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Maternal Supplementation of Vitamin D during Lactation to Support Infant Vitamin D Needs: A Systematic Review

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Abstract

Human milk is generally considered to be insufficient in vitamin D. However, research completed in the 1980s showed that the vitamin D content of human milk is directly related to maternal serum vitamin D levels and therefore may potentially be adequate if the mother's vitamin D levels are sufficient. Approximately one-third of the adult population, which includes breastfeeding women, in the United States have vitamin D insufficiency or deficiency. Among infants, 90.4% of breastfed infants are vitamin D deficient compared to 15.4% of formula fed infants. The American Academy of Pediatrics (AAP) has therefore recommended all breastfed infants be directly supplemented with 400 IU per day of vitamin D to decrease the risk of vitamin D insufficiency and rickets. According to the AAP, compliance rates with this recommendation ranges between 2% - 36%. Because the recommendation to supplement may undermine breastfeeding, many pediatricians do not inform their patients of the need to supplement. Additionally, some parents are concerned about directly supplementing their infant as risks may include allergic reactions to the ingredients, aspiration pneumonia, accidental overdose, and changes in intestinal flora and pH which may compromise the immune benefits of human milk. A literature review was conducted to examine the effect of maternal supplementation with vitamin D during lactation on human milk vitamin D content and maternal and infant serum vitamin D levels. Although there is no current consensus regarding dosage and timing of maternal vitamin D supplementation, the literature suggests that high-dose vitamin D supplementation of the lactating mother is as effective at maintaining infant vitamin D levels as direct infant supplementation, while also correcting the mother's vitamin D deficiency.

1. Introduction

Vitamin D is a steroid hormone which is naturally synthesized in the deep skin layers from 7-dehydrocholesterol when exposed to ultraviolet B wavelengths [1] [2] [3] [4]. Ninety percent of the vitamin D in non-supplemented individuals' bodies arises from natural synthesis in response to sunlight [5] [6]. Vitamin D is found in a limited number of foods including fortified milk or juice, egg yolk, liver, and fatty fish [2] [3] [5] [6] [7] [8]. Based upon results of the National Health and Nutrition Examination Survey (NHANES) 2005-2006, estimated total vitamin D availability in adult females ranges from 144 to 276 IU/day [8] resulting in low serum levels of 25-hydroxyvitamin D (25(OH)D) [5] While vitamin D has historically been thought to be primarily responsible for calcium homeostasis and bone health, new research is showing that vitamin D may also be important in immunomodulation, regulation of cell growth, and cardiovascular health [5]. Although D_3 is the preferred form, as it is more effective in increasing serum 25(OH) D levels, vitamin D_2 is often used in fortified foods.

There is a lack of consensus on vitamin D levels of sufficiency, insufficiency, and deficiency as a scientific committee process has not been established to define these levels [1] [8]. This is exacerbated by studies finding that levels once considered "normal" may actually be insufficient based upon current evidence [7]. The Institute of Medicine (IOM), based on a review of data, set the following guidelines for these levels: [8] (**Table 1**).

Several studies reported that 25(OH)D levels must exceed 32 ng/mL to maximize skeletal integrity. The Endocrine Society issued clinical practice guidelines in 2011 stating that the desirable serum concentration of 25(OH)D is greater than 75 nmol/L (30 ng/mL) to maximize the effect on calcium, bone, and muscle metabolism [8].

Using the IOM definitions, results from the National Health and Nutrition Examination Surveys (NHANES) 2001-2006 showed that two-thirds of the

Table 1. Institute of Medicine definition of vitamin D status.

nmol/L	ng/mL	Vitamin D Status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥50	≥20	Generally considered adequate for bone and overall health in healthy individuals
>125	>50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

population had sufficient vitamin D; one-quarter were insufficient; and eight percent were deficient [9]. A South Korean study assessed vitamin D deficiency among infants and noted that 48.7% had insufficient 25(OH)D levels [10]. Among breastfed infants, vitamin D deficiency prevalence was significantly higher at 90.4% than formula fed infants, who had a prevalence of 15.4%. Mean serum 25(OH)D of breastfed infants was significantly lower compared to formula fed infants, even when vitamin D was sufficient (p < 0.001).

Vitamin D deficiency rates have increased with the modern lifestyle characterized by decreased sun exposure related to urbanization, increased indoor activities, and use of sunscreen [7]. Caucasian individuals require 10 - 12 minutes of full body sun exposure to synthesize 10,000-20,000 IU of vitamin D; in comparison, an individual with dark skin would need 60 - 72 minutes of exposure to synthesize the same amount of vitamin D [6] [7]. During the winter months, individuals living at a latitude above 40˚ do not synthesize an adequate amount of vitamin D, regardless of exposure [7].

Only small amounts of 25(OH)D pass from the maternal circulation to human milk [1]. Instead, vitamin D is passed into human milk as cholecalciferol (vitamin D_3, the parent form of 25(OH)D) [1]. It has been shown that 20% - 30% of maternal vitamin D is expressed in human milk compared to only 1% of maternal 25(OH)D [6] [7] [11].

The Institute of Medicine (IOM) and the American College of Obstetrics and Gynecologists (ACOG) recommends 600 IU of vitamin D daily for all adults, including pregnant and lactating women (increased in 2008 from the Adequate Intake of 200 IU per day, which was previously arbitrarily set) [1] [8] [12]. The Endocrine Society shares this recommendation but suggest that 1500 to 2000 IU may be necessary to maintain adequate serum 25(OH)D [1]. The Recommended Dietary Allowance (RDA) for infants 0 - 12 months, as set by the Food and Nutrition Board (FNB) at the IOM of the National Academies, is 400 IU [8].

The Tolerable Upper Intake Level for vitamin D has been set at 4000 IU in pregnancy and lactation, and at 1000 IU for infants [8]. However, most reports suggest a toxicity threshold for vitamin D between 10,000 and 40,000 IU per day [3] [8]. Symptoms of toxicity are unlikely at daily intakes below 10,000 IU per day; however, the Food and Nutrition Board suggests that even lower vitamin D intakes may have adverse health effects over time, based on national survey data, observational studies, and clinical trials [8]. The No Observed Adverse Effect Level (NOAEL) has been set at 10,000 IU daily by the IOM [4] [6].

Setting adequacy levels is difficult since the relationship between serum 25(OH)D levels and vitamin D intake is non-linear, for reasons that are not entirely clear [8]. Doses greater than or equal to 1000 IU per day are associated with a 1 nmol/L rise in serum 25(OH)D per 40 IU of intake [8]. Doses up to 600 IU per day are associated with a 2.3 nmol/L increase in serum 25(OH)D per 40 IU consumed [8].

Traditionally, it has been thought that the vitamin D content of human milk was inadequate to meet infant vitamin D needs [1] [8] [13]. Vitamin D activity

in human milk has been found to range between five to 80 IU/L [3] [4] [13]. However, research completed in the 1980s showed that vitamin D content of human milk is directly related to maternal serum vitamin D levels and, therefore has the potential to be adequate when mothers' vitamin D levels are sufficient [1] [7] [8] [11] [13].

In infants and young children, long-term vitamin D deficiency leads to rickets [5]. While rickets were thought to be eradicated in the United States, recent reports show that prevalence is rising once again [2] [12]. A review from the United States included 166 patients with nutritional rickets during the time period of 1986-2003; 96% of the children with rickets were breastfed. Therefore, the American Academy of Pediatrics (AAP) recommends that all breastfed infants receive 400 IU of oral vitamin D daily starting at birth [1] [4] [6] [7] [8] [11] [12]. This recommendation is a result of poor transfer of vitamin D from the maternal circulation into human milk in addition to the guidance to minimize sun exposure to infants up to six months of age [1] [4] [6] [7] [8] [12].

Many parents do not supplement their infants according to the AAP recommendation [6] [11]. Of 1140 exclusively breastfed infants, only 15.9% received any vitamin D supplements [6]. Other reports show compliance rates between 2% - 36% [2] [4] [13]. Only 5% of those with rickets are reported to have received vitamin D supplementation [5] [6]. This guideline may undermine breastfeeding success by implying that human milk is an inadequate source of complete nutrition for infants [6]. In fact, 36.4% of surveyed pediatricians in Seattle, WA chose not to recommend vitamin D supplements to breastfed infants due to concerns that parents would cease breastfeeding [6]. There is also some concern surrounding direct supplementation of the infant. Risks are currently unclear, but may include allergic reactions to the ingredients, aspiration pneumonia, accidental overdose, and changes in intestinal flora and pH may compromise. Given these concerns, the purpose of this review was to evaluate the impact of high-dose maternal vitamin D during lactation on human milk content and infant vitamin D status.

2. Methods

2.1. Data Source and Searches

Medline and Google scholar were searched from January 2003 through May 2018. Earlier studies were excluded due to the unacceptably large variance in vitamin D assays prior to this time [13]. The key words and MESH terms used to gather and classify the research both independently and in combination were maternal, breastfeed(ing) or lactation, Vitamin D, dietary supplements, milk/human, cholecalciferol, infants/physiologic phenomena. References found in articles were examined to identify any additional articles but no studies within the search delimitations were identified. The search was delimited to English language and humans. The search strategies for breastfeed* and vitamin D (or Vitamin D status or cholecalciferol) and milk/human and infant/physiologic phe-

nomena yielded 173 articles. Substitution of lactation instead of breastfeed* yielded 184 articles; all but 11 were duplicates. Adding maternal to the search strategy did not alter the number of titles retrieved. Adding the term dietary supplements did not improve the final yield.

Abstracts were reviewed for eligibility. Complete articles of those accepted were independently reviewed by two investigators (KS and MAH) and accepted if they met the inclusion criteria of maternal supplementation during lactation, included data on vitamin D status of infants, evaluated the effect of maternal dose and exclusive breastfeeding or minimal, and documented, formula supplementation. Articles were excluded if they were not published in English, full text was unavailable (1 article), did not evaluate infant vitamin D status in relation to maternal supplementation with vitamin D, evaluated more than one micronutrient or were commentaries on previous studies. Articles were also excluded if they examined vitamin D supplementation during pregnancy since the association between vitamin D supplementation during pregnancy and offspring vitamin D status and outcomes has been the subject of a current systematic review and meta-analysis [14].

2.2. Study Selection

Of the 184 articles which were identified, 86 articles titles were outside of the inclusion criteria, 98 were considered for review of abstracts. This review yielded 11 studies that met inclusion criteria with a variety of strengths, weaknesses, and overall contribution to the present research question. The PRISMA diagram is presented in Figure 1.

2.3. Assessment of Quality

Quality was evaluated using the Academy of Nutrition and Dietetics EAL Quality Assessment Checklists [15].

An overall positive rating indicates that criteria were adequately addressed. A negative rating was assigned if the criteria were not adequately addressed and a neutral rating was assigned if indicators were mixed and the study design was neither exceptionally strong nor exceptionally weak. The checklists include 10 validity criteria: clearly stated research question (procedures, outcomes, inclusion/exclusion criteria) potential bias, comparability of groups, handling of withdrawn subjects, appropriate statistical analysis and conclusions supported by the results. The quality checklists are shown in Table 2 and Table 3.

3. Results

A summary of study populations, interventions and outcomes and overall quality ratings are shown in Table 4.

3.1. Interventions with Vitamin D_2

Vitamin D_2 supplementation was chosen in several studies in an effort to better
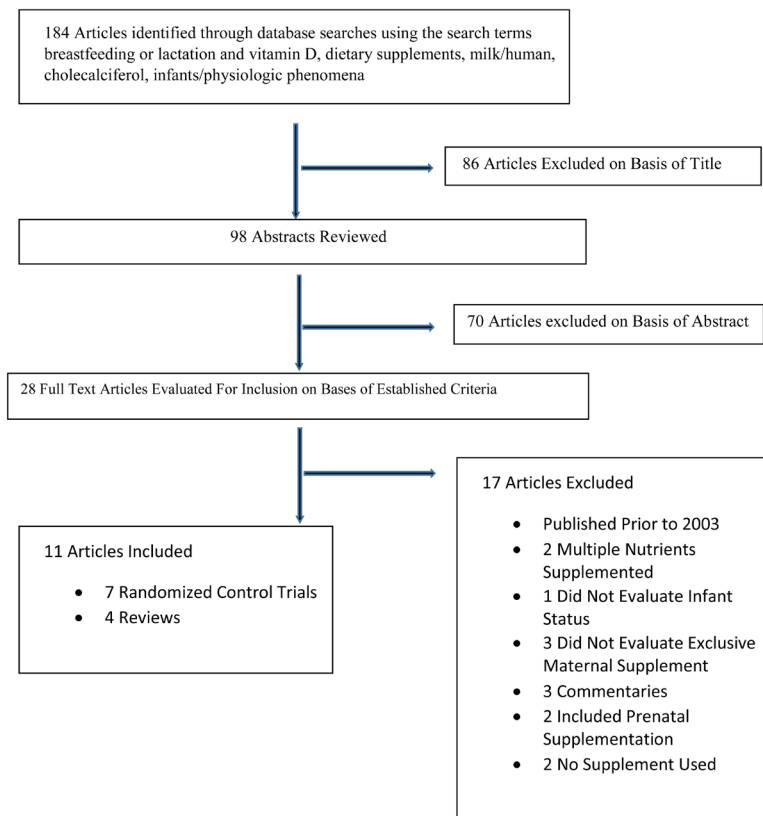
Figure 1. PRISMA diagram.

Table 2. Quality criteria checklist intervention studies.

Validity Question	Nalk, 2017	Wheeler, 2016	Hollis, 2015	Basile, 2006	Wagner, 2006	Oberhelman, 2013	Hollis, 2004
1. Was research question stated clearly?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was selection of study subjects free from bias?	Yes	Yes	Yes	No	No	Yes	Yes
3. Were study groups comparable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4. Was method of handling withdrawals described?	n/a	No	n/a	No	Yes	n/a	n/a
5. Was blinding used to prevent introduction of bias?	Yes	Yes	Yes	Yes	Yes	No	No
6. Were intervention and comparison described in detail?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7. Were outcomes clearly defined and the measurements valid and reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8. Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9. Are conclusions supported by results with biases and limitations taken into consideration?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Is bias due to study's funding or sponsorship unlikely?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

track the effects of supplementation, as contribution from other sources is unlikely [3] [12]. Hollis and Wagner examined two groups of exclusively breastfeeding mother-infant pairs (n = 18) [12]. In the first intervention group, mothers

Table 3. Quality criteria checklist review studies.

Validity Question	Haggerty, 2011	Taylor, 2008	Thiele, 2013	Dawodu, 2012
1. Was the question for the review clearly focused?	Yes	Yes	Yes	Yes
2. Was the search strategy used to locate studies comprehensive? Were databases and search terms described?	Yes	No (unclear)	Yes	No (unclear)
3. Were explicit methods used to select studies?	No (unclear)	No (unclear)	Yes	No
4. Was there a specified and valid methods for appraisal of quality and validity of studies?	No	No (unclear)	Yes	No
5. Were specific treatments, interventions, exposures described?	No	No (unclear)	Yes	Yes
6. Was the outcome of interest clearly indicated?	Yes	Yes	Yes	Yes
7. Were processes for data abstraction, synthesis and analysis described and applied consistently? Was variation among findings analyzed? Were heterogeneity issues considered? If studies aggregated for meta-analysis, were procedures described?	No (unclear)	No (unclear)	Yes	No (unclear)
8. Were results clearly presented in narrative and/or quantitative terms?	Yes	Yes	Yes	Yes
9. Are conclusions supported by results with biases and limitations taken into consideration?	No	No	No	No
10. Is bias due to study's funding or sponsorship unlikely?	Yes	Yes	Yes	Yes

Table 4. Summary of evidence.

Citation	Study Design	Quality Rating	Population/ Sample	Intervention/ Comparisons	Outcomes
Nalk, Nalk P., Faridi, M.M.A., Batra, P., Madhu, S.V. Oral Supplementation of Parturient Mothers with Vitamin D and its Effect on 25OHD Status of Exclusively Breastfed Infants at 6 Months of Age: A Double-blind Randomized Placebo Controlled Trial. 2017, Breastfeed Med. 12:621-9. Reference [19]	Randomized Controlled Trial	Positive	100 exclusively breastfeeding mother/infant pairs in Turkey	Group 1: Maternal supplement of 600,000 IU vitamin D_3 in 10 divided doses in early postpartum Group 2: Placebo Measurement of maternal and infant 5(OH)D at initiation of study and at 6 months of age. Radiographically determined and biochemical indices (Alkaline phosphatase) in infants	Maternal 25(OH)D levels after 6 months of study were greater (40.3 ± 21.6 ng/mL) in supplemented vs (22.9 ± 20.18 ng/mL) in controls. Infant levels were also higher (29.29 ± 14.67 ng/m) in those fed by supplemented mothers compared to 15.73 ± 17.73 ng/mL in controls. After 6 months of exclusive breastfeeding only one mother and four infants had serum 25 (OH) D levels < 11ng/ml in the supplemented group (n = 53) vs 9 mothers and 25 infants (n = 57) in the control. 2 infants in each group developed clinical rickets.
Wheeler BJ, Taylor BJ, Herbison P, *et al.* High-Dose Monthly Maternal Cholecalciferol Supplementation during Breastfeeding Affects Maternal and Infant Vitamin D Status at 5 Months Postpartum: A Randomized Controlled Trial. J Nutr. 2016, 146:1999-2006. Reference [2]	Randomized Controlled Trial	Positive	87 exclusively breastfeeding mother/infant pairs in New Zealand	Group 1: Placebo Group 2: 50,000 IU vitamin D_3 per month Group 3: 100,000 IU vitamin D_3 per month	Maternal supplementation with 50,000 IU and 100,000 IU vitamin D resulted in significantly higher serum 25(OH)D concentrations at study end compared to placebo (p = 0.043; p = 0.001, respectively). Infant change in serum 25(OH)D was not significant between groups (p = 0.67; p = 0.13, respectively). 26% of mothers in the placebo group exhibited vitamin D deficiency, compared to 4% in the 50,000 IU group and 0% in the 100,000 IU group at study end (p = 0.002). Deficiency rates between infants in all groups were similar (27%, 29%, and 19%, respectively; p = 0.65).

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Hollis BW, Wagner CL, Howard CR, *et al.* Maternal Versus Infant Vitamin D Supplementation During Lactation: A Randomized Controlled Trial. Pediatrics. 2015, 136:625-34. Reference [16]	Randomized Controlled Trial	Positive	95 exclusively/ fully breastfeeding mother/infant pairs in Charleston, South Carolina and Rochester, New York	Group 1: Maternal supplement 400 IU vitamin D_3 per day; 400 IU vitamin D_3 per day for infants Group 2: Maternal supplement 2400 IU vitamin D_3; placebo for infants (discontinued due to safety concerns, not included in analysis) Group 3: Maternal supplement 6400 IU vitamin D_3; placebo for infants	Maternal 25(OH)D levels were significantly higher in mothers supplemented with 6400 IU than those with 400 IU at visits 4 and 7 (p < 0.001; p < 0.001, respectively). Infant 25(OH)D was similar between groups at all visits (p = 0.35 at V1, p = 0.10 at V4, and p = 0.94 at V7). Maternal supplementation with 6400 IU/day is as effective at meeting infant vitamin D needs as directly supplementing the infant 400 IU/day
Basile LA, Taylor SN, Wagner CL, Horst RL, Hollis BW. The effect of high-dose vitamin D supplementation on serum vitamin D levels and milk calcium concentration in lactating women and their infants. Breastfeed Med. 2006, 1:27-35. Reference [3]	Randomized Controlled Trial	Neutral	25 fully breastfeeding mother-infant pairs in South Carolina	Group 1: Maternal supplement 400 IU vitamin D_3 + 1600 IU vitamin D_2 Group 2: Maternal supplement 400 IU vitamin D_3 + 3600 IU vitamin D_2	Women in both study groups had significantly elevated circulating 25(OH)D concentrations after the 3 months of supplementation (2000 IU group: p = 0.002; 4000 IU group: p = 0.0008). Women receiving 4000 IU/day exhibited significantly higher 25(OH)D concentrations than those in the 2000 IU/day group (p = 0.03). Infants experienced a significant increase in 25(OH)D. Infants in the 4000 IU group exhibited a higher 25(OH)D concentration compared to 2000 IU (p = 0.01).
Wagner CL, Hulsey TC, Fanning D, Ebeling M, Hollis BW. High-dose vitamin D_3 supplementation in a cohort of breastfeeding mothers and their infants: a 6-month follow-up pilot study. Breastfeed Med. 2006.1:59-70. Reference [11]	Randomized Controlled Trial	Neutral	10 fully lactating mother-infant pairs in South Carolina (of note, only 4 continued breastfeeding through the entire study, but intent-to-treat included all 10 women)	Group 1: Maternal supplement 400 IU vitamin D_3/day; 300 IU/day vitamin D_3 for infants Group 2: Maternal supplement 6400 IU vitamin D_3/day; placebo for infants	The total circulating 25(OH)D levels of mothers in group 1 decreased through visit 5; there was a slight improvement at visits 6 and 7 that corresponded to increased outdoor activities and sun exposure (significance not provided). Mothers in group 2 had an immediate increase in 25(OH)D levels that was sustained throughout the study period (significance not provided). Despite the increased outdoor activities and an increase in sunlight exposure that paralleled group 1, after achieving steady-state by month 3, there was very little change in maternal 25(OH)D from months 3 to 7. Compared to group 1, the mean milk ARA in group 2 significantly increased to 873 IU/L (p < 0.0003), which resulted in a dramatic rise in infant circulating 25(OH)D levels. This rise in infant 25(OH)D was almost identical to that in the infants receiving 300 IU/day vitamin D_3 directly via oral supplementation.
Oberhelman SS, Meekins ME, Fischer PR, *et al.* Maternal vitamin D supplementation to improve the vitamin D status of breastfed infants: a randomized controlled trial. Mayo Clin Proc. 2013,	Randomized Controlled Trial	Positive	40 exclusively breastfeeding mother-infant pairs in Rochester, Minnesota	Group 1: Maternal supplement 150,000 IU vitamin D_3 monthly Group 2: Maternal supplement 5000 IU vitamin D_3/day	The single dose group had significantly greater maternal 25(OH)D concentrations than the daily dose group on days 1, 3, and 7, but not on days 14 and 28. In the single dose group, maternal 25(OH)D values peaked on day 3, and the maximum value observed in any mother was 72 ng/mL. By day 28 the increase in 25(OH)D between baseline and day 28 was 11.9 +/− 4.2 ng/mL in the single dose group and 15.0 +/− 5.7 ng/mL in the daily dose group (p = 0.06). None of the mothers' serum 25(OH)D concentration remained < 20 ng/mL

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88:1378-87. Reference [4]					on day 28 (daily dose group 43.9 +/− 11.8, range 22 - 71 ng/mL; single dose group 41.2 +/− 8.9, range 26 - 60 ng/mL). Human milk cholecalciferol concentrations mirrored serum concentrations, with peak values approximately 25% of serum values on day 1 in the single dose group. Human milk 25(OH)D was undetectable in all samples. By day 28, serum 25(OH)D had a nearly identical increase in the infants of both groups (significance not provided). By day 28, all infants achieved a serum 25(OH)D concentration > 20 ng/mL. The increase of the infant's 25(OH)D concentration was not related to their mother's increase of 25(OH)D concentration ($r = 0.07$, $P = 0.64$). No adverse events during the study were attributed to vitamin D.
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, 80:1752S-8S. Reference [12]	Randomized Controlled Trial	Positive	18 fully breastfeeding mother-infant pairs in Charleston, South Carolina	Group 1: Maternal supplement 1600 IU vitamin D_2 + 400 IU vitamin D_3 Group 2: Maternal supplement 3600 IU vitamin D_2 + 400IU vitamin D_3 Infants not supplemented	No adverse events were observed from taking up to 10 times the DRI for vitamin D for lactating women for a period of 3 months. Group 1 exhibited decreased vitamin D_3 ($P < 0.02$) but increased vitamin D_2 ($P < 0.0001$). The total circulating 25(OH)D (vitamin D_2 and D_3) increased from 27.6 +/− 3.3 to 36.1 +/− 2.3 ng/mL ($P < 0.05$). In group 2, total circulating 25(OH)D increased from 32.9 +/− 2.4 to 44.5 +/− 3.9 ng/mL ($P < 0.04$). Both vitamin D_2 and D_3 also increased ($P < 0.04$ and $P < 0.06$, respectively). Although 25(OH)D_3 concentrations did not differ between groups during the study period, there were significant differences between the 2 groups with respect to 25(OH)D_2 concentrations ($P < 0.01$), with higher concentrations in the 4000 IU group. Group 1 exhibited increases in milk ARA from 35.5 +/− 3.5 to 69.7 +/− 3.0 IU/L ($P < 0.0001$). Group 2 exhibited increases in milk ARA from 40.4 +/− 3.7 to 134.6 +/− 48.3 IU/L ($P < 0.0001$). Group 1 infants exhibited increases in circulating vitamin D_3 and D_2 concentrations (7.9 +/− 1.1 to 21.9 +/− 4.7 ng/mL and <0.5 to 6.0 +/− 1.0 ng/mL, respectively) ($P < 0.02$ and $P < 0.0007$, respectively). Total circulating 25(OH)D concentrations increased from 7.9 +/− 1.1 to 27.8 +/− 3.9 ng/mL ($P < 0.02$). Group 2 infants exhibited vitamin D_3 increases (12.7 +/− 3.4 to 18.8 +/− 4.1 ng/mL, $P < 0.2$) and vitamin D_2 increases (0.8 +/− 0.4 to 12.0 +/− 1.4 ng/mL, $P < 0.0001$). Total circulating 25(OH)D concentrations increased from 13.4 +/− 3.3 to 30.8 +/− 5.0 ng/mL ($P < 0.01$). Compared with infants in group 1, infants in group 2 exhibited higher vitamin D_2 concentrations at the end of the study period ($P < 0.003$).
Haggerty LL. Maternal supplementation for prevention and treatment of vitamin D deficiency in exclusively breastfed infants. Breastfeed Med. 2011, 6:137-44. Reference [6]	Narrative Review	Negative	5 articles reviewed	Study 1: All mothers received 400IU of vitamin D_3 /day Group 1 + 1600 IU vitamin D_2 /day. Group + 3600 IU of vitamin D_2/day	Study 1: There was a significantly higher increase in maternal serum 25(OH)D levels ($p < 0.01$) and directly correlated increase in infant serum 25(OH)D levels ($p < 0.003$) in the group that received 4000 IU/day compared to those who received 2000 IU/day. Human milk ARA in the 4000 IU group increased significantly higher than the other group ($p < 0.0001$). There were no adverse events in mothers or infants from

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				Study 2: All mothers received 400 IU of vitamin D_3/day. Group 1 infants received 300 IU of vitamin D_3 daily; mothers received no additional supplement Group 2 mothers a received + 6000 IU of vitamin D_3 daily. Study 3: Group 1 Maternal supplement 2000 IU vitamin D_2/day. Group 2 Maternal supplement 60,000 IU D_2 monthly. Infants were not supplemented or tested in study 3. Study 4: Mothers and infants supplemented simultaneously at undefined levels.	consuming a daily intake of vitamin D up to 10 times the daily recommended intake. Study 2: There were significantly higher increases in maternal serum 25(OH)D levels for the high-dose-supplemented mothers than those taking 400 IU daily (p < 0.0028). The mean maternal 25(OH)D levels in the 6400 IU group rose quickly within the first month and stabilized after 3 months. Maternal 25(OH)D levels of those receiving 400 IU daily rose slightly, but still within the insufficient range. There was no significant difference between groups with infant mean 25(OH)D. Both groups of infants had increases from baseline 25(OH)D means, but still at insufficient levels. Considering levels were similar, this suggests that maternal supplementation of 6400 IU of vitamin D daily is equally effective as supplementing the infant with 300 IU of vitamin D daily. Human milk ARA correlated with the mother's 25(OH)D level. Those taking 6400 IU/day showed significantly increased ARA (p < 0.0003). There was no evidence of toxicity in either group, based on serum calcium, phosphorus levels, and urine calcium/creatinine ratios. Study 3: Lactating women had significantly lower baseline 25(OH)D means compared to nulliparous women (p < 0.001). Although the serum 25(OH)D levels in lactating women increased significantly in both intervention groups (p < 0.001), the 25(OH)D levels reached greater than or equal to 50 nmol/L in only 35% of the daily dosage group and 20% of the monthly intervention group. Nulliparous women had similar results for sufficient levels of 25(OH)D (36% in the daily group and 33% in the monthly group). Monthly doses, with a spike of milk vitamin D levels within 24 hours of maternal dosing and then a rapid decrease of milk vitamin D levels, are significantly efficacious than daily dosing for maintaining adequate milk vitamin D levels. Monthly dosing may still be preferred in an extremely noncompliant patient population versus no supplementation at all. Study 4: 94% of infants were deficient at baseline. Combined maternal and infant supplementation increased the infant mean 25(OH)D levels by 33.2 nmol/L. A 64% reduction of vitamin D deficiency (p < 0.0001) was demonstrated without adverse effects. Mean 25(OH)D remained considerably below the insufficient level of 32 ng/mL. Mean ARA at baseline was undetectable (<20 IU/L) and increased to a median vitamin D level of 50.9 IU/L after 3 months of supplementation.
Taylor SN, Wagner CL, Hollis BW. Vitamin D supplementation during lactation to support infant and mother. J Am Coll Nutr. 2008, 27:690-701. Reference [7]	Narrative Review	Negative	3 studies reviewed	Study 1: Group 1: 2000 IU vitamin D_3 maternal intake, Group 2: 400 IU vitamin D_3 infant intake. Study 2: Group 1: 1600 IU vitamin D_2 + 400	Study 1 showed equivalent vitamin D status in the 2 infant comparison groups. Maternal supplementation of 1000 IU/day vitamin D_3 did increase serum 25(OH)D concentrations in infants to levels considered sufficient to avoid rickets. Study 2 found that mothers experienced significant increases in total circulating 25(OH)D concentrations and 25(OH)D_2, but there were decreases in 25(OH)D_3. The significant

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				IU D$_3$, Group 2: 3600 IU vitamin D$_2$ + 400 IU D$_3$. Study 3: Group 1: 400 IU D$_3$ for mothers + 300 IU D$_3$ for infants, Group 2: 6400 IU D$_3$ for mother.	improvement in maternal vitamin D status translated into increases in the vitamin D activity in the milk, but it did not reach 400 IU/L. The 2000 IU group had a mean milk ARA of 69.7 +/− 3.0 IU/L. Mothers in the 4000 IU group had a mean milk ARA of 134.6 +/− 48.3 IU/L. Infants experienced a significant improvement in 25(OH)D levels in both groups, though still insufficient. Study 3 found that mothers receiving 6400 IU/day for 6 months had an increase in milk ARA from 82 to 873 IU/L. This increase in vitamin D supply to the infant achieved infant vitamin D status equal to that observed with direct infant supplementation of 300 IU/day. Mothers demonstrated significant improvement in vitamin D status. No toxicity was observed in mothers or infants throughout the 6 month study period.
Thiele DK, Senti JL, Anderson CM. Maternal vitamin D supplementation to meet the needs of the breastfed infant: a systematic review. J Hum Lac. 2013, 29:163-70. Reference [1]	Systematic Review	Positive	3 articles were reviewed	Study 1: Group 1 Maternal supplement 2000 IU vitamin D/day (400 as D$_3$ and 1600 as D$_2$). Group 2 Maternal supplement 4000 IU/day (400 as D$_3$ and 3600 as D$_2$). Study 2: Group 1 Maternal supplement 400 IU vitamin D$_3$/day, infants received 300 IU vitamin D$_3$. Group 2 Maternal supplement 6400 IU vitamin D$_3$/day; infants received a placebo. Study 3: Group 1 Maternal supplement 2000 IU vitamin D$_2$/day. Group 2 Maternal supplement 60,000 IU vitamin D$_2$ monthly. Infants received 400 IU vitamin D$_2$/day.	Maternal and infant serum 25(OH)D levels increased in direct relationship to maternal vitamin D intake. Maternal vitamin D supplementation during lactation has an equivalent effect on infant 25(OH)D status as direct infant supplementation but also the potential to benefit both mother and child. There is no evidence to suggest that maternal vitamin D supplementation that results in physiologic 25(OH)D levels in the mother and breastfeeding infant lead to any ill effects, as demonstrated by no change in vitamin D toxicity markers.
Dawodu A, Tsang RC. Maternal vitamin D status: effect on milk vitamin D content and vitamin D status of breastfeeding infants. Adv *Nutr. 2012, 3:353-61. Reference [5]	Narrative Review	Negative	3 studies reviewed	Study 1: Group 1 Maternal supplement 2000 IU vitamin D/day. Group 2 Maternal supplement 1000 IU vitamin D/day. Group 3 No maternal supplementation; infants received 400 IU/day. Study 2: Group 1 Maternal supplement	High-dose supplementation of 4000 IU/day and 6400 IU/day of vitamin D in healthy lactating mothers can increase the vitamin D concentration of milk to a level that supplies adequate vitamin D intake for the breastfeeding infant even though both mother and infant were limited in sunlight exposure. Vitamin D deficiency in exclusively breastfed infants appears to be an underdiagnosed public health problem in many countries and that rickets may be an underrepresentation of the magnitude of vitamin D deficiency. Multiple studies from the US and Europe show that supplementation of breastfeeding infants with 400 IU/day of vitamin D is sufficient to prevent

Continued

	2000 IU/day (400 as D_3 and 1600 as D_2). Group 2 Maternal supplement 4000 IU/day (400 as D_3 and 3600 IU as D_2). Study 3: Group 1 Maternal supplement 400 IU D_3/day; infants received 300 IU D_3/day. Group 2 Maternal supplement 6400 IU D_3/day; infants received placebo.	vitamin D deficiency when sun exposure is limited. It is unknown whether such intake is adequate in dark-skinned infants in parts of the world where there is a high prevalence of severe vitamin D deficiency. There is also poor compliance with vitamin D supplementation of breastfeeding infants. The strategy of vitamin D supplementation of the breastfeeding infant does not address the concomitant high prevalence of vitamin D deficiency in their mothers. Maternal vitamin D supplementation of at least 2000 IU/day is required to provide a significant amount of vitamin D in the human milk for breastfeeding infants. Study 1 mothers who were supplemented with 2000 IU or 1000 IU had significantly higher 25(OH)D ($p < 0.01$). In Study 2, after 3 months of supplementation, the infants in the 2000 IU group had significantly lower serum 25(OH)D_2 levels than infants of mothers in the 4000 IU group ($p = 0.003$). In Study 3, after the 6 months of vitamin D supplementation, the mean ARA in milk was significantly higher in the 6400 IU group than the 400 IU group (p value not provided). Infants serum 25(OH)D were similar between groups: infants in the 400 IU group was 43 ug/L at the end of the study compared to 46 ug/L in the 6400 IU group. There was no evidence of toxicity in mothers or infants in either group.

Quality Rating Scale for Original Studies: Positive Quality—Most of the answers to the quality/validity questions were "yes" (including criteria 2, 3, 6, 7 and at least one other additional criterion); Neutral Quality—Answers on quality criteria 2, 3, 6, and 7 did not indicate that the study was exceptionally strong; Negative Quality—If six or more of answers on validity questions were no. Quality Rating Scale for Reviews: Positive Quality—if most of the answers on validity questions 1 - 4 were "yes"; Neutral Quality—if answers to any one of the first four validity questions was "no"; Negative Quality—if most (six or more) or the answers to validity questions are "no".

were supplemented with 1600 IU vitamin D_2 plus 400 IU vitamin D_3 from a multivitamin. Mothers in this group exhibited decreased serum D_3 ($p < 0.02$); a comparison group which received 3600 IU vitamin D_2 plus 400 IU vitamin D_3 demonstrated an increase in circulating total vitamin D species ($p < 0.06$). Both groups had increased vitamin D_2 ($p < 0.0001$; $p < 0.04$, respectively). Total circulating 25(OH)D increased in group 1 mothers from 27.6 ± 3.3 to 36.1 ± 2.3 ng/mL ($p < 0.05$), compared to group 2 mothers whose circulating 25(OH)D increased from 32.9 ± 2.4 to 44.5 ± 3.9 ng/mL ($p < 0.04$). Between groups, maternal 25(OH)D_3 did not differ; however, 25(OH)D_2 was significantly higher in the group receiving the larger dose of D_2 ($p < 0.01$). Milk ARA was doubled in the first group from 35.5 ± 3.5 to 69.7 ± 3.0 IU/L ($p < 0.0001$) compared with a much greater increase in those supplemented at the higher level in which the change was from 40.4 ± 3.7 to 134.6 ± 48.3 IU/L ($p < 0.0001$). In breastfed infants, vitamin D_3 increased in both groups, from 7.9 ± 1.1 to 21.9 ± 4.7 ng/mL ($p < 0.02$) with the lower level supplement from 12.7 ± 3.4 to 18.8 ± 4.1 ng/mL ($p < 0.2$). Vitamin D_2 increased in both groups, the increase being twice as great in the infants whose mothers were supplemented at the higher level ($p < 0.0001$). Total circulating 25(OH)D concentrations increased to the same extent in both groups. Although milk ARA never reached concentrations high enough to meet

the DRI of 400 IU per day, infants in this study did not show signs of deficiency after 3 months of supplementation.

Basile *et al.* completed a similar randomized controlled trial using the same vitamin D_2 and vitamin D_3 intervention [3]. Researchers enrolled 25 fully breastfeeding mother-infant pairs. In the group receiving the lowest level of D_2, maternal serum D_2 increased from 22.4 ± 8.8 to 33.9 ± 6.5 (p = 0.002); and with the higher level of supplement, increased from 28.5 ± 8.6 to 43.0 ± 11.6 (p = 0.0008). Between groups, the highest level supplement resulted in significantly higher serum 25(OH)D levels (p = 0.03). Serum 25(OH)D levels increased in both groups of infants but infants breastfed by mothers given the highest level of D_2 had significantly greater increases in serum 25(OH)D. Milk ARA was not measured in this study.

3.2. Daily Vitamin D Supplementation Interventions

In 2006, Wagner *et al.* studied 10 fully breastfeeding mother-infant pairs [11]. Mothers in Group 1 were supplemented with 400 IU vitamin D_3 and infants were supplemented with 300 IU vitamin D_3. In the second group, mothers were supplemented with 6400 IU vitamin D_3 and infants received a placebo. Of note, only four mother-infant pairs completed the entire study, but using an intent-to-treat approach, all 10 pairs were included in analysis. Total circulating 25(OH)D levels decreased in mothers in group 1 through visit 5; there was a slight improvement at visits 6 and 7 that corresponded to increased outdoor activities and sun exposure. Mothers in group 2 had an immediate increase in 25(OH)D levels that was sustained throughout the study period (significance not provided). Compared to group 1, the mean milk ARA in group 2 significantly increased to 873 IU/L (p < 0.0003), which resulted in a dramatic rise in infant circulating 25(OH)D levels. This rise in infant 25(OH)D was almost identical to that in the infants receiving 300 IU per day vitamin D_3 directly via oral supplementation.

Hollis *et al.* conducted a study of 95 fully breastfeeding mother-infant pairs in 2015 [13]. The intervention began with three groups: 400 IU vitamin D_3 for mothers plus 400 IU vitamin D_3 for infants; 2400 IU vitamin D_3 to mothers, placebo for infant; and 6400 IU vitamin D_3 for mothers, placebo to infants. Partway through the study, the 2400 IU group was discontinued due to safety concerns regarding low infant 25(OH)D levels. Therefore, only the 400 IU group (group 1) and the 6400 IU group (group 2) were included in analysis. Maternal 25(OH)D decreased −10.5 nmol/L from visit 1 (V1) to visit 7 (V7) in group 1 (p = 0.02) and increased +51.3 nmol/L in group 2 between V1 and V7 (p < 0.0001). At V1, maternal 25(OH)D was similar between groups (p = 0.17); at V4, group 2 had significantly higher 25(OH)D (150.5 ± 47.1 nmol/L compared to 83.0 ± 29.1 nmol/L, p < 0.0001). At V7, group 2 continued to have significantly higher maternal 25(OH)D (151.2 ± 51.3 nmol/L compared to 79.0 ± 31.3 nmol/L, (p < 0.0001). Infant 25(OH)D increased in both groups from V1 to V7 (Group 1: 36.0

± 26.1 nmol/L to 109.1 ± 31.8 nmol/L, significance not provided; Group 2: 41.0 ± 25.6 nmol/L to 108.5 ± 38.0 nmol/L, significance not provided). Between groups, there was no statistical significance at any time point (V1 p = 0.35; V4 p = 0.10; V7 p = 0.94). This suggests that high-dose maternal supplementation of 6400 IU vitamin D_3 daily is as effective as direct infant supplementation of 400 IU daily.

3.3. Monthly Vitamin D Supplementation Interventions

Wheeler, *et al.* completed a randomized controlled trial in 2016 with 87 exclusively breastfeeding mother-infant pairs in New Zealand [2]. Group 1 mothers received a placebo; Group 2 mothers received 50,000 IU vitamin D_3 per month; and Group 3 mothers received 100,000 IU vitamin D_3 per month. Vitamin D supplemented mothers had a significantly higher serum 25(OH)D concentrations at study end compared to placebo (p = 0.043 in group 2; p = 0.001 in group 3). Infant change in serum 25(OH)D was not significantly different between groups (p = 0.67 in group 2; p = 0.13 in group 3). In group 1, 26% of mothers exhibited vitamin D deficiency, compared to 4% of women in group 2, and 0% in group 3 (p = 0.002). Deficiency rates between infants in all groups were similar (27%, 29%, and 19%, respectively; p = 0.65).

3.4. Daily versus Monthly Vitamin D Supplementation

Oberhelman, *et al.* conducted a randomized controlled trial of 40 exclusively breastfed mother-infant pairs to evaluate the difference between monthly supplementation with 150,000 IU vitamin D and daily supplementation with 5000 IU vitamin D per day for 1 month [4]. The monthly supplement was provided to mothers at study visits. Compliance with daily supplementation was monitored and found to be excellent (98%). Those receiving the once monthly dose had significantly higher 25(OH)D concentrations than on days 1, 3, and 7, but not on days 14 and 28 (significance not provided). With monthly supplementation, maternal 25(OH)D levels peaked on day 3, and the maximum value observed in any mother was 72 ng/mL. By day 28, the increase in 25(OH)D between baseline and day 28 was 11.9 ± 4.2 ng/mL in those receiving the once monthly dose and 15.0 ± 5.7 ng/mL with daily dosing. (p = 0.06). None of the mothers' serum 25(OH)D concentrations remained < 20 ng/mL on day 28 (group 1 values: 43.9 ± 11.8 ng/mL, range 22 - 71; group 2 values: 41.2 ± 8.9 ng/mL, range 26 - 60 ng/mL). Human milk cholecalciferol concentrations mirrored serum 25(OH)D concentrations, with peak values approximately 25% of serum values. By day 28, serum 25(OH)D levels increased in the infants of both groups and all infants achieved a serum 25(OH)D concentration >20 ng/mL. However, increases in infant's 25(OH)D levels did not directly correlate with maternal increases in maternal 25(OH)D (r = 0.07, p = 0.64). A recent study (Nalk, 2017) evaluated effectiveness of maternal supplementation with 600,000 IU vitamin D in divided doses over 10 days in the early postpartum period on maternal and infant serum

25(OH) D levels and measures of rickets in exclusively breastfed infants. Maternal 25(OH)D levels after 6 months of study were greater 40.3 ± 21.6 ng/mL in supplemented vs 22.9 ± 20.18 ng/mL in controls. Infant levels were also higher (29.29 ± 14.67 ng/mL) in those fed by supplemented mothers and 15.73 ± 17.73 ng/mL in controls. After 6 months of exclusive breastfeeding, only one mother and four infants had serum 25 (OH) D levels < 11 ng/ml in the supplemented group (n = 53) vs 9 mothers and 25 infants (n = 57) in the control. Although 2 infants in each group developed clinical rickets. This study suggests that large divided doses may be effective in preventing vitamin D deficiency in mothers and infants during the first six months of breastfeeding [19].

4. Discussion

Healthy people 2020 set a breastfeeding target of 81.9% of infants "ever being breastfed" [17]. Breast milk is considered to be the gold-standard for infant nutrition, providing all the nutrients the young infant requires. It is therefore important to evaluate whether the adequacy of Vitamin D in breast milk can be insured through maternal intake.

The results of the available studies demonstrate that high-dose daily maternal vitamin D supplementation (ranging from 4000 IU to 6000 IU/day) during lactation is effective in improving both maternal and infant vitamin D status. Monthly supplementation at levels of 150,000 IU corrected both maternal and infant deficiency but not at lower levels (50,000 IU and 100,000 IU). This is likely because cholecalciferol is quickly converted to 25(OH)D by the mother; cholecalciferol is the main form of vitamin D transferred into human milk [1] [4]. Therefore, daily supplementation may be preferred to optimize infant vitamin D status. There is some concern surrounding compliance. Mothers who received monthly vitamin D supplementation in the reviewed studies were administered their dose on-site; mothers who received daily supplementation were largely responsible for their own administration. An unrelated study in Japan found that monthly dosing of bisphosphonates for osteoporosis had higher compliance compared to daily and weekly dosing [18]. Additional studies assessing compliance in relation to maternal self-administered vitamin D supplementation need to be conducted to confirm these results. Previous studies demonstrate that vitamin D_3 is more bioavailable than vitamin D_2; [6] [7] [11] this needs to be confirmed in the current context as studies with varying types of vitamin D did not assess similar doses.

Limitations of the research to support the question of vitamin D supplementation is a general lack of standards for acceptable levels of serum 25(OH)D, the diagnosis of vitamin D insufficiency and vitamin D deficiency. The studies were heterogeneous with respect to intervention protocol, timing and levels of supplementation. Additional studies assessing safety of long-term, high-dose vitamin D supplementation are warranted. The longest study follow-up was 7 months, the effects of longer term supplementation on infant outcomes and ma-

ternal and infant toxicity are lacking.

5. Conclusion

Seven randomized controlled trials and four reviews demonstrate that maternal supplementation of vitamin D may be an effective method of improving breastfed infants' vitamin D status. However, there is no consensus as to which dose is ideal, both in timing (monthly versus daily) and quantity. This is further compounded by the fact that there is no agreement on the classification of vitamin D deficiency on the basis of serum 25(OH) D levels. Furthermore, the dose apparently necessary to correct both the mother's and infant's vitamin D status is well above the Adequate Intake of 600 IU per day. In fact, the Tolerable Upper Limit is set at 4000 IU during lactation, which appears to be the minimum dose necessary to meet the nursing infant's vitamin D needs. The Food and Nutrition Board of the National Academies of Science, Engineering, and Medicine should consider revising the Dietary Reference Intakes for vitamin D, given the evidence that higher doses show no signs of adverse events and are necessary to meet the vitamin D needs of both the mother and infant. Additionally, the AAP should likewise consider revising their statement on infant supplementation of vitamin D to include high-dose maternal supplementation of approximately 4000 IU per day as adequate in lieu of direct infant supplementation. Ideally, further studies evaluating the ideal dose and confirming other studies' results should be conducted. It appears that daily dosing is the most effective method for improving both maternal and infant vitamin D status. Based on this evidence, practitioners may confidently recommend maternal-only supplementation of vitamin D at a minimum dose of 4000 IU per day.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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