown an association between dietary manganese exposure, blood magnesium concentrations and poor cognitive development in children (47). Manganese deposition in the brain can be detected with magnetic resonance imaging and recent studies have suggested that commercially available manganese containing parenteral trace element supplements can result in pathological manganese deposits in basal ganglia. This has been described in adult patients on long term total parenteral nutrition (48).

The main regulation of manganese homeostasis occurs at the absorption step. Intestinal absorption of manganese is usually assumed to be low. In a study performed in adults, fractional absorption of manganese was about 8% from human milk, 2% from cow's milk, 0.7% from soy formula and 2-6% from cow's milk based infant formulas with different iron contents (49). However, studies in rodents have shown that manganese absorption is higher in the postnatal period than later in life and it has been suggested that this is true also for humans. In rat pups, manganese absorption is 85% from preterm infant formula (50). The actual fractional absorption of manganese in preterm infants is unknown and may be higher than usually assumed.

The main excretory route for manganese is via the bile and a small amount is lost in urine. In conditions with poor bile excretion, e.g. parenteral nutrition associated cholestasis, manganese retention is increased.

Average manganese concentrations in breast milk range from 0.8 µg/L to 30 µg/L and in European studies, reported median concentrations vary between 3.2-11.8 µg/L (51). There is no clear correlation between maternal dietary manganese intake and breast milk manganese concentration. Assuming a breast milk manganese content of 6.5 µg/L and a milk intake of 150 ml/kg/day, a breastfed infant would receive 1.0 µg/kg/day of manganese.

Manganese is sometimes added as a supplement but may also be present as a contaminant in preterm formulas. Current European preterm formulas contain 5-13 µg of manganese per 100 mL, corresponding to an intake of 7.5-20 µg/kg/day.

Similar to their enteral counterparts, parenteral nutrition products can also be contaminated with manganese. Manganese excretion via bile is low, especially in long term TPN with cholestasis, so retention approaches 100%.

Based on fetal tissue concentration data by Casey et al, (52) the intrauterine accretion rate of manganese in a 1 kg fetus would be about 7 µg/kg/day.

There are no published intervention studies or observational studies comparing different doses of enteral or parenteral manganese in preterm infants.

Previous recommendations for enteral manganese intakes in preterm infants range from 0.7-7.5 µg/kg/d (53) and 6.3-25 µg/kg/d (ESPGHAN 2010) (36).

Conclusions

It seems to be prudent to recommend a lower intake than the estimated fetal accretion rate since manganese deficiency has never been described in a preterm infant and there is legitimate concern for manganese toxicity. LOE 4

Recommendations

Based on the average breast milk manganese content and the lower range of manganese in current preterm formulas, an enteral manganese intake of 1-15 µg/kg/d can be recommended. LOE 4, RG0

Iodine

Iodine is a trace element which is an integral part of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), which are essential for regulating and stimulating metabolism, temperature control and normal growth and development.

Iodine deficiency results in hypothyroidism, thyroid enlargement (goiter), mental retardation (cretinism), poor growth and increased neonatal and infant mortality.

In utero iodine deficiency causes irreversible damage to the developing fetal brain. Iodine deficiency in pregnant mothers, which occurs in areas where iodine deficiency is endemic, results in cretinism in the newborn. Cretinism is characterized by severe mental retardation, deafness, strabismus and motor spasticity. There is also some evidence that even moderate or mild iodine deficiency in pregnant women increases the risk of neurodevelopmental deficits in the offspring (54).

Salt iodisation programmes have meant that iodine deficiency is now rare in the US, Canada, Australia and also in many European countries. However, iodine deficiency is still relatively common in some European countries, e.g. France and Belgium, due to a low proportion of households using iodized salt (55).

Excessive iodine has a well-known inhibitory effect on thyroid hormone synthesis and release, also resulting in hypothyroidism. In hospitals where iodine is routinely used as a disinfectant, preterm infants can be exposed to high doses of topical iodine, which is absorbed through the skin and can result in mild or severe hypothyreosis (56). Hypothyroidism has also been described in a breast-fed preterm infant whose mother was exposed to topical iodine disenfectants (57). We therefore recommend to avoid the use of iodine containing antiseptics during care of preterm infants and their lactating mothers.

Iodine is effectively absorbed in the intestine; in healthy adults the absorption is >90 % and it is assumed to be high in term and preterm infants. Excretion of iodine occurs through the urine.

Urinary iodine in spot urine samples is often used to assess iodine status at a population level but it cannot be used to determine individual iodine status due to variation in urine production and hydration status.

In the newborn, thyroid stimulating hormone (TSH) in serum is a sensitive marker of iodine status. Serum T4 is often used, even though it is a less sensitive biomarker of iodine

nutrition status. It is well documented that many preterm infants have low serum T4 concentrations, especially those with a very low gestational age at birth and severe illness. It is unclear whether this transient hypothyreosis is caused by developmental changes or related to iodine nutritional status (58).

Average iodine concentration in European mothers' breast milk is 70-90 µg/L, corresponding to an intake of 12 µg/kg/d, assuming an intake of 150 ml/kg/d. Breast milk iodine concentrations in earlier US studies gave concentrations that were about twice as high but a recent, small study showed iodine content in US breast milks to be 33-117 µg/L (59).

Based on urinary iodine in healthy, iodine-sufficient newborns, it has been estimated that the mean daily iodine intake during the first week of life is 30-50 µg/day, suggesting that the iodine requirement in term newborns is 8-10 µg/kg/d (60).

A 3-day metabolic balance study of 29 preterm infants and 20 full term controls in Belgium showed that 40% of the preterm infants had a negative iodine balance even when iodine intake was 17-25 µg/100 kcal (61).

Roghan randomized 121 preterm infants with an average birth weight of 1.4 kg to receive preterm formula with standard (68 µg/L) or increased (272 µg/L) iodine concentrations, resulting in iodine intakes of 10-13 µg/kg/day vs 32-52 µg/kg/day (58). No significant difference was observed in TSH, T3, free T4 or total T4 up to term age, suggesting that the lower intake may be sufficient. Long-term effects on neurodevelopment were not assessed in this study, but were performed in the UK, where iodine deficiency is rare in the general population (36). Iodine-containing topical antiseptics were not used on the infants in this study.

Williams et al randomized 1273 preterm infants (< 31 wk) to iodine supplementation (30 µg/kg/day) or placebo from 1 day after birth to 34 postmenstrual weeks (62). The primary outcome was neurodevelopmental status at 2 years. There were no significant differences between intervention groups in Bayley score (cognitive, motor or language). Infants supplemented with iodine had higher TSH levels (but not T4 or TBG) than the placebo group. In a prespecified subgroup analysis of hypothyroxinemic infants (n=288), iodine supplemented infants had significantly higher scores in the Bayley Language Composite Score and its subtest score Receptive Communication. No adverse effects were observed.

The iodine intake in the placebo group was not measured but was assumed to be low (about 1-3 µg/kg/day).

A Cochrane meta-analysis from 2019 has concluded that there is currently no convincing evidence of beneficial clinical effects of iodine supplementation of preterm infants (63).

The previous recommendations according to ESPGHAN 2010 was 11-55 µg/kg/d (36).

There have been reports of clinical cases of iodine deficiency in patients receiving long term parenteral nutrition. A preterm infant with short bowel syndrome, was diagnosed with hypothyroidism due to iodine deficiency at 11 months of age. The infant was being fed almost exclusively parenteral nutrition and was receiving only chlorhexidine-based skin antisepsis after 3 months of age (64).

Conclusions

There is not enough conclusive evidence to change the previous recommendation. LOE 4.

Recommendations

An enteral iodine intake of 11-55 µg/kg/d is recommended. LOE 4, RG0

Chromium

Chromium is considered to be an essential nutrient, even though this has been challenged (65). Its proposed main role is to potentiate the action of insulin and thereby improve glucose tolerance through a mechanism which has not yet been elucidated.

There have been no clinical reports of chromium deficiency in term or preterm infants, or any reports of adverse effects of excessive chromium intakes from enteral or parenteral nutrition. There are isolated case reports of adult patients with long-term parenteral nutrition who have developed chromium deficiency but also some reports of high serum chromium concentrations in this patient group since parenteral nutrition solutions can be contaminated with chromium (66).

There is large variation between different studies with regard to reported chromium concentrations in breast milk, with mean concentrations ranging between 180-1000 ng/L. Even higher concentrations have been reported, but these may be caused by contamination

of samples. In previous reviews, a chromium concentration or 250-500 ng/L in breast milk has been assumed (20, 53).

Chromium concentrations in preterm formulas are generally much higher than in breast milk and have been reported to range between 7.5-22 µg/L (20).

Chromium is poorly bioavailable with intestinal absorption in adults being <2% (67). Urinary excretion is proportional to dietary intake (67).

There is some evidence from an observational study that early parenteral administration of chromium (0.2 µg/kg/day) improves glucose tolerance in newborns, especially very low birth weight infants (68).

Conclusions

There is insufficient scientific data upon which to base recommendations for chromium intake in preterm infants LOE 4.

There is no reason to change previous recommendations for enteral chromium intake in preterm infants of 0.1-2.25 µg/kg/d (53) or 0.03-1.23 µg /kg/d (36), which were based on the concentrations of chromium in breast milk and preterm formulas respectively. LOE 4

Recommendations

A chromium supply in the range of 0.03-2.25 µg/kg/d can be recommended as prudent. LOE 4, GPP.

Molybdenum

Molybdenum is an essential cofactor for several enzymes involved in oxidation and reduction, including xanthine oxidase, sulfite oxidase and aldehyde oxidase.

There is only a single report of molybdenum deficiency in humans; this was an adult patient receiving long-term parenteral nutrition without molybdenum who developed neurological symptoms and biochemical findings suggesting impaired metabolism of sulphur-containing amino acids, purines and pyrimidines. The biochemical abnormalities in this case were normalized after administration of molybdenum. There are no reports of molybdenum deficiency in children, including preterm infants.

Molybdenum has a very high bioavailability and > 90% of dietary molybdenum is absorbed in infants (69). Molybdenum homeostasis is regulated primarily by urinary excretion and a large proportion of absorbed molybdenum is excreted in the urine.

Balance studies in adults have suggested a minimum requirement of 25 µg/d, corresponding to 0.4 µg/kg/d (70).

Molybdenum concentrations in breast milk vary between mothers but the mean concentration is regarded to be approximately 2 µg/L (71), corresponding to an intake of 0.3 µg/kg/d, assuming an intake of 150 mL/kg/d. Molybdenum concentrations in preterm formulas are generally much higher than in breast milk, often between 20-30 µg/L (20), corresponding to an intake of 3-4.5 µg/kg/d.

There have been no randomized trials of different molybdenum intakes in preterm infants. Based on an observational balance study in 16 VLBW infants, Friel et al suggested that an enteral intake of 4-6 µg/kg/d or a parenteral intake of 1 µg/kg/d would be adequate (72). A stable isotope metabolic balance study in preterm infants by Sievers et al suggested that an intake of 3 µg/kg/d or lower may be sufficient (73).

Conclusions

There is no convincing evidence to change the previous recommendations. LOE 4.

Recommendations:

An enteral molybdenum intake of 0.3-5 µg/kg/d is recommended. RG0.

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