

[Review article]

**Breastfeeding and vitamin D**

**Running title:** Breastfeeding and vitamin D

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## **Abstract**

The recent re-emergence of vitamin D deficiency (VDD) and rickets among breastfed infants without adequate sunlight exposure and vitamin D supplementation has been reported worldwide. Breastfed infants are particularly vulnerable to VDD because of the low vitamin D content of breast milk, restricted sunlight exposure, increased pollution, and limited natural dietary sources of vitamin D. The prevalence of VDD in breastfed infants differs vastly between studies and nations at 0.6–91.1%. The recommended intake of vitamin D for lactating mothers to optimize their overall vitamin D status and, consequently, of their breast milk is 200–2000 IU/day, indicating a lack of consensus. Some studies have suggested that maternal high-dose vitamin D supplementation (up to 6400 IU/day) can be used as an alternate strategy to direct infant supplementation. However, concern persists about the safety of maternal high-dose vitamin D supplementation. Direct infant supplementation is the currently available option to support vitamin D status in breastfed infants. The recommended dose for vitamin D supplementation in breastfed infants according to various societies and organizations worldwide is 200–1200 IU/day. Most international guidelines recommend that exclusively or partially breastfed infants be supplemented with 400 IU/day of vitamin D during their first year of life. However, domestic studies on the status and guidelines for vitamin D in breastfed infants are insufficient. This review summarizes the prevalence of VDD in breastfed infants, vitamin D content of breast milk, and current guidelines for vitamin D supplementation of lactating mothers and infants to prevent VDD in breastfed infants.

**Keywords:** Vitamin D, Breastfeeding, Infant

## **Key Message**

- Exclusively breastfed infants are at risk of developing vitamin D deficiency associated with hypocalcemia, rickets, and various health outcomes.
- The prevalence of vitamin D deficiency in breastfed infants differs vastly between studies and nations at 0.6–91.1%.
- The vitamin D content of breast milk does not meet the requirements of exclusively breastfed infants.
- Most international guidelines recommend that breastfed infants be supplemented with 400 IU/day of vitamin D during the first year of life.
- Vitamin D intake (milk+supplements) of 800 IU/day can be considered in preterm infants along with biochemical monitoring.

## Introduction

Vitamin D (calciferol), a fat-soluble steroid hormone, is important for regulating calcium homeostasis and bone health.<sup>1)</sup> Moreover, the importance of vitamin D is emphasized as evidence supports an association between vitamin D and other health outcomes, such as immune function, respiratory diseases, allergy, olfactory function, cardiovascular diseases, obesity, insulin resistance, and cancer in pediatric and adolescent populations.<sup>2-24)</sup>

Vitamin D exists in two forms: vitamin D<sub>3</sub> (cholecalciferol), the mammalian form; and vitamin D<sub>2</sub> (ergocalciferol), the fungal form.<sup>25)</sup> In vivo, vitamin D<sub>3</sub> can be synthesized in the epidermis through photochemical transformation of 7-dihydrocholesterol after exposure to ultraviolet radiation B (wavelength 280–320 nm) energy.<sup>26-29)</sup> Vitamin D<sub>2</sub> and D<sub>3</sub> can also be obtained through dietary intake; both follow the same metabolic pathways, and their actions are qualitatively similar.<sup>30)</sup> Vitamin D is converted by 25-hydroxylase to 25-hydroxyvitamin D [25(OH)D] in the liver and further metabolized to the biologically active form 1,25-dihydroxyvitamin D through 1 $\alpha$ -hydroxylation action in the kidney. Sunlight exposure often has a major influence on vitamin D status, accounting for over 90% of its level.<sup>31)</sup> However, skin synthesis of vitamin D is negatively influenced by a dark skin color, living in northern latitudes during winter, use of sunscreen with a high Sun Protection Factor, body covering, air pollution, and staying indoors for much of the day.<sup>32,33)</sup> In comparison, the dietary intake of vitamin D, in addition to fortified foods, has little impact on an individual's overall vitamin D status.<sup>33)</sup>

Breast milk is an important source of energy and nutrients for children until 2 years of age. To ensure optimal infant growth, development, and health, the World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life and the introduction of nutritionally adequate and safe complementary foods at 6 months together with continued

breastfeeding up to 2 years of age or beyond.<sup>34)</sup> However, human milk typically contains a small amount of vitamin D (approximately  $\leq 25\text{--}50$  IU/L),<sup>1,25,35)</sup> and the concentration is affected by the lactating mother's vitamin D status and season.<sup>36,37)</sup> It is well known that a smaller amount of vitamin D is supplied to infants by lactating mothers with vitamin D deficiency (VDD). Therefore, exclusively breastfed infants are more likely to develop VDD, resulting in hypocalcemia and rickets if sunlight exposure is limited.<sup>30,38)</sup> Vitamin D plays an important role in bone mineralization as well as the regulation of skeletal muscle function and the immune, nervous, and cardiovascular systems.<sup>39-42)</sup> Therefore, it is very important to maintain an appropriate vitamin D level while continuing to breastfeed.

This review aims to examine the relationship between breastfeeding and vitamin D and review guidelines for vitamin D supplementation in lactating mothers and infants to prevent VDD in breastfed infants.

### **Definition of deficiency, insufficiency, and sufficiency of vitamin D**

In the blood, 25(OH)D has a long half-life of 2–3 weeks and does not need to be strictly controlled to maintain homeostasis. Therefore, it is a good indicator of the level of vitamin D intake (cutaneous synthesis and dietary intake).<sup>36,43)</sup> On the other hand, 1,25-dihydroxyvitamin D has a short half-life of 5–8 h and is always maintained at a constant blood level in healthy people.<sup>44)</sup> The use of serum levels of 1,25-dihydroxyvitamin D is limited to monitoring certain conditions, such as acquired and inherited disorders of vitamin D and phosphate metabolism.<sup>45)</sup> Guidelines for VDD/insufficiency/sufficiency defined by serum 25(OH)D concentrations have been published by many societies in many countries.<sup>25,30,32,33,45-51)</sup> These guidelines are summarized in Table 1. According to published guidelines, a 25(OH)D level of  $\leq 12\text{--}20$  ng/mL is deficient, while a level of  $\geq 20\text{--}30$  ng/mL is sufficient.

In South Korea, there are no consensus guidelines regarding the definition of VDD/insufficiency or sufficiency based on 25(OH)D levels. In the 2020 Dietary Reference Intakes (DRIs) for Koreans, the optimal 25(OH)D level for bone health was determined to fall within the range that minimizes parathyroid hormone secretion and maximizes calcium absorption.<sup>36)</sup> Based on previous studies, a 25(OH)D level of 20–30 ng/mL is considered the cut-off level that satisfies these conditions.<sup>52,53)</sup> The clinical guidelines of the Korean Society of Pediatric Endocrinology do not recommend additional vitamin D supplementation when the 25(OH)D level is greater than 20 ng/mL.<sup>54)</sup> However, there are insufficient domestic data to support this suggestion.

### **Vitamin D status of breastfed infants**

There are increasing reports of VDD among breastfed infants who do not receive vitamin D supplementation.<sup>55)</sup> The vitamin D statuses of exclusively or nearly exclusively breastfed infants and their mothers are shown in Table 2. The prevalence of VDD differs greatly between studies and nations at 0.6–91.1%.<sup>56-66)</sup> Among these studies, 7 (63.6%) reported a prevalence of VDD of 50% or higher in breastfed infants. A prevalence as high as 83% was reported among 1-month-old infants in Qatar despite the region having abundant sunshine.<sup>61)</sup> One study in India reported a prevalence of VDD of 91.1% among 6-month-old infants who were not on vitamin D supplementation.<sup>58)</sup> VDD in infants exclusively breastfed without vitamin D supplementation and sufficient sun exposure is a major cause of nutritional rickets, with a high prevalence in North America, South America, Europe, and parts of the Middle East.<sup>67)</sup>

In South Korea, a few studies have reported on the vitamin D status of breastfed infants (Table 2).<sup>68-71)</sup> The prevalence of VDD varied among the studies according to definitions of VDD. In studies conducted before 2010, VDD was defined as a 25(OH)D level of <11 ng/mL. Park et

al. found that the prevalence of VDD was 44% among breastfed infants, higher than the 6% among formula-fed infants.<sup>71)</sup> Kim et al. reported that concentrations of vitamin D were measured at 0, 6, and 12 months.<sup>70)</sup> Among breastfed infants without supplementation, the prevalence of VDD gradually decreased from birth (26.9%) to 12 months of age (0%). In studies published after 2013, however, the prevalence of VDD increased up to 81–90.4%.<sup>68,69)</sup> This increase may have been caused by changes in the definition of VDD as 25(OH)D level <20 ng/mL, although the possibility of an increase in actual VDD infants cannot be ruled out. Based on previous studies, the prevalence of VDD is high in exclusively breastfed infants, even in South Korea. Further large-scale domestic studies are necessary to evaluate the exact vitamin D status of breastfed infants.

### **Vitamin D content of breast milk**

According to studies conducted in the 1980s, breast milk contains both vitamin D and 25(OH)D.<sup>72,73)</sup> Vitamin D and 25(OH)D, known for their antirachitic activity (ARA; expressed in IU/L), are responsible for  $\geq 90\%$  of the total vitamin D activity in breast milk.<sup>73)</sup> The dihydroxylated metabolites did not contribute significantly to the total vitamin D activity. ARA is calculated as  $1 \text{ IU/L} = 25 \text{ pg/mL vitamin D} = 5 \text{ pg/mL vitamin 25(OH)D}$ .<sup>74)</sup> A very small amount (approximately 1%) of the 25(OH)D circulating in the maternal blood crosses into the breast milk,<sup>75)</sup> in contrast, 20–30% of the circulating vitamin D is expressed in the breast milk.<sup>76)</sup> However, vitamin D is rapidly converted to 25(OH)D; therefore, the concentration of vitamin D circulating in the maternal blood decreases rapidly unless recent sunlight exposure and adequate vitamin D supplementation are provided.

Previous studies reported that the ARA levels in the breast milk of Western mothers were 14–170 IU/L (Table 3).<sup>72-74,77-79)</sup> However, there is a dearth of studies on vitamin D content of the

breast milk of Asian mothers. A recent study compared vitamin concentrations of the breast milk of women from South Korea, China, Pakistan, and Vietnam.<sup>80)</sup> However, the concentrations of vitamin D<sub>2</sub> and D<sub>3</sub> in the breast milk samples from all four countries were lower than the limit of detection of D<sub>2</sub> = 0.5 ng/mL and D<sub>3</sub> = 1 ng/mL. Three studies in Japan evaluated vitamin D concentrations of breast milk. One study compared the vitamin D concentrations of breast milk between 1989 and 2016–2017.<sup>37)</sup> The mean total ARA of breast milk from 1989 to 2016–2017 decreased from 31.3 IU/L to 25.5 IU/L, respectively. In the other two studies from Japan, the mean ARA of vitamin D<sub>3</sub> and 25(OH)D<sub>3</sub> were 3.2–3.5 IU/L and 16.2 IU/L, respectively.<sup>81,82)</sup> The study conducted in Malaysia reported higher 25(OH)D levels (80.8–100.8 IU/L) than those reported in Japanese studies.<sup>83)</sup> On combining studies from different countries, the levels of vitamin D of breast milk did not meet the vitamin D requirements of exclusively breastfed infants despite the mothers being exposed to abundant lifetime sunlight.<sup>74)</sup>

### **Effects of vitamin D supplementation of lactating mothers on vitamin D status and bone health of breastfed infants**

The vitamin D content of breast milk is related to the vitamin D status of lactating mothers.<sup>74,84-87)</sup> Lactating mothers with VDD would have a reduced amount of vitamin D in their breast milk, resulting in VDD in breastfed infants.<sup>88)</sup> Therefore, there have been some efforts to supply adequate vitamin D to the nursing infants through maternal vitamin D supplementation.

The dietary recommendations of vitamin D for lactating mothers differ among advisory bodies, ranging from 200 to 2000 IU/day.<sup>25,33,45,46,51,89,90)</sup> The Institute of Medicine suggested 600 IU/day for lactating mothers,<sup>25)</sup> whereas the Endocrine Society suggested 1500–2000 IU/day.<sup>45)</sup> Consensus is lacking on the recommended intake of vitamin D for lactating mothers, and the



supplemental vitamin D dose that optimizes the vitamin D status of mothers and breast milk is unclear. In South Korea, the 2020 DRIs for Koreans recommended vitamin D supplementation of 400 IU/day for lactating mothers.<sup>36)</sup> In previous studies, however, the breast milk of a mother receiving a vitamin D dose of 400 IU/day contains very low vitamin D concentrations of approximately 25–80 IU/L, which is far below the recommended daily vitamin D intake for infants.<sup>84,87,91,92)</sup> The WHO panel acknowledged that supplementation during lactation to improve the vitamin D content of breast milk may require a maternal intake much higher than 600 IU/day.<sup>91,93-95)</sup>

A recent meta-analysis evaluated the effects of maternal vitamin D supplementation on the vitamin D status and bone health of term breastfed infants.<sup>96)</sup> It included five randomized controlled trials (RCTs) comparing supplementation with placebo or no treatment.<sup>58,62,97-99)</sup> These studies reported a mean vitamin D level of 266 for vitamin D-supplemented mothers and 246 for controls, and the converted daily doses of vitamin D were 1785–4000 IU/day, higher than the current recommended dose. The results showed that high-dose vitamin D supplementation of lactating mothers may increase the 25(OH)D level (mean difference, 24.62 nmol/L; 95% confidence interval [CI], 21.59–27.60) in their children and reduce the incidence of vitamin D insufficiency (risk ratio [RR], 0.47; 95% CI, 0.39–0.57), VDD (RR, 0.15; 95% CI, 0.09–0.24), and biochemical rickets (RR, 0.06; 95% CI, 0.01–0.44) in breastfed infants compared with placebo or no treatment.<sup>96)</sup> However, there was insufficient evidence of the effects on bone mineral content and radiological rickets.

Studies have focused on methods of maternal supplementation to achieve vitamin D–replete milk to avoid direct infant supplementation. Wagner et al. found that the supplementation of lactating women with 6400 IU/day of vitamin D for 6 months significantly improved maternal vitamin D status and increased the ARA of the breast milk from 82 IU/L to 873 IU/L.<sup>87)</sup> The

mean plasma 25(OH)D level in exclusively breastfed infants was 46 ng/mL, similar to that of the unsupplemented mothers' infants receiving 300 IU/day of vitamin D. Maternal and infant urinary calcium-to-creatinine ratios remained within the reference range for both groups. This was confirmed by a large RCT in which maternal intake of 6400 IU/day resulted in a supply of breast milk with adequate vitamin D to satisfy their nursing infants' requirements.<sup>100)</sup> Maternal high-dose supplementation (6400 IU/day) resulted in similar 25(OH)D levels in infants supplemented with 400 IU/day. Another RCT recently evaluated the effects of intermittent mega-dose of vitamin D on lactating mothers in India.<sup>58)</sup> In this study, mothers received either vitamin D<sub>3</sub> 60,000 IU at 24–48 hours postpartum and at 6, 10, and 14 weeks amounting to 240,000 IU of vitamin D<sub>3</sub> or placebo. They reported that the intervention groups had higher serum 25(OH)D concentrations in exclusively breastfed infants and a 94.6% and 48.1% reduction in the risk of VDD and vitamin D insufficiency, respectively, at 6 months of age. Neither the mother nor the infant experienced adverse effects.

However, concern persists about maternal high-dose vitamin D supplementation despite the lack of adverse effects. These high vitamin D doses are above the recommended upper limit of 4000 IU/day for lactating mothers.<sup>25,101)</sup> The global consensus recommendations highlight that lactating women should not consume high amounts of vitamin D to supplement their infants.<sup>33)</sup> The clinical protocol of the Academy of Breastfeeding Medicine recommends maternal high-dose supplementation only if direct infant supplementation is contraindicated.<sup>102)</sup>

Thus far, the final consensus is that supplementing both mothers and infants with vitamin D, rather than supplementing mothers alone with high-dose vitamin D, ensures a healthy vitamin D status in their infants.

### **Guidelines for vitamin D supplementation in breastfed infants**

Direct infant supplementation is the currently available option to improve vitamin D levels. This supplement should be vitamin D<sub>3</sub> because of its superior absorption compared to vitamin D<sub>2</sub>.<sup>102)</sup> The recommended dose for vitamin D supplementation in breastfed infants is available from various societies and organizations worldwide and differs among them (Table 4). The WHO provides general recommendations for specific vulnerable groups. The WHO recommends 200 IU/day of vitamin D for infants aged <1 year.<sup>89)</sup>

In 2003, the American Academy of Pediatrics (AAP) recommended that all infants, including those who are exclusively breastfed, should have a minimum intake of 200 IU/day of vitamin D beginning in the first 2 months of life.<sup>35)</sup> In 2008, the AAP, with the primary intention of preventing rickets considering new evidence from clinical trials, increased the recommended intake of vitamin D for infants aged <1 year from 200 IU/day to 400 IU/day beginning soon after birth.<sup>103)</sup> The guidelines stated that exclusively or partially breastfed infants should be supplemented with 400 IU/day of vitamin D. For non-breastfed infants ingesting <1000 mL/day of vitamin D–fortified formula or milk, the AAP recommended vitamin D supplementation of 400 IU/day as well.<sup>103)</sup> In 2011, the Institute of Medicine (now known as the National Academy of Medicine) agreed with this recommendation,<sup>25)</sup> and the AAP, through an endorsement of the Institute of Medicine report in 2012<sup>104)</sup> and a clinical report in 2014,<sup>48)</sup> re-emphasized its original 2008 recommendation.

Most European countries as well as the United States recommend vitamin D supplementation with at least 400 IU/day for infants during the first year of life.<sup>46)</sup> The European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) also stated that all infants should receive oral supplementation of 400 IU/day of vitamin D. However, the Committee on Nutrition of the French Society of Pediatrics recommended higher doses of vitamin D.<sup>105)</sup> The recommendations were as follows: 1000–1200 IU/day for breastfed infants, 600–800 IU/day

for children  $\leq 18$  months of age receiving milk supplemented with vitamin D; and 1000–1200 IU for children less than 18 months of age receiving milk not supplemented with vitamin D. Closely followed supplementation of breastfed infants with 1000 IU/day of vitamin D has helped prevent the resurgence of rickets in France.<sup>105)</sup>

In Japan, the DRIs were revised in 2020.<sup>106)</sup> The Japanese DRIs are influenced by tentative dietary goals to prevent lifestyle-related diseases. Adequate intake (AI) in infants was defined as the vitamin D concentration in the breast milk multiplied by the typical intake of 0.78 L/day. However, considering the evidence of the re-emergence of VDD rickets and low content of vitamin D of breast milk,<sup>107)</sup> the AI was set at 200 IU/day for both male and female infants aged  $<1$  year.<sup>106)</sup>

In South Korea, there are no national guidelines regarding vitamin D intake in breastfed infants. The 2020 DRIs for Koreans recommend a dose of 200 IU/day of vitamin D as the AI for infants, similar to the 2015 DRIs for Koreans.<sup>36)</sup> The Korean Society of Pediatric Endocrinology suggested 400–600 IU/day of vitamin D supplementation for infants, children, and adolescents<sup>54)</sup> based on the guidelines of the Institute of Medicine and the AAP.<sup>25,48)</sup> It is necessary to develop Korean guidelines for vitamin D supplementation based on evidence from domestic studies on vitamin D levels in the blood considering sunlight exposure and food intake.

Most international guidelines recommend 400 IU/day of vitamin D for infants aged  $<1$  year after birth. A recent meta-analysis showed that vitamin D supplementation of 400 IU/day may increase the 25(OH)D level (mean difference, 22.63 nmol/L; 95% CI, 17.05–28.21) and may reduce the incidence of vitamin D insufficiency [25(OH)D] (RR, 0.57; 95% CI, 0.41–0.80) compared with placebo or no treatment among term breastfed infants.<sup>96)</sup> However, there is insufficient evidence of the effect of supplementation on VDD and bone health.

### **Vitamin D supplementation for preterm infants**

Preterm infants are at a high risk of VDD for several reasons: 1) decreased transplacental transfer, 2) minimal vitamin D formation mediated by ultraviolet B due to prolonged hospitalization, 3) minimal fat mass in which vitamin D and its metabolites are stored, and 4) a relatively high vitamin D requirement.<sup>108-110)</sup> A lack of vitamin D supplementation in the early postnatal period is a risk factor for metabolic bone disease in preterm infants.<sup>111,112)</sup> Therefore, supplementation with an optimal dose of vitamin D is very important for preterm infants.

The AAP recommends vitamin D intake of 200–400 IU/day for very low birth weight infants (birth weight <1500 g) (Table 5).<sup>108)</sup> For preterm infants with a birth weight  $\geq$ 1500 g, the recommended intake of vitamin D was 400 IU/day with a maximum upper level of 1000 IU/day, similar to the recommended intake for full-term infants. Meanwhile, the ESPGHAN guidelines generally suggest a daily vitamin D intake of 800–1000 IU/day for preterm infants up to a weight of approximately 1800 g and at least 400 IU/day for late and moderately preterm infants.<sup>110,113)</sup>

Several RCTs published after 2011 compared the efficacy of low-dose (200–400 IU/day) and high-dose (800–1000 IU/day) supplementation of vitamin D for preterm infants (Table 5). In all studies, serum 25(OH)D levels after supplementation were significantly higher in the high-dose versus low-dose group.<sup>114-119)</sup> The prevalence of VDD was also significantly lower in the high-dose group.<sup>114,116,118,120)</sup> Two studies showed that the high-dose group experienced bone density benefits.<sup>117,120)</sup> One study reported that the high-dose group had better growth results,<sup>120)</sup> consistent with the results of a recent meta-analysis.<sup>121)</sup> Despite the benefits of high-dose supplementation, concern persists about the adverse effects of excess vitamin D intake, such as hypercalciuria or nephrocalcinosis.<sup>114,116,122)</sup> The risk of vitamin D overdose could be

increased upon achieving a total dose of 1000 IU/day, combining supplements and diets, especially in neonates with a birth weight < 1000 g.<sup>123)</sup>

Based on the results of the trials mentioned above, a vitamin D intake of 800 IU/day can be considered in preterm infants along with biochemical monitoring. The total vitamin D intake of 800 IU/day should include the vitamin D content of human milk fortifier or formula as well as vitamin D supplementation. The vitamin D contents of human milk fortifiers and formulas commonly fed in Korea are summarized in Table 6.

### **Three sources of vitamin D**

#### *Sun exposure*

Ultraviolet radiation B from sun exposure is a major source of vitamin D. Several studies reported a positive correlation between sun exposure and serum vitamin D levels in breastfed infants.<sup>124,125)</sup> Meena et al. suggested a minimum 30-minute weekly afternoon sunlight exposure between 10 am and 3 pm over 40% of the body area (infant clothed in a diaper in the prone position) for at least 16 weeks to achieve sufficient vitamin D levels by 6 months of age.<sup>125)</sup> However, despite intense sun exposure, 90% of infants continued to have vitamin D insufficiency and required supplementation.<sup>126)</sup>

The harmful effects of ultraviolet rays must also be considered despite their beneficial effects associated with vitamin D synthesis. It is known to increase the risk of photodamage and melanoma or non-melanoma skin cancer, especially in the Caucasian population.<sup>127)</sup> The AAP recommends that infants younger than 6 months be kept out of direct sunlight.<sup>128,129)</sup> Outdoor activities should be planned to minimize peak-intensity midday sun exposure (10 am to 4 pm).<sup>128)</sup> Current guidelines recommend that vitamin D requirements be met through supplementation rather than deliberate sun exposure in infants.<sup>127,128)</sup>

### *Food sources of vitamin D*

Vitamin D is present in a pre-active form in several foods. Foods rich in vitamin D are summarized in Table 6. Vitamin D<sub>3</sub> is found in foods of animal origin, such as blue fatty fish, egg yolk, liver, and milk. Vitamin D<sub>2</sub> is found in small amounts in food of vegetable origin and wild mushrooms.<sup>130)</sup>

### *Vitamin D supplementation*

As mentioned earlier, 400 IU/day of vitamin D supplementation for breastfed infants is recommended by most international guidelines. This supplement should be cholecalciferol, vitamin D<sub>3</sub>, due to its superior absorption.<sup>102)</sup> However, there were major concerns about parental compliance,<sup>131)</sup> pediatrician practices,<sup>63)</sup> and incorrect dosing risk.<sup>132,133)</sup> In 2020, a systematic review reported on infant intermittent vitamin D supplementation as an alternative to daily supplementation.<sup>134)</sup> The doses varied from a single bolus of 30,000–600,000 IU, an intermittent bolus of 50,000 IU × 3 to 600,000 IU × 2, and 1400 IU/week from postnatal 7 days to 6 months. Overall, bolus dosing (>50,000 IU) achieves higher 25(OH)D repletion rates earlier than daily dosing, but it is likely to have similar efficacy at preventing vitamin D deficiency in later infancy. Considering the findings of trials to date, the evidence remains too weak to recommend intermittent vitamin D supplementation as an alternative to daily supplementation.

### **Conclusion**

Breastfed infants are vulnerable to VDD because of the low vitamin D content of breast milk, restricted sunlight exposure, and limited access to natural dietary sources of vitamin D. These infants are at major risk for VDD rickets, which appears to have re-emerged on a global scale. Most international guidelines recommend that exclusively or partially breastfed infants be

supplemented with 400 IU/day of vitamin D during their first year of life. However, domestic studies of the status and guidelines for vitamin D in breastfed infants are insufficient. Therefore, further research with a larger number of subjects is needed to clarify the status of VDD in Korean infants and guidelines to ensure adequate vitamin D status.

Accepted Article



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Table 1. Definitions of deficiency, insufficiency, and sufficiency of vitamin D according to clinical guidelines

Society/Organization	Year	25-hydroxyvitamin D [25(OH)D], ng/mL <sup>a</sup>		
		Deficiency	Insufficiency	Sufficiency
Institute of Medicine <sup>25)</sup>	2011	<12	12-19	≥20
The Endocrine Society <sup>45)</sup>	2011	<20	21–29	≥30
European Society for Pediatric Gastroenterology Hepatology and Nutrition <sup>32)</sup>	2013	<20	-	≥20
Central Europe <sup>46)</sup>	2013	<20	20–29	≥30
Society for Adolescent Health and Medicine <sup>47)</sup>	2013	<20	20–29	≥30
American Academy of Pediatrics <sup>48)</sup>	2014	<20	-	≥20
European Food Safety Authority <sup>49)</sup>	2016	-	-	≥20
Global Consensus for Rickets <sup>33)</sup>	2016	<12	12–19	≥20
Japanese Society for Bone and Mineral Research, Japan Endocrine Society <sup>30)</sup>	2017	<20	20–29	≥30
United Arab Emirates <sup>50)</sup>	2018	<20	20–29	≥30
Korean Society of Pediatric Endocrinology <sup>54)</sup>	2019			≥20
Australasia Paediatric Endocrine Group Bone and Mineral Working Group <sup>51)</sup>	2020	<12	12-19	≥20

<sup>a</sup>1 ng/mL = 2.5 nmol/L

Table 2. Vitamin D statuses of exclusively breastfed infants and their mothers

First author, year	Nation	No. of participants	Age of infants	25(OH)D (ng/mL) of mothers <sup>a</sup>	25(OH)D (ng/mL) of infants <sup>a</sup>	Prevalence of VDD in infants	Remark
Parian-de los Angeles, 2021 <sup>56)</sup>	Philippines	131 infants	<6 mo	-	-	VDD (<15 ng/mL) 77%	
Said, 2020 <sup>57)</sup>	Kenya	98 infants	-	-	-	VDD (<12 ng/mL) 11.2% VDI (15-20 ng/mL) 10%	
Trivedi, 2020 <sup>58)</sup>	India	56 M-I pairs	6 mo	6.29±4.11	6.43±3.76	VDD (<11 ng/mL) 91.1% VDI (11-19 ng/mL) 8.9%	Control group
Terashita, 2017 <sup>59)</sup>	Japan	9 infants	5 mo	-	16.0±6.5	VDD (<20 ng/mL) 67%	Vitamin D supplementation (-)
Haugen, 2016 <sup>60)</sup>	Nepal	500 M-I pairs	1-12 mo	21.2±8.1	34.8±7.6	VDD (<12 ng/mL) 0.6% VDI (12-19 ng/mL) 3.0%	BM (full or partly)
Salamch, 2016 <sup>61)</sup>	Arab in Doha, Qatar	60 M-I pairs	1 mo	13 (10-18)	8 (5-13.5)	VDD (<20 ng/mL) 83%	
Wheeler, 2016 <sup>62)</sup>	New Zealand	30 M-I pairs	5 mo	-	-	VDD (<20 ng/mL) 27%	71% exc BM at 5 mo, control group
Dawodu, 2014 <sup>63)</sup>	USA	120 M-I pairs	4 weeks	28.1±9.3	16.4±6.5	VDD (<20 ng/mL) 77%	87.5% exc BM at 4 weeks

Wall, 2013 <sup>64)</sup>	New Zealand	94 infants	2-3 mo	-	21.2 (5.6-40)	VDD (<11 ng/mL) 24%	
Jain, 2011 <sup>65)</sup>	India	98 M-I pairs	2.5-3.5 mo	9.8 (5.0-13.8)	10.1 (2.5-17.1)	VDD (<15 ng/mL) 66.7% VDI (15-20 ng/mL) 19.8%	70.6% exc BM
Agarwal, 2010 <sup>66)</sup>	India	97 M-I pairs	10 weeks	9.34±6.18	11.55±7.27	VDD (<11 ng/mL) 55.67%	
Kang, 2015 <sup>68)</sup>	South Korea	70 M-I pairs	4-24 mo	12.4±4.4	11.4±8.6	VDD (≤20 ng/mL) 81%	
Choi, 2013 <sup>69)</sup>	South Korea	52 infants	1-6 mo	-	9.35	VDD (<20 ng/mL) 90.4%	Feeding BM>80% of total feeding volume/day
Kim, 2010 <sup>70)</sup>	South Korea	28 M-I pairs	0-12 mo	24.5±12.5	*0 → 6 → 12 mo 18.0±10.3 → 22.5±9.24 → 33.2±7.89	*0 → 6 → 12 mo VDD (<11 ng/mL) 26.9 → 10.7 → 0% VDI (11-30 ng/mL) 61.5 → 67.9 → 50.0%	Exc BM without supplementation
Park, 1998 <sup>71)</sup>	South Korea	18 infants	2-5 mo	-	16.0±11.3	VDD (<11 ng/mL) 44%	

25(OH)D, 25-hydroxyvitamin D; BM, breast milk; exc BM, exclusive breast milk; M-I, mother-infant; VDD, vitamin D deficiency; VDI, vitamin D insufficiency

<sup>a</sup>Values are shown as mean ± standard deviations or median (interquartile range)

Table 3. Antirachitic activity of breast milk in examined studies

Author (Ref)	Year	Country	ARA of vitamin D and 25-hydroxyvitamin D [25(OH)D] in breast milk*
Hollis <sup>72)</sup>	1981	USA	Vitamin D: 1.56±0.36 IU/L 25(OH)D: 62.2±6.2 IU/L
Reeve <sup>73)</sup>	1982	USA	Vitamin D <sub>2</sub> and D <sub>3</sub> : 14-16 IU/L 25(OH)D: 33 IU/L
Ala-Houhala <sup>77)</sup>	1988	Finland	124 (19-332) IU/L in summer, 14 (8-30) IU/L in winter
Sakurai <sup>81)</sup>	2005	Japan	Vitamin D <sub>3</sub> : 3.2±4.3 IU/L
Kamao <sup>82)</sup>	2007	Japan	Vitamin D <sub>3</sub> : 3.5 IU/L 25(OH)D <sub>3</sub> : 16.2 IU/L
Jan Mohamed <sup>83)</sup>	2014	Malaysia	25(OH)D: 80.8-100.8 IU/L
við Streyrn <sup>78)</sup>	2016	Denmark	Vitamin D Foremilk in winter: 1.6 (1.6-6.4) IU/L Foremilk in summer: 6.4 (1.6-20.8) IU/L Hindmilk in winter: 4.8 (1.6-14.4) IU/L Hindmilk in summer: 14.4 (4.8-48) IU/L 25(OH)D Foremilk in winter: 64 (40-88) IU/L Foremilk in summer: 72 (56-120) IU/L Hindmilk in winter: 96 (64-128) IU/L Hindmilk in summer: 128 (88-176) IU/L
Stoutjesdijk <sup>74)</sup>	2017	Netherland Curaçao Vietnam Malaysia Tanzania	46 (3-51) IU/L 31 (5-113) IU/L Halong Bay 58 (23-110) IU/L Phu Tho 28 (1-62) IU/L Tien Giang 63 (26-247) IU/L Ho-Chi-Minh-City 49 (24-116) IU/L Hanoi 37 (11-118) IU/L Kuala Lumpur 14 (1-46) IU/L Ukerewe 77 (12-232) IU/L Maasai 88 (43-189) IU/L
Oberson <sup>79)</sup>	2020	USA	33.4-172.3 IU/L
Tsugawa <sup>37)</sup>	2021	Japan	31.3±30.3 IU/L in 1989, 25.5±12.0 IU/L in 2016-2017

Values are shown as mean ± SD or median (range).

\*ARA (calculated antirachitic activity) = biological activity of 25(OH)D + biological activity of vitamin D. Biological activity of vitamin D, 1 IU/L = 25 pg/mL; biological activity of 25(OH)D, 1 IU/L = 5 pg/mL.

Table 4. Dietary recommended intakes (IU) of vitamin D for infants and children

Society/Organization	Age 0–1 yr	Age 1–3 yr	Age 4–10yr
Worldwide (WHO/FAO, 2014) <sup>135)</sup>	200	200	200
Global consensus, 2016 <sup>33)</sup>	400	600	600
USA (Endocrine Society, 2011) <sup>45)</sup>	400–1000	600–1000	600–1000
USA (IOM, 2011) <sup>25)</sup>	400	600	600
USA (AAP, 2014) <sup>48)</sup>	400	600	600
France (French Society of Pediatrics, 2012) <sup>105)</sup>	1000–1200	<18 mo: fortified milk 600–800, not fortified milk 1000–1200 ≥18 mo: 2 × 80,000–100,000 (1 Nov and 1 Feb)	<5 yr: 2 × 80,000–100,000 (1 Nov and 1 Feb) ≥5 yr: (-)
Central Europe (Polish Scientific Committee on Vitamin D, 2013) <sup>46)</sup>	400–600	600–1000	600–1000
Europe (ESPGHAN, 2013) <sup>32)</sup>	400	-	-
Japan (DRIs, 2020) <sup>106)</sup>	200	Male: 120–140 Female: 140–160	Male: 140–200 Female: 160–240
Korea (KSPE, 2019) <sup>54)</sup>	400	600	600
Korea (DRIs by MOHW and KNS, 2020) <sup>36)</sup>	200	200	200

AAP, American Academy of Pediatrics; DRIs, Dietary Reference Intakes; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; IOM, Institute of Medicine; KNS, Korean Nutrition Society; KSPE, Korean Society of Pediatric Endocrinology; MOHW, Ministry of Health and Welfare; WHO/FAO, World Health Organization/Food and Agriculture Organization

Table 5. Summary of recommendations and randomized controlled trials of different doses of vitamin D for preterm infants

<b>Organ, year</b>	<b>Population</b>	<b>Recommendations</b>	
AAP, 2013 <sup>108)</sup>	< 1500 g	200-400 IU/day	
	≥ 1500 g	400-1000 IU/day	
ESPGHAN, 2010 <sup>110)</sup>	< 1800 g	800-1000 IU/day	
ESPGHAN, 2019 <sup>113)</sup>	32-36 weeks	at least 400 IU/day	
<b>First author, year</b>	<b>Population</b>	<b>No. of participants according to the groups</b>	<b>Findings</b>
Natarajan, 2014 <sup>114)</sup>	28-34 weeks	800 IU (n = 48) vs 400 IU (n = 48)	800 IU (vs 400 IU) - VDD at 40 weeks' PMA ↓ (38.1% vs 66.7%) - VDD at 3 month's CA ↓ (12.5% vs 35%) - Bone mineral content, bone mineral density → - Vitamin D excess (100-150 ng/mL): 1 (2.4%) in the 800 IU group
Fort, 2016 <sup>115)</sup>	23-27 weeks	800 IU (n = 30) vs 200 IU (n = 34) vs placebo (n = 36)	800 IU (vs 200 IU vs placebo) - 25(OH)D at day 28 ↑ (84.5 ng/mL vs 39 ng/mL vs 22 ng/mL) - VDD (0% vs 16% vs 41%, p = 0.2) - days alive, respiratory outcomes →
Mathur, 2016 <sup>120)</sup>	< 1500 g	1000 IU (n = 25) vs 400 IU (n = 25)	1000 IU (vs 400 IU) - Serum 25(OH)D after 6 weeks of supplementation ↑ (50.9 ng/mL vs 29.7 ng/mL) - VDD ↓ (0% vs 20%) - Calcium ↑, ALP ↓, parathyroid hormone ↓ - Skeletal hypomineralization ↓, growth ↑

Tergestina, 2016 <sup>116)</sup>	27-34 weeks	1000 IU (n = 60) vs 400 IU (n = 60)	<p>1000 IU (vs 400 IU)</p> <ul style="list-style-type: none"> <li>- VDD at 40 weeks' PMA ↓ (2% vs 64.6%)</li> <li>- 25(OH)D at 40 weeks' PMA ↑ (47.47 ng/mL vs 17.48 ng/mL)</li> <li>- Parathyroid hormone ↓, calcium →, phosphorus →, ALP →</li> <li>- Vitamin D excess (&gt;70 ng/mL): 9.8% of 1000 IU group, but not associated with clinical or biochemical evidence of toxicity</li> <li>- Hypercalcemia →, elevated urine calcium/creatinine →</li> </ul>
Anderson-Berry, 2017 <sup>117)</sup>	24-32 weeks	800 IU (n = 16) vs 400 IU (n = 16)	<p>800 IU (vs 400 IU)</p> <ul style="list-style-type: none"> <li>- 25(OH)D at 4 weeks ↑ (42.12 ng/mL vs 33.84 ng/mL)</li> <li>- DEXA bone density measurements &lt; 10p ↓ (16% vs 56%)</li> </ul>
Bozkurt, 2017 <sup>118)</sup>	24-32 weeks	1000 IU (n = 40) vs 800 IU (n = 41) vs 400 IU (n = 40)	<p>1000 IU (vs 800 IU vs 400 IU)</p> <ul style="list-style-type: none"> <li>- 25(OH)D at 36 weeks' PMA ↑ (43 ng/mL vs 40 ng/mL vs 29.4 ng/mL)</li> <li>- VDD at 36 weeks' PMA compared to 400 IU ↓ (2.5% vs 22.5%)</li> <li>- Vitamin D insufficiency at 36 weeks' PMA compared to 400 IU ↓ (12% vs 23%)</li> <li>- Calcium, phosphorus, ALP, parathyroid hormone →</li> <li>- Urine calcium/creatinine →</li> </ul>
Abdel-Hady, 2019 <sup>119)</sup>	28-36 weeks with LOS	800 IU (n = 25) vs 400 IU (n = 25)	<p>800 IU (vs 400 IU)</p> <ul style="list-style-type: none"> <li>- VDD at 40 weeks' PMA →</li> <li>- 25(OH)D at 40 weeks' PMA ↑ (67.4 ng/mL vs 54.8 ng/mL)</li> <li>- IL-6, TNF-<math>\alpha</math>, growth, duration of oxygen and respiratory support, duration of antimicrobial use, length of hospital stay, mortality →</li> <li>- Vitamin D toxicity (-)</li> </ul>



25(OH)D, 25-hydroxyvitamin D; AAP, American Academy of Pediatrics; ALP, alkaline phosphatase; CA, corrected age; DEXA, dual-energy x-ray absorptiometry; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; IL, interleukin; LOS, late-onset sepsis; PMA, postmenstrual age; TNF, tumor necrosis factor; VDD, vitamin D deficiency

↑: significantly higher in the high-dose group; ↓: significantly lower in the high-dose group; →: no significant differences between groups

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Table 6. Vitamin D contents of formulas and foods

<b>Formula and foods</b>	<b>IU per serving</b>
Human milk fortifier, 1 pack	30-37.5
Preterm formula, 100 mL	56-128
Term formula, 100 mL	33.2-52
Cod liver oil, 1 table spoon (1 table spoon = 15 mL)	1,360
Salmon, cooked, 100 g	360
Mackerel, cooked 100 g	345
Sardine, oiled and canned, 100 g	270
Eel, cooked, 100 g	200
Milk, vitamin D fortified, 200 mL	100
Egg, 1 large (vitamin D is found in yolk)	25
Mushroom, 100 g	20

Source of vitamin D contents of foods: National Health Information Portal, Korea Disease Control and Prevention Agency. <http://health.kdca.go.kr/healthinfo>