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ABM Clinical Protocol #29: Iron, Zinc, and Vitamin D Supplementation During Breastfeeding

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A central goal of The Academy of Breastfeeding Medicine is the development of clinical protocols, free from commercial interest or influence, for managing common medical problems that may impact breastfeeding success. These protocols serve only as guidelines for the care of breastfeeding mothers and infants and do not delineate an exclusive course of treatment or serve as standards of medical care. Variations in treatment may be appropriate according to the needs of an individual patient.

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Human milk is designed to deliver comprehensive nutrition through the first 6 months of age and complementary nutrition through the early years. However, micronutrient supplementation may be appropriate, especially when a mother is deficient or an infant has special needs such as prematurity. In contemporary high- and low-resource settings, concern has been raised regarding iron, zinc, and vitamin D status of human milk-fed infants. This protocol reviews the available evidence regarding iron, zinc, and vitamin D supplementation of the breastfeeding dyad. Quality of evidence (levels of evidence [LOE] IA, IB, IIA, IIB, III, and IV) is provided and based on levels of evidence used for the National Guidelines Clearing House.[1] From currently available evidence, recommendations are provided and areas for future study are identified. A brief summary of recommendations is presented first, followed by more in-depth discussion of the three micronutrients.

Recommendations

Iron

Iron supplementation is not required for the non-anemic breastfeeding mother. Iron supplementation to the 4-month-old full-term, exclusively breastfed infant is associated with improved hematological indices. However, the long-term benefit of improved hematologic indices at 4–6 months is not known. If iron supplementation is given before 6 months, it should be given as a 1 mg/kg/day distinct iron supplement until iron-fortified cereals (7–7.5 mg ferrous sulfate/day) or other iron-rich foods such as meat, tofu, beans, and others are initiated at 6 months of age with other complementary foods. (LOE IB)

Zinc

Zinc supplementation, above dietary intake, to the lactating mother or breastfeeding infant is not associated with improved outcomes and, therefore, is not recommended. (LOE IB)

Vitamin D

The breastfeeding infant should receive vitamin D supplementation shortly after birth in doses of 10–20 μg/day (400–800 IU/day) (LOE IB). This supplement should be cholecalciferol, vitamin D_3, because of superior absorption unless a vegetable source such as ergocaliferol vitamin D_2, is desired (LOE IIA). Randomized trials demonstrate that safe vitamin D supplementation may be provided to a nursing mother to achieve healthy vitamin D status in her breastfeeding infant, when there is objection or contraindication to direct infant supplementation. A maternal dose of 160 μg/day (6,400 IU/day) is suggested.

Iron

Background section

Iron is a mineral critical to infant somatic growth and neurodevelopment. It is most commonly recognized for its role in iron-deficiency anemia, but it importantly has direct effects on brain maturation. Iron deficiency during infancy is associated with poor cognitive and behavioral outcomes that may persist after iron repletion. Therefore, ensuring adequate iron stores in infancy is essential.

Infants born at term have transplacentally acquired hepatic iron stores that are mobilized and utilized over the first 4–6 months. Preterm infants, term infants born growth-restricted, and infants born to mothers with iron deficiency during pregnancy may have smaller iron stores. The iron in human milk has high bioavailability ($\sim$50%) to complement the infant's iron stores.[2] Research has investigated whether these two sources, fetal accretion and human milk iron concentration, provide adequate supply and for how long this supply

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alone is adequate. Studies have also examined the role of iron-containing or fortified complementary foods in protecting iron stores, especially in the second half of the first year when the fetal supply is diminished.

Iron is a pro-oxidant and some studies have shown supplemental iron to negatively affect immune function. In fact, iron may mitigate the antipathogenic actions of human milk.[3–5]

Iron-deficiency anemia is diagnosed by abnormal hematological values. Studies of iron supplementation in infants have used serum iron, ferritin, iron binding capacity, mean corpuscular volume (MCV), and hemoglobin as indicators of sufficient iron to avoid the risk of anemia. Other potential markers of adequate iron supplementation include anthropemetric growth and neurodevelopment. Randomized controlled trials (LOE IB) of iron supplementation to the lactating mother or to the infant have included serum and milk iron concentrations, ferritin and iron binding capacity, hematologic indices, growth, and neurodevelopment as outcomes.

There are few studies investigating iron supplementation directly to the breastfeeding mother to support infant iron status. One study recruited 168 healthy, nonanemic mothers in the first 10–20 postnatal days if they planned to exclusively breastfeed for at least 4 months. These mothers were randomized to receive 80 mg elemental iron daily or placebo. No difference was seen in maternal or infant iron studies, rate of iron-deficiency anemia, or infant growth. In the intervention group, both mother and infant had significantly increased serum iron binding capacity but the significance of this single difference is not known (LOE IB).[6]

When evaluating the evidence of direct infant supplementation, it is necessary to consider the age at which supplementation occurred—in the first 4 months, starting at 4–6 months, or starting at 6 months of age. Two small randomized controlled trials have evaluated iron supplementation initiated before 4 months of age. The first study included 77 term breastfed infants who were randomized to receive either 7.5 mg elemental iron as ferrous sulfate or placebo from 1 to 6 months of age (LOE IB).[7] At 6 months, the supplemented group had significantly higher hemoglobin (124 versus 116 g/L) and MCV (81 versus 77 fL). Forty-six of the 77 study subjects had neurodevelopmental assessment at 12–18 months; the intervention group exhibited higher Bayley psychomotor development indexes and visual acuity. No significant differences were seen in mental development indices.

A second study of early iron supplementation specifically focused on the term low birth weight (<2,500 g) infant. Healthy infants ($n = 62$) who were predominantly breastfed at 50–80 days were randomized to iron 3 mg/kg/day (25 mg Fe/mL ferric ammonia citrate) or placebo for 8 weeks (LOE IB).[8] Infant hemoglobin levels were significantly higher in the iron-supplemented group at 2 months of therapy (117 versus 107 g/L). No difference was found between groups in serum ferritin, infant growth, or morbidity. These two studies of early iron supplementation suggest that early iron may lead to higher hemoglobin levels, but the studies are too small to promote a specific recommendation for the breastfed term infant. Given small sample size and significant methodologic limitations, we cannot draw conculsions about the effect of early iron supplementation for term newborns on neurodevelopmental outcomes.

Large randomized controlled trials have examined iron supplementation at 4–9 months of age. Some studies have specifically compared iron initiation at 4 or 6 months. Others have compared iron drops and iron-fortified foods. In one study of 609 infants in Thailand, both iron and zinc supplementation were evaluated with initiation at 4–6 months. Infants receiving 10 mg iron as iron sulfate (with or without zinc) exhibited significantly higher hemoglobin and ferritin concentrations at 6 months of therapy compared with infants receiving only zinc or placebo. When controlling for gender and birth weight, infants receiving iron had significantly higher Ponderal weight growth and weight-for-length z-score (LOE IB).[9]

One double-blinded randomized placebo-controlled trial, occurring in Honduras and Sweden, evaluated iron supplementation alone. In this study, 232 near-exclusive or exclusively breastfeeding infants at 4 months of age were randomized to receive (1) placebo until 9 months of age, (2) placebo for 4–6 months followed by iron (1 mg/kg/day) for 6–9 months, or (3) iron (1 mg/kg/day) until at least 9 months.[10,11] The primary aim, to detect a difference in hemoglobin, was demonstrated for the infants receiving iron supplementation starting at 4 months. When iron supplementation started at 6 months, the infants in Honduras demonstrated significantly higher hemoglobin while the Swedish infants did not (LOE IB).[11] In evaluation of growth, the Swedish infants supplemented with iron had significantly lower length and head circumference gains than those infants receiving placebo from 4 to 9 months (LOE IB).[10] In Honduras, a negative effect on linear growth was evident at 4–6 months only among iron-sufficient infants (with an initial Hb ≥110 g/L). In addition, in both sites, iron supplementation increased the likelihood of diarrhea among iron-sufficient infants.

The question as to whether iron should be provided as a daily or weekly dose has been evaluated by one randomized trial without study blinding. No difference in iron deficiency or iron-deficiency anemia was observed with ferrous sulfate suspension dosed at 1 mg/kg daily, 7 mg/kg weekly, versus no supplement provided to breastfeeding infants at 4–10 months of age ($n = 79$) (LOE IB).[12]

Studies of whether iron should be provided as a distinct dose or instead through fortified cereal are open-label studies. In 2004 in Honduras, 4-month-old, exclusively breastfeeding infants were randomized to iron-fortified cereal or no cereal until 6 months of age (LOE IB).[13] In this study, infants who exhibited anemia at study initiation (58% of the iron-fortified group and 47% of exclusively breastfeeding group) also received iron drops. Of the infants who were not anemic at study initiation, those receiving iron-fortified cereal had significantly higher hemoglobin and lower prevalence of anemia than those exclusively breastfed. However, when analysis also included infants receiving iron drops for preexisting anemia, hemoglobin was higher in the exclusively breastfed group. This study raises concern that iron-fortified cereals may hinder the action of iron drops to improve hemoglobin.

Further study of iron-fortified cereal has occurred in the United States. The first study was an open-label randomized trial comparing iron drops (7–7.5 mg ferrous sulfate/day), iron-fortified cereal (7–7.5 mg ferrous sulfate/day), and no intervention from 4 to 9 months of age in 93 infants who were exclusively breastfeeding at 1 month (LOE IB).[14] In this

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study, the group with no intervention demonstrated significantly lower plasma ferritin concentrations throughout the intervention period and up to 15 months of age. There was no significant difference in serum ferritin levels between the group receiving iron drops and iron-fortified cereal. The iron-fortified cereal was well tolerated. Of interest, the infants receiving iron drops demonstrated significantly lower length growth during the intervention, although this difference dissipated in the second year. Further study of iron-fortified cereal compared electrolytic iron (54.5 mg Fe/100 g cereal) and ferrous fumarate (52.2 mg Fe/100 g cereal) from 4 to 9 months and demonstrated no difference in iron deficiency or iron-deficiency anemia between groups ($n = 95$) (LOE IB).[15]

One further randomized controlled trial evaluated whether iron supplementation of the breastfeeding infant at 4–9 months of age had an effect on copper status and showed that infants receiving iron supplementation had significantly lower copper-zinc oxide dismutase when compared with controls at 9 months. In addition to the negative effect on growth parameters exhibited in the iron supplementation trials mentioned previously, this potential negative effect on copper status warrants further investigation.[16]

Both the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the American Academy of Pediatrics (AAP) have reviewed the existing literature up to 2014 and 2010, respectively, and have published a position article or clinical report, respectively.[17,18] ESPGHAN reports that ''there is insufficient evidence to support general iron supplementation of healthy European infants and toddlers of normal birth weight.'' In contrast, the AAP Committee on Nutrition concludes that breastfeeding infants should be ''supplemented with 1 mg/kg per day of oral iron beginning at 4 months of age until appropriate iron-containing complementary foods (including iron containing cereals) are introduced in the diet.'' Of note, when the AAP Section on Breastfeeding reviewed the evidence, they concluded that studies demonstrating benefit of iron supplementation before 6 months of age were inadequate both in number and in the clinical importance of the outcomes.[19]

In summary of the literature regarding direct infant supplementation, two small studies demonstrate potential for hematologic and neurodevelopmental benefit with supplementation as early as 1 month of age. Specifically, one small study of 77 term breastfed newborns who were supplemented at some time between 1 and 6 months of age showed improved psychomotor, but not cognitive, development at 13 months. Larger studies with initiation of iron supplementation at 4 or 6 months of age demonstrate improved hematologic indices. Both iron drops and iron-fortified cereal appear to increase laboratory indices of iron deficiency and iron-deficiency anemia but, when given together, the fortified cereal may hinder the action of the drops. Of note, iron supplementation is not only associated with improved weight for length measurements but also shows a negative association with both length and head circumference parameters.

Recommendations

Iron supplementation is not required for the nonanemic breastfeeding mother. Iron supplementation to the 4-month-old full-term, exclusively breastfed infant is associated with improved hematological indices. However, the long-term benefit of improved hematologic indices at 4–6 months is not known. There are potential harms of iron supplementation, especially on immune function and in possibly decreasing the bioavailability of iron contained in human milk. In addition, there is potential harm in infant growth and morbidity when iron supplementation is provided to iron-sufficient infants. If iron supplementation is given before 6 months, it should be given as a 1 mg/kg/day distinct iron supplement until iron-fortified cereals (7–7.5 mg ferrous sulfate/day) or other iron-rich foods such as meat, tofu, beans, and the like are initiated at 6 months of age with other complementary foods. (LOE IB)

Recommendations for future research

Future research is essential to evaluate the neurodevelopmental outcomes associated with iron supplementation. Moreover, the process of delayed cord clamping at birth may also have significant effects on iron stores.[20,21] Other areas of potential evaluation include earlier supplementation (as early as one postnatal month), the potential for positive or negative effects on growth, potential for negative effects on immune function, and potential for positive or negative effect on the homeostasis of other minerals such as zinc and copper.

Zinc

Background section

Zinc is involved in many functions of human health including enzymatic; cell differentiation; protein, lipid, and carbohydrate metabolism; gene transcription; and immunity. Zinc deficiency is associated with growth failure and increased susceptibility to infection and skin inflammation, diarrhea, alopecia, and behavioral disturbances. Randomized controlled trials (LOE IB) of zinc supplementation to lactating mothers or to infants have evaluated serum and milk zinc concentrations, growth, infection, neurodevelopment, hematologic indices, and copper levels as outcomes.

A blinded randomized controlled trial of zinc supplementation (zinc sulfate 10 mg/day) to lactating mothers demonstrated increased maternal zinc concentrations and increased milk zinc concentrations[22] (LOE IB). In contrast, another study of supplementation of mothers with preterm infants with 50 mg/day zinc chelate showed no difference in maternal serum zinc levels (LOE IIA).[23] Neither study showed a difference in infant zinc levels or in infant growth when compared with infants whose mothers did not receive zinc supplementation.[22,23]

Double-blind randomized controlled trials of direct zinc supplementation to the breastfed infant in Thailand have evaluated 4–10 month-old infants receiving 5 mg elemental zinc sulfate for 10 months[24] (LOE IB) and 4–6 month old infants receiving 10 mg zinc either with or without iron for 6 months (LOE IB).[9] Of note, these infants also received complementary foods. Wasantwisut et al. studied infants who received zinc alone and demonstrated significantly higher zinc levels than those who received iron alone (no zinc) (LOE IB).[9] In both studies, no difference in growth was observed. The Heinig et al. study that also monitored for diarrhea, otitis media, respiratory illness, fever, total illness, and motor development found no difference between groups.[24]

Of note, though only case series are published, infant zinc deficiency has been reported in breastfeeding infants. This

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rare disorder is called Transient Neonatal Zinc Deficiency and is due to a maternal mutation in the zinc transporter gene.[25,26] When a breastfeeding infant develops zinc deficiency, mother should be evaluated for this rare genetic disorder.

Recommendations

Zinc supplementation, above dietary intake, to the lactating mother or breastfeeding infant is not associated with improved outcomes and, therefore, is not recommended. (LOE IB)

Recommendations for future research

Evidence regarding the role of zinc in susceptibility to infection or in the severity of infection requires further investigation in the breastfed infant population. Studies specifically evaluating these health outcomes, and studies in populations at risk for deficiency or at increased risk for infection, such as preterm infants, are warranted.

Vitamin D

Background

Vitamin D is a hormone involved in calcium absorption, bone mineralization, and immune function. In its most severe form, vitamin D deficiency appears as rickets—bony abnormalities including bowed legs, splayed wrists, and associated muscle weakness. In the past three decades, both high and low resource countries have experienced a resurgence in rickets associated with dark skin pigmentation, living at higher latitude, practices of body covering, and exclusive breastfeeding.[27] The breast milk of a mother receiving a vitamin D dose of 10 μg/day (400 IU/day) will contain ~80 IU/L, thereby putting her infant at risk for vitamin D deficiency.[28] Vitamin D supplementation is therefore routinely recommended for the breastfeeding infant.

Vitamin D deficiency currently is defined by the Institute of Medicine and ESPGHAN as a 25-hydroxyvitamin D [25(OH)D] concentration less than 50 nmol/L (20 ng/mL).[29,30] Some authors choose to define vitamin D sufficiency, the threshold associated with optimal function of vitamin D-dependent processes. Vitamin D sufficiency definitions range from 75 to 110 nmol/L (30–44 ng/mL) based mostly on studies in the adult population. Further investigation defining vitamin D sufficiency for infants is warranted.

Recent research has investigated the vitamin D needs of both mother and infant, seeking to identify a maternal vitamin D dose that is both efficacious and safe for mother and infant. The majority of randomized trials have compared the vitamin D levels, as measured by 25(OH)D, achieved by specific doses. Additionally, studies have evaluated whether a vitamin D dose is associated with avoidance of vitamin D deficiency. A few trials have measured infant bone health as an outcome.

Randomized trials of direct supplementation to the exclusively breastfeeding infant have compared doses up to 40 μg/day (1,600 IU/day). Some of these studies have a placebo arm. Others provide at least 5 μg/day (200 IU/day) vitamin D. One study compared the efficacy of vitamin D_2 or ergocalciferol (from plants) and vitamin D_3 or cholecalciferol (from animals) given as 10 μg/day (400 IU/day) to 52, 1 month-old, breastfeeding infants for 3 months. The change in 25(OH)D levels from baseline to study end was not significantly different between groups (change of 56 and 44 nmol/L, respectively). However, 25% of the infants in the vitamin D_2 group and only 4% of infants in the vitamin D_3 exhibited vitamin D deficiency after 3 months (LOE IB).[31]

Randomized trials with a true placebo control have evaluated doses of 5 μg/day (200 IU/day) in Korea and 10 μg/day (400 IU/day) in Italy. In the study of 5 μg/day (200 IU/day), the supplemented infants demonstrated significantly higher mean 25(OH)D status at both 6 and 12 months. However, lumbar spine bone mineral density was not significantly different between groups (LOE IIA).[32] In the study of 10 μg/day (400 IU/day), bone strength was measured by ultrasound and found to be significantly higher in vitamin D supplemented group (LOE IIA).[33] Of note, the utility of ultrasound measurement of bone strength has not been established.

Randomized trials without a true placebo have compared 5, 10, 15, and 20 μg/day (200, 400, 600, and 800 IU/day);[34] 10, 20, 30, and 40 μg/day (400, 800, 1,200, and 1,600 IU/day);[35] and 6.25 and 12.5 μg/day (125 and 250 IU/day).[36] For the comparison of 6.25 and 12.5 μg/day (125 and 250 IU/day) in Greece, no significant difference in vitamin D outcomes was observed (LOE IB).[36] For the comparison of 5 up to 20 μg/day (200 up to 800 IU/day) beginning at one postnatal month and continued for 9 months, at the end of winter (average of 7 months of therapy) in the United States, the four doses achieved mean serum 25(OH)D levels ranging 78 to 107 nmol/L and were not significantly different. Of note, the infants receiving 20 μg/day (800 IU/day) had no vitamin D deficiency through the study time period (LOE IB).[34] In the double-blind randomized trial of doses ranging from 10 to 40 μg/day (400 to 1,600 IU/day), 97% of infants in all dose groups achieved 25(OH)D >50 nmol/L by 3 months of age (LOE IB).[35] The study's primary aim for 97.5% of infants to achieve 25(OH)D >75 nmol/L was only achieved by the 40 μg/day (1,600 IU/day) group. However, this dosing was discontinued early due to concern that the 25(OH)D levels achieved were too high. Additionally, no difference in bone mineral content was seen between dosing groups during the study or at 3 years of age.[35,37]

In addition to study of direct infant supplementation with vitamin D, recent investigation has focused on methods to provide vitamin D to the infant by supplementing the mother and thereby augmenting the level of vitamin D in her breast milk. These studies have addressed the question—is there a maternal vitamin D dose that is efficacious and safe for both the mother and infant? Two studies, based on previous research,[28,38] were designed and performed to address this question. One randomized, blinded clinical trial compared maternal intake of 10, 60, and 160 μg/day (400, 2,400, and 6,400 IU/day) in 334 mother/infant dyads.[39] For the group with maternal dose of 10 μg/day (400 IU/day), the infant also received 10 μg/day (400 IU/day). For the other two groups, no vitamin D was provided to the infant. The maternal 60 μg/day (2,400 IU/day) dose group was discontinued early due to vitamin D deficiency in the infant, demonstrating that maternal 60 μg/day (2,400 IU/day) was not sufficient to provide adequate vitamin D to the breastfeeding infant. In the remaining two dose groups, 148 mothers were exclusively breastfeeding at 4 months and 95 at 7 months. At both visits, for the mothers receiving 160 μg/day (6,400 IU/day),

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the infants' mean 25(OH)D status was similar to the status of infants receiving 10 μg/day (400 IU/day) directly (at 7 months, 109 nmol/L in each group). Mothers in the 160 μg/day (6,400 IU/day) group had significantly higher 25(OH)D levels than mothers in the 10 μg/day (400 IU/day) group (151.2 and 79 nmol/L, respectively). No vitamin D toxicity was observed.

A second study to address maternal supplementation to achieve vitamin D-replete milk compared maternal and infant vitamin D status for 28 days with either a daily oral dose of 125 μg/day (5,000 IU/day) or a one-time oral dose of 3,750 μg (150,000 IU). In both groups, the 40 infants achieved mean 25(OH)D levels of 97.5 nmol/L. For mothers, the 3,750 μg (150,000 IU) group, demonstrated a mean peak 25(OH)D concentration of 125 nmol/L on day 3. At day 28, mothers receiving the 3,750 μg (150,000 IU) dose and those receiving 125 μg/day (5,000 IU/day) exhibited mean 25(OH)D of 103 and 110 nmol/L, respectively. Vitamin D status remained in the normal range for all mothers in the study. However, four mothers in the one-dose group and three mothers in the daily-dose group demonstrated urinary calcium excretion above the acceptable range defined by the study.[40]

One further study evaluated the effect of maternal supplementation initiated in pregnancy (13–24 weeks' gestation) in 100 women who exclusively breastfed through 8 weeks.[41] With maternal doses of 10, 25, and 50 μg/day (400, 1,000, 2,000 IU/day), rates of infant vitamin D deficiency (<50 nmol/L) at 8 weeks were 59%, 48%, and 13%, respectively. This study demonstrates improved vitamin D status with maternal supplementation, but, as observed in the previous dose of 60 μ/day (2,400 IU/day),[39] 50 μg/day (2,000 IU/day) may not be an adequate maternal dose to avoid vitamin D deficiency in all infants.

In summary, randomized trials have not shown a specific dose of vitamin D, to the breastfeeding infant, to be associated with optimal bone mineralization. Therefore, vitamin D supplementation recommendations are based on the amount of supplementation needed to achieve an infant 25(OH)D >50 nmol/L, the level associated with a reduced risk of rickets. In studies evaluating the ability of infant vitamin D dosing to achieve 25(OH)D >50 nmol, one study in the United States in winter found a dose of 20 μg/day (800 IU/day) to achieve this goal. In a second study in Canada, avoidance of vitamin D deficiency was achieved only with the 40 μg/day (1,600 IU/day) dose, but this dose also was associated with abnormally high vitamin status as defined by the authors.

For vitamin D supplementation of mother to provide vitamin D in her milk to achieve adequate vitamin D status in the infant, a maternal dose of 160 μg/day (6,400 IU/day) maintained adequate status in the infant for 7 months and maternal doses of 125 μg/day (5,000 IU/day) and a single dose of 3,750 μg (150,000 IU) maintained infant status for 28 days. Maternal doses as high as 60 μg/day (2,400 IU/day) were not adequate to support the infant. This research demonstrates the ability for mother's milk to be replete with vitamin D with adequate supplementation to mother.

Recommendations

The breastfeeding infant should receive vitamin D supplementation for a year, beginning shortly after birth in doses of 10–20 μg/day (400–800 IU/day) (LOE IB). This supplement should be cholecalciferol, vitamin D_3, because of superior absorption unless a vegetable source such as ergocaliferol vitamin D_2, is desired (LOE IIA).

Randomized trials demonstrate that safe vitamin D supplementation may be provided to a nursing mother to achieve healthy vitamin D status in her breastfeeding infant, when there is objection or contraindication to direct infant supplementation. Current studies point to 160 μg/day (6,400 IU/day) for 7 months and 125 μg/day (5,000 IU/day) for 28 days or 3,750 μg (150,000 IU) in a single dose (lasting at least 28 days) as appropriate to achieve 25(OH)D status in the normal range for both mother and infant (LOE IB), although infant outcomes beyond those time periods were not evaluated. Data are lacking as to which option, infant versus mother supplementation, may result in greater maternal adherence to recommendations.

Recommendations for future research

The amount of vitamin D supplementation required to avoid vitamin D deficiency likely varies due to differences in baseline vitamin D status and sun exposure in populations around the world. Further study to assess the role of skin pigmentation, seasons, latitude, and sun exposure to ensure healthy vitamin D status for all populations is warranted. Currently, the 25(OH)D status associated with toxicity is not defined. Identifying this upper limit of healthy vitamin D status is critical to future research. In addition, identifying infant vitamin D sufficiency, the 25(OH)D status associated with optimal outcomes, is needed. Further research is also needed to determine the extent to which maternal vitamin D supplementation will produce levels of Vitamin D in human milk that meet infant needs.

Preterm Infants

Preterm infants are known to be deficient in zinc and iron compared with term-born infants. Their vitamin D status at birth is similar to term infants, but, like term infants, they require vitamin D supplementation. Human milk fortifier delivers zinc, vitamin D, and sometimes iron. Randomized controlled trials specific to the human milk-fed preterm infants are mostly studies of multi-component fortifier, including zinc and vitamin D, and demonstrate improved infant weight and length gain, head growth, and neurodevelopmental outcome.[42] Further research is required, but, at this point, AAP and World Health Organization recommendations for iron (2–4 mg/kg/day) and vitamin D supplementation (at least 400–800 IU/day) and also supplementation with a zinc-containing fortifier should be followed.[18,43–45] Routine iron and vitamin D supplementation for the late preterm infant is also recommended.[46]

Summary

Current evidence points to sufficiency in iron, zinc, and vitamin D for the exclusively breastfeeding infant in the first 6 months when mother is sufficient in these nutrients. Current research shows that human milk delivers adequate zinc and iron at least through the first 4–6 months. The need for supplemental iron may overlap with the introduction of iron-containing foods at 6 months, but current published studies demonstrate that initiating iron drops at 4 months is

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associated with better hematological outcomes. However, it is not clear that universal direct iron supplementation starting at 4 months and continued until receiving iron-containing feeds should be considered. For zinc, human milk delivers a sufficient supply. Vitamin D also may be delivered adequately through human milk. Maternal vitamin D deficiency is common enough, however, that routine supplementation is recommended for the breastfeeding infant. The randomized controlled trials described in this protocol demonstrate that this risk is mitigated by maternal vitamin D supplementation at a dose that is both safe for her and efficacious for the infant.

References

1. Shekelle PG, Woolf SH, Eccles M, et al. Clinical guidelines: Developing guidelines. *BMJ* 1999;318:593–596.
2. Saarinen UM, Siimes MA, Dallman PR. Iron absorption in infants: High bioavailability of breast milk iron as indicated by the extrinsic tag method of iron absorption and by the concentration of serum ferritin. *J Pediatr* 1977;91: 36–39.
3. Chan GM. Effects of powdered human milk fortifiers on the antibacterial actions of human milk. *J Perinatol* 2003;23: 620–623.
4. Ovali F, Ciftci I, Cetinkaya Z, et al. Effects of human milk fortifier on the antimicrobial properties of human milk. *J Perinatol* 2006;26:761–763.
5. Campos LF, Repka JC, Falcao MC. Effects of human milk fortifier with iron on the bacteriostatic properties of breast milk. *J Pediatr* 2013;89:394–399.
6. Baykan A, Yalcin SS, Yurdakok K. Does maternal iron supplementation during the lactation period affect iron status of exclusively breast-fed infants? *Turk J Pediatr* 2006;48:301–307.
7. Friel JK, Aziz K, Andrews WL, et al. A double-masked, randomized control trial of iron supplementation in early infancy in healthy term breast-fed infants. *J Pediatr* 2003; 143:582–586.
8. Aggarwal D, Sachdev HP, Nagpal J, et al. Haematological effect of iron supplementation in breast fed term low birth weight infants. *Arch Dis Child* 2005;90:26–29.
9. Wasantwisut E, Winichagoon P, Chitchumroonchokchai C, et al. Iron and zinc supplementation improved iron and zinc status, but not physical growth, of apparently healthy, breast-fed infants in rural communities of northeast Thailand. *J Nutr* 2006;136:2405–2411.
10. Dewey KG, Domellof M, Cohen RJ, et al. Iron supplementation affects growth and morbidity of breast-fed infants: Results of a randomized trial in Sweden and Honduras. *J Nutr* 2002;132:3249–3255.
11. Domellof M, Cohen RJ, Dewey KG, et al. Iron supplementation of breast-fed Honduran and Swedish infants from 4 to 9 months of age. *J Pediatr* 2001;138:679–687.
12. Yurdakok K, Temiz F, Yalcin SS, et al. Efficacy of daily and weekly iron supplementation on iron status in exclusively breast-fed infants. *J Pediatr Hematol Oncol* 2004;26: 284–288.
13. Dewey KG, Cohen RJ, Brown KH. Exclusive breast-feeding for 6 months, with iron supplementation, maintains adequate micronutrient status among term, low-birthweight, breast-fed infants in Honduras. *J Nutr* 2004;134:1091–1098.
14. Ziegler EE, Nelson SE, Jeter JM. Iron status of breastfed infants is improved equally by medicinal iron and iron-fortified cereal. *Am J Clin Nutr* 2009;90:76–87.
15. Ziegler EE, Fomon SJ, Nelson SE, et al. Dry cereals fortified with electrolytic iron or ferrous fumarate are equally effective in breast-fed infants. *J Nutr* 2011;141:243–248.
16. Domellof M, Dewey KG, Cohen RJ, et al. Iron supplements reduce erythrocyte copper-zinc superoxide dismutase activity in term, breastfed infants. *Acta Paediatr* 2005;94: 1578–1582.
17. Domellof M, Braegger C, Campoy C, et al. Iron requirements of infants and toddlers. *J Pediatr Gastroenterol Nutr* 2014;58:119–129.
18. Baker RD, Greer FR. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics* 2010;126:1040–1050.
19. AAP Section on Breastfeeding SREC, Feldman-Winter L, Landers S, Noble L, Szucs KA, Viehmann L. Concerns with early universal iron supplementation of breastfeeding infants. *Pediatrics* 2011;127:e1097.
20. Committee on Obstetric Practice. Committee opinion no. 684: Delayed umbilical cord clamping after birth. *Obstet Gynecol* 2017;129:e5–e10.
21. McDonald SJ, Middleton P, Dowswell T, et al. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2013:Cd004074.
22. Shaaban SY, AzizEl-Hodhod MA, Nassar MF, et al. Zinc status of lactating Egyptian mothers and their infants: Effect of maternal zinc supplementation. *Nutr Res* 2005;25: 45–53.
23. de Figueiredo CS, Palhares DB, Melnikov P, et al. Zinc and copper concentrations in human preterm milk. *Biol Trace Elem Res* 2010;136:1–7.
24. Heinig MJ, Brown KH, Lonnerdal B, et al. Zinc supplementation does not affect growth, morbidity, or motor development of US term breastfed infants at 4–10 mo of age. *Am J Clin Nutr* 2006;84:594–601.
25. Krieger I, Alpern BE, Cunnane SC. Transient neonatal zinc deficiency. *Am J Clin Nutr* 1986;43:955–958.
26. Miletta MC, Bieri A, Kernland K, et al. Transient neonatal zinc deficiency caused by a heterozygous G87R mutation in the zinc transporter ZnT-2 (SLC30A2) gene in the mother highlighting the importance of Zn (2+) for normal growth and development. *Int J Endocrinol* 2013;2013:259189.
27. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest* 2006;116:2062–2072.
28. Hollis BW, Wagner CL. Vitamin D requirements during lactation: High-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. *Am J Clin Nutr* 2004;80(6 Suppl):1752s–1758s.
29. Review Institute of Medicine (US) Committee. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press (US), 2011.
30. Braegger C, Campoy C, Colomb V, et al. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr* 2013;56:692–701.
31. Gallo S, Phan A, Vanstone CA, et al. The change in plasma 25-hydroxyvitamin D did not differ between breast-fed infants that received a daily supplement of ergocalciferol or cholecalciferol for 3 months. *J Nutr* 2013;143:148–153.
32. Kim MJ, Na B, No SJ, et al. Nutritional status of vitamin D and the effect of vitamin D supplementation in Korean breast-fed infants. *J Korean Med Sci* 2010;25:83–89.
33. Bagnoli F, Casucci M, Toti S, et al. Is vitamin D supplementation necessary in healthy full-term breastfed infants?

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A follow-up study of bone mineralization in healthy full-term infants with and without supplemental vitamin D. *Minerva Pediatr* 2013;65:253–260.
34. Ziegler EE, Nelson SE, Jeter JM. Vitamin D supplementation of breastfed infants: A randomized dose-response trial. *Pediatr Res* 2014;76:177–183.
35. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: A randomized trial. *JAMA* 2013;309:1785–1792.
36. Siafarikas A, Piazena H, Feister U, et al. Randomised controlled trial analysing supplementation with 250 versus 500 units of vitamin D3, sun exposure and surrounding factors in breastfed infants. *Arch Dis Child* 2011;96:91–95.
37. Gallo S, Hazell T, Vanstone CA, et al. Vitamin D supplementation in breastfed infants from Montreal, Canada: 25-hydroxyvitamin D and bone health effects from a follow-up study at 3 years of age. *Osteoporos Int* 2016;27:2459–2466.
38. Wagner CL, Hulsey TC, Fanning D, et al. High-dose vitamin D3 supplementation in a cohort of breastfeeding mothers and their infants: A 6-month follow-up pilot study. *Breastfeed Med* 2006;1:59–70.
39. Hollis BW, Wagner CL, Howard CR, et al. Maternal versus infant vitamin D supplementation during lactation: A randomized controlled trial. *Pediatrics* 2015;136:625–634.
40. Oberhelman SS, Meekins ME, Fischer PR, et al. Maternal vitamin D supplementation to improve the vitamin D status of breast-fed infants: A randomized controlled trial. *Mayo Clin Proc* 2013;88:1378–1387.
41. March KM, Chen NN, Karakochuk CD, et al. Maternal vitamin D(3) supplementation at 50 mug/d protects against low serum 25-hydroxyvitamin D in infants at 8 wk of age: A randomized controlled trial of 3 doses of vitamin D beginning in gestation and continued in lactation. *Am J Clin Nutr* 2015;102:402–410.
42. Brown JV, Embleton ND, Harding JE, et al. Multi-nutrient fortification of human milk for preterm infants. *Cochrane Database Syst Rev* 2016:Cd000343.
43. Wagner CL, Greer FR. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics* 2008;122:1142–1152.
44. Noble L, Okogbule-Wonodi A, Young M. ABM Clinical Protocol #12: Transitioning the breastfeeding preterm infant from the neonatal intensive care unit to home, revised 2018. *Breastfeed Med* 2018;13:230–236.
45. WHO Guidelines Approved by the Guidelines Review Committee. In: Guideline: Daily Iron Supplementation in Infants and Children. Geneva: World Health Organization; Copyright (c) World Health Organization 2016; 2016.
46. Boies E, Vaucher Y. ABM Clinical Protocol #10: Breastfeeding the late preterm (34–36 6/7 weeks of gestation) and early term infants (37–38 6/7 weeks of gestation), second revision 2016. *Breastfeed Med* 2016;11:494–500.

ABM protocols expire 5 years from the date of publication. The content of this protocol is up-to-date at the time of publication. Evidence-based revisions are made within 5 years or sooner if there are significant changes in the evidence.

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