Trial of Daily Vitamin D Supplementation in Preterm Infants

WHAT’S KNOWN ON THIS SUBJECT: Despite widespread prevalence of vitamin D deficiency, there is a paucity of evidence on the appropriate supplemental dose in preterm infants. Various professional organizations empirically recommend different doses of vitamin D, ranging from 400 to 1000 IU per day.

WHAT THIS STUDY ADDS: Daily vitamin D supplementation at a dose of 800 IU compared with 400 IU significantly reduces the prevalence of vitamin D deficiency in preterm infants. The clinical significance of achieving vitamin D sufficiency needs to be studied in larger trials.

abstract

OBJECTIVE: To compare the effect of 800 vs 400 IU of daily oral vitamin D₃ on the prevalence of vitamin D deficiency (VDD) at 40 weeks’ postmenstrual age (PMA) in preterm infants of 28 to 34 weeks’ gestation.

METHODS: In this randomized double-blind trial, we allocated eligible infants to receive either 800 or 400 IU of vitamin D₃ per day (n = 48 in both groups). Primary outcome was VDD (serum 25-hydroxyvitamin D levels <20 ng/mL) at 40 weeks’ PMA. Secondary outcomes were VDD, bone mineral content, and bone mineral density at 3 months’ corrected age (CA).

RESULTS: Prevalence of VDD in the 800-IU group was significantly lower than in the 400-IU group at 40 weeks (38.1% vs 66.7%; relative risk: 0.57; 95% confidence interval: 0.37–0.88) and at 3 months’ CA (12.5% vs 35%; relative risk: 0.36; 95% confidence interval: 0.14–0.90). One infant (2.4%) in the 800-IU group had vitamin D excess (100–150 ng/mL). Bone mineral content (mean ± SD: 79.6 ± 16.8 vs 84.7 ± 20.7 g; P = .27) and bone mineral density (0.152 ± 0.019 vs 0.158 ± 0.021 g/cm²; P = .26) were not different between the 2 groups.

CONCLUSIONS: Daily supplementation with 800 IU of vitamin D reduces the prevalence of VDD at 40 weeks’ PMA and at 3 months’ CA in preterm infants without showing any improvement in bone mineralization. However, there is a possibility that this dose may occasionally result in vitamin D excess. Pediatrics 2014;133:e628–e634


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KEY WORDS
DXA, preterm, supplementation, vitamin D

ABBREVIATIONS

ALP—alkaline phosphatase
BMC—bone mineral content
BMD—bone mineral density
CA—corrected age
CI—confidence interval
DXA—dual-energy radiograph absorptiometry
GA—gestational age
NNT—number needed to treat
PMA—postmenstrual age
PTH—parathyroid hormone
RR—relative risk
UCa/Cr—urine calcium:creatinine ratio
VDD—vitamin D deficiency
25(OH)D—25-hydroxyvitamin D

Dr Natarajan conceptualized and designed the study and drafted the initial manuscript; Drs Sankar and Agarwal helped in designing the study and with data collection instruments and analysis and critically reviewed the manuscript; Dr Pratap helped in data collection and analysis; Drs Jain, A. K. Gupta, Deorari, and Paul helped in designing the study and critically reviewed the manuscript; Dr N. Gupta helped in designing the study and with analysis of the samples for vitamin D and parathyroid hormone; Dr Sreenivas helped in designing the study and with analysis and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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Vitamin D, a fat-soluble vitamin, is essential for absorption of calcium from intestine, which, in turn, determines the skeletal health and other physiologic processes such as neuromuscular function. Inadequate serum vitamin D levels have been reported to result in a multitude of health problems in children, including rickets and increased susceptibility to infections, among others.1–4 Vitamin D deficiency (VDD) is common among infants, children, and pregnant and lactating mothers.5–7 Preterm infants often have less vitamin D stores due to decreased transplacental transfer from deficient mothers and may also have a higher requirement.8,9 The prevalence of vitamin D insufficiency (serum 25-hydroxyvitamin D [25(OH)D] <30 ng/mL) in preterm infants was 97.4% in a study from India,7 whereas severe deficiency (serum 25(OH)D levels <5 ng/mL) was found in 44% of the preterm infants in an Arab population.10 Vitamin D requirements in adults and older children are met from foods of animal origin, fortified foods, and/or through de novo synthesis in skin after UV-B exposure. Breast milk from mothers who are not receiving vitamin D supplementation or who have inadequate exposure to sunlight contains only 20 to 60 IU of antirachitic activity, which is insufficient to meet the requirements of the infant.11–14 Moreover, de novo synthesis of vitamin D in skin after UV-B exposure may not be safe.15 Therefore, newborn infants have to be supplemented with vitamin D. The American Academy of Pediatrics recommends that breastfed and partially breastfed infants should be supplemented with 400 IU/day of vitamin D.16 On the other hand, the European Society of Pediatric Gastroenterology, Hepatology and Nutrition recommends daily supplementation of 800 to 1000 IU/day for preterm infants in the first months of life.8 The World Health Organization recommends 400 IU to 1000 IU/day of vitamin D supplementation in low birth weight infants.17 Lack of evidence and the consequent disparate recommendations have resulted in varying practices among treating physicians. Therefore, we planned this randomized trial to determine the optimal dose of vitamin D supplementation in preterm infants.

The objective of this study was to compare the prevalence of VDD (serum 25(OH)D levels <20 ng/mL) at 40 weeks’ postmenstrual age (PMA) in preterm infants born at 28 to 34 weeks’ gestational age (GA) and randomly assigned to receive either 800 or 400 IU of vitamin D3/day.

METHODS

Subjects and Setting

We conducted this randomized double-blind trial in a level 3 neonatal unit in North India between August 2011 and March 2012. All preterm infants born between 28 and 34 weeks’ GA and receiving at least 100 mL/kg per day of enteral feedings by 2 weeks’ postnatal age were eligible for inclusion in the study. Infants with major malformations, those who received parenteral nutrition for ≥2 weeks, or those born to mothers receiving phenytoin therapy or with HIV infection were excluded. GA was ascertained by using either the first day of the last menstrual period, the first-trimester ultrasound, or Expanded New Ballard Score.18 Eligible infants were stratified by GA into 2 strata: 280/7 to 316/7 weeks and 320/7 to 346/7 weeks. Informed written consent was obtained from the parents before enrollment. The study was approved by the Ethics Committee of All India Institute of Medical Sciences (AIIMS).

Randomization

Infants in both strata were randomly assigned to receive oral vitamin D3 at a dose of 800 or 400 IU/day. We used computer-generated random numbers to allocate infants to 1 of the study groups with a fixed block size of 4. Random allocation was concealed by assigning sequential numbers to identical-appearing bottles containing 2 different strengths of vitamin D preparations as per random allocation. Amber-colored bottles containing identical-appearing drug suspensions ensured blinding of investigator and parents.

Intervention

The intervention was started after drawing a blood sample from the infants for estimation of serum 25(OH)D, parathyroid hormone (PTH), calcium, phosphorus, and alkaline phosphatase (ALP). The study drug preparations (Basic Human Health Care Private Ltd, Delhi, India) were tested for vitamin D3 content at Sigma Testing and Research Center, Delhi, a nationally accredited laboratory. It was found that the high-dose preparation (800 IU/mL) contained 859 IU/mL and the low-dose preparation (400 IU/mL) contained 422 IU/mL of vitamin D3.

The drug bottles were labeled with a unique study enrollment number. One milliliter of drug measured to the accuracy of 0.1 mL was administered once daily to the infant either directly or mixed in expressed breast milk. Mothers were counseled for exclusive breastfeeding at discharge. In those infants who were also receiving human milk fortifier in breast milk or formula feedings, the dose of the study drug was reduced as per the vitamin D content of human milk fortifier or formula, so that the total intake did not exceed 800 or 400 IU/day in the respective groups. We ensured compliance of the drug intake by asking the mother to maintain a daily diary of doses administered after discharge.

Outcome Variables

The primary outcome variable was prevalence of VDD at the PMA of 40 ± 2 weeks. Secondary outcomes included the following: VDD at the corrected age (CA) of 3 months; serum levels of calcium, phosphorus, ALP, and PTH at a PMA of 40 ± 2 weeks and at 3 months’ CA; the proportion of infants with vitamin D
excess, nephrocalcinosis, or hypercalcemia (urine calcium:creatinine ratio [UCa/Cr] >0.8 mg/mg) at 40 weeks and at 3 months’ CA, and bone mineral content (BMC) and bone mineral density (BMD) measured by dual-energy radiograph absorptiometry (DXA) at 3 months’ CA. VDD was defined as serum 25(OH)D levels <20 ng/mL,16 severe VDD as levels <5 ng/mL, and vitamin D excess as levels of 100 to 150 ng/mL.2

**Outcome Measurement**

Serum 25(OH)D was assayed by an autoanalyzer (DiaSorin Liaison, Stillwater, MN) using a chemiluminescent tracer, with a measuring range of 4 to 150 ng/mL. Serum PTH levels were estimated by using electrochemiluminometric assay using a Beckman Coulter Synchron-CX9 PRO clinical system (Beckman Coulter, Inc). Blood samples were analyzed for serum 25(OH)D and PTH on the same day. Sera were stored at −20°C for the subsequent analysis of calcium, phosphorus, and ALP, with infant-specific software using fan beam technology with a precision of 1%. Daily quality control of DXA was performed by using a spine phantom with an area of 54.7 cm², a BMC of 1.4 g, and a BMD of 0.94 g/cm².

**Statistical Analysis**

Statistical analysis was performed by using Stata 11.2 version (StataCorp, College Station, TX). Analysis was performed by intention to treat. Continuous data were expressed as means and SDs or medians with ranges, whereas categorical variables were expressed as proportions. Student’s t test was used for the analysis of continuous variables that were normally distributed, whereas Wilcoxon rank-sum test was used for skewed data. Categorical variables were analyzed by using χ² test or Fisher’s exact test. We also calculated the relative risk (RR), risk difference, and number needed to treat (NNT) with 95% confidence intervals (CIs) for categorical variables and mean differences with 95% CIs for continuous variables.

**Sample Size**

In an earlier study by Backström et al,19 mean (±SD) 25(OH)D levels at 6 weeks’ postnatal age were found to be 18.3 ± 7.4 and 26.7 ± 12.1 ng/mL in low-dose (≤400 IU/day) and high-dose (960 IU/day) groups, respectively. Assuming that the levels were normally distributed, we estimated that ~70% to 75% of the infants in the low-dose group would be categorized as vitamin D–deficient (serum 25(OH)D <20 ng/mL) at 6 weeks’ postnatal age. Assuming an estimate of prevalence of deficiency of 75% in the 400-IU group, we needed to enroll 40 infants per group to detect a 50% decrease in the prevalence of VDD after supplementation with 800 IU/day, with a power of 90% and an α error of 0.05. We planned to enroll 48 infants per group to account for loss to follow-up.

**RESULTS**

Of the 1461 live births during the study period, 130 infants were born between 28 and 34 weeks’ gestation. After excluding 34 infants on the basis of pre-specified criteria, we enrolled 96 infants in the study (Fig 1). Clinical and baseline characteristics of the study population were comparable between the 2 groups (Table 1).

Study intervention was initiated in 94 infants because consent was withdrawn by 2 parents soon after randomization. Of these 94 infants, 3 infants died before follow-up at 40 weeks (1 due to stage 3 necrotizing enterocolitis and 2 due to probable milk aspiration); another 4 infants were lost to follow-up. Thus, a total of 87 infants (95.6% of those who survived) were available for follow-up at 40 ± 2 weeks. At 3 months’ CA, 80 infants (88.9% of those who survived) were available for analysis because 6 infants were lost to follow-up and 1 infant had died due to sudden infant death (Fig 1).

**Baseline Characteristics**

VDD at baseline in the 800-IU and the 400-IU groups was 79% and 83%, respectively (P = .57). Serum levels of 25(OH)D, PTH, calcium, phosphorus, and ALP were also comparable at baseline (Table 1). There was no difference in exclusive breastfeeding rates in both groups at 40 weeks’ PMA (78.6% vs 64.4%; P = .15) and at 3 months’ CA (67.5% vs 50.0%; P = .12). Regular oral vitamin D intake (≤500 IU/day) by mothers was high at 40 weeks (97.6% vs 84.4%; P = .06), whereas at 3 months’ CA it decreased (56.4% vs 53.8%; P = .82) in both groups.

**Primary Outcome**

The proportion of infants with VDD was significantly lower in the 800-IU group than in the 400-IU group at 40 weeks (38.1% vs 66.7%; RR: 0.57; 95% CI: 0.37–0.88; P < .01). The NNT was 4 (95% CI: 2–12). Serum 25(OH)D levels at 40 weeks were significantly higher in the 800-IU group compared with the 400-IU group (median [range]: 22.6 [6.2–88.4] vs 15.7 [4–43.1] ng/mL; P < .001) (Table 2, Fig 2).

**Secondary Outcomes**

**VDD at 3 Months’ CA**

Serum 25(OH)D levels increased further and the proportion of infants with VDD decreased from 40 weeks to 3 months’ CA in both groups. The prevalence of VDD was again lower in the 800-IU group (12.5% vs 35%; RR: 0.36; 95% CI: 0.14–0.90; NNT: 4; 95% CI: 3–20) (Table 2).

**Markers of Vitamin D Status**

Serum levels of PTH, calcium, phosphorus, and ALP were not significantly
different between the groups at 40 weeks and 3 months’ CA (Table 3).

Bone Mineralization
DXA was performed in 85% (68 of 80) of the infants at 3 months’ CA. BMC was comparable between the groups (mean ± SD: 79.6 ± 16.8 vs 84.7 ± 20.7 g; P = .27). BMD also did not differ significantly between the groups (Table 3).

Vitamin D Excess
One infant in the 800-IU group had serum 25(OH)D of 141 ng/mL at 3 months’ CA. However, there was no hypercalcemia, hypercalciuria, or nephrocalcinosis. Serum 25(OH)D level was in the deficiency range at baseline (16.9 ng/mL) and in the insufficiency range at 40 weeks (26.7 ng/mL) in this infant. The infant was not receiving any supplements other than the trial drug, and there was no inadvertent excess intake of the drug at any time. We could not check the actual vitamin D content in the drug that the infant was receiving.

Vitamin D Toxicity Profile
UCa/Cr was measured in 66% (58 of 87) of infants at 40 weeks and in 63% (50 of 80) at 3 months’ CA, and it was comparable in both groups. There was no difference in the proportion of infants with UCa/Cr >0.8 at 40 weeks (64% vs 43%) and at 3 months’ CA (15.4% vs 20.8%) (Table 3). None of the infants had nephrocalcinosis on renal ultrasound at 40 weeks and at 3 months’ CA (Table 3).

DISCUSSION
This randomized trial of vitamin D supplementation was planned to determine the optimal dose of daily vitamin D supplementation required to achieve sufficient vitamin D levels in preterm infants and to study the effect of supplementation on bone mineralization. Despite the fact that the prevalence of VDD was comparable in infants in both groups at baseline, a significant decline in VDD was observed at 40 weeks and at 3 months in the 800-IU group. This improvement in VDD status at 40 weeks could be attributed solely to daily supplementation with 800 IU of vitamin D given that breast milk probably is a poor source of vitamin D due to the high prevalence of VDD in lactating mothers in India and de novo synthesis from sun exposure is not a reliable source of vitamin D in infants. More than one-third of infants in the 800-IU group were still vitamin D–deficient at 40 weeks, raising concerns that even 800 IU of vitamin D daily may be inadequate in achieving sufficient vitamin D levels by 40 weeks, at least in some infants. This finding was probably due to the duration of vitamin D supplementation being not long enough, in the presence of low baseline serum 25(OH)D levels. The efficacy and safety of a bolus dose of vitamin D in rapidly increasing serum 25(OH)D levels >20 ng/mL need to be studied in preterm infants, even though the clinical significance of maintaining sufficient vitamin D levels is uncertain.

To our knowledge, this study is the first trial of this kind with an adequate sample
TABLE 1  Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>800-IU Group (n = 48)</th>
<th>400-IU Group (n = 48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Age, y</td>
<td>28.1 ± 5.4</td>
<td>28.3 ± 4.7</td>
<td>.87</td>
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<tr>
<td>Parity, n</td>
<td>4 (1–7)</td>
<td>4 (1–6)</td>
<td>.76</td>
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<tr>
<td>Gestational hypertension, n (%)</td>
<td>13 (28)</td>
<td>10 (21)</td>
<td>.47</td>
</tr>
<tr>
<td>Gestational diabetes mellitus, n (%)</td>
<td>5 (10)</td>
<td>8 (17)</td>
<td>.55</td>
</tr>
<tr>
<td>Receiving vitamin D supplementation at 40 weeks, n (%)</td>
<td>41 (88)</td>
<td>38 (84)</td>
<td>.06</td>
</tr>
<tr>
<td>Receiving vitamin D supplementation at 3 months, n (%)</td>
<td>22 (56)</td>
<td>21 (54)</td>
<td>.82</td>
</tr>
</tbody>
</table>

| Neonatal                              |                       |                       |       |
| GA, wk                                | 32.4 ± 1.9            | 32.5 ± 1.8            | .78   |
| Male gender, n (%)                    | 28 (54)               | 28 (58)               | .68   |
| Small for GA, n (%)                   | 17 (35)               | 12 (25)               | .52   |
| Apgar score at 5 minutes              | 9 (8–9)               | 9 (4–9)               | .68   |
| Birth weight, g                       | 1655 ± 411            | 1684 ± 513            | .68   |
| Length, cm                            | 41 ± 3                | 41.6 ± 4              | .39   |
| Occipitofrontal circumference, cm     | 29.4 ± 2.1            | 29.5 ± 2.3            | .91   |
| Respiratory distress syndrome, n (%)  | 7 (14)                | 7 (14)                | .99   |
| Bronchopulmonary dysplasia, n (%)     | 2 (4)                 | 1 (2)                 | .62   |
| Patent ductus arteriosus, n (%)       | 3 (6)                 | 3 (6)                 | .99   |
| Shock requiring inotropes, n (%)      | 4 (8)                 | 2 (4)                 | .68   |
| Feeding intolerance, n (%)            | 8 (17)                | 6 (13)                | .39   |
| Sepsis (clinical and culture positive), n (%) | 6 (13) | 5 (10) | .72   |
| Mechanical ventilation, n (%)         | 6 (13)                | 3 (6)                 | .49   |
| Continuous positive airway pressure, n (%) | 15 (31) | 14 (29) | .5    |
| Parenteral nutrition, n (%)           | 8 (17)                | 7 (15)                | .78   |

Vitamin D status

| VDD (<20 ng/mL), n (%) | 37 (79) | 40 (83) | .57   |
| Vitamin D severe deficiency (<5 ng/mL), n (%) | 7 (15)  | 6 (13)  | .73   |
| Serum calcium, mg/dL    | 9.6 ± 1.2 | 9.5 ± 1.1 | .83 |
| Serum phosphorus, mg/dL | 6.1 ± 1.6 | 6 ± 1.8  | .88  |
| Serum ALP, IU/L         | 173 (89–1037) | 150 (88–563) | .06 |
| Serum PTH, pg/mL        | 78.7 (52.2–379) | 83.7 (44.4–440) | .87 |
| Age at baseline sampling and initiation of intervention, d | 3 (1–14) | 3 (1–12) | .69 |

Data are presented as n (%), medians (range), or means ± SDs.

TABLE 2  VDD and Vitamin D Severe Deficiency at 40 Weeks’ PMA and 3 Months’ CA

<table>
<thead>
<tr>
<th>Variable</th>
<th>800-IU Group</th>
<th>400-IU Group</th>
<th>RR (95% CI)</th>
<th>P</th>
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<tbody>
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<td>40 ± 2 weeks’ PMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>42</td>
<td>45</td>
<td></td>
<td></td>
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<tr>
<td>VDD (&lt;20 ng/mL)</td>
<td>16 (38)</td>
<td>30 (67)</td>
<td>0.57 (0.37–0.88)</td>
<td>.008</td>
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<tr>
<td>Vitamin D severe deficiency (&lt;5 ng/mL)</td>
<td>0</td>
<td>2 (4.4)</td>
<td>0.21 (0.01–4.53)</td>
<td>.50</td>
</tr>
<tr>
<td>3 months’ CA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>40</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VDD (&lt;20 ng/mL)</td>
<td>5 (12.5)</td>
<td>14 (35)</td>
<td>0.36 (0.14–0.90)</td>
<td>.02</td>
</tr>
<tr>
<td>Vitamin D severe deficiency (&lt;5 ng/mL)</td>
<td>0</td>
<td>1 (2.5)</td>
<td>0.33 (0.01 to 7.94)</td>
<td>.99</td>
</tr>
</tbody>
</table>

Data are presented as n (%) unless otherwise indicated.

size that investigated the prevalence of VDD in preterm infants after daily vitamin D supplementation with 2 different doses. Previous randomized trials in preterm infants were conducted in smaller numbers of infants and found almost similar vitamin D levels in high- and low-dose groups.18–21 These studies reported only serum vitamin D levels and not the prevalence of VDD and had large losses to follow-up. In contrast, our study had a high follow-up rate of 95.6% and was powered for the primary outcome.

Improvement in serum vitamin D levels did not result in significant improvement in bone mineralization variables at 3 months. We presume 1 of the following 2 factors to be the possible reason for this result: (1) our study was not powered to determine any meaningful difference in the bone mineralization and/or (2) the duration of vitamin D supplementation was not long enough to produce any significant difference in these variables. Our finding is consistent with those of others that showed that achieving vitamin D sufficiency does not translate into better BMC or BMD.19,20 Nevertheless, marginally higher BMC and BMD were observed in infants in the 400-IU group. This finding was probably due to a higher mean birth weight of the infants in the 400-IU group because there is a positive association between birth weight and BMC.22 Lack of improvement in BMC could also be due to the fact that our study included a few (n = 7) very low birth weight infants (<1000 g), who are likely to have maximum changes in BMC and BMD due to higher risk of metabolic bone disease.23,24

Even though daily supplementation with 800 IU significantly reduced the prevalence of VDD at 40 weeks and at 3 months’ CA, there is concern that 800 IU/day could result in vitamin D excess in a small proportion of infants. We found an incidence of 2.4% (95% CI: 0.06%–12.5%) in the intervention group. The infant with vitamin D excess was, however, asymptomatic. As far as we know, the vitamin D excess in this infant was not due to inadvertent excess intake. Exaggerated response to vitamin D supplementation could be explained by genetic polymorphisms in enzymes involved in vitamin D metabolism.25,26 However, we did not investigate the infant from this angle.
Also, routine monitoring for markers of vitamin D toxicity, such as hypercalciumia and nephrocalcinosis, did not reveal any significant clinical adverse effects in the 800-IU group. Despite improving vitamin D levels, UCa/Cr declined from 40 weeks to 3 months’ CA in both groups, indicating maturation of tubular function and thus improved tubular reabsorption of calcium in preterm infants. The role of UCa/Cr as a marker of vitamin D toxicity needs further evaluation.

The major limitation of our study is that we did not quantify exposure to sunlight by the mothers in the 2 groups is unlikely to have changed our results.

CONCLUSIONS

In preterm infants of 28 to 34 weeks’ gestation with significant deficiency at baseline, daily supplementation of vitamin D in doses of 800 IU compared with 400 IU appears to reduce the prevalence of VDD at 40 weeks’ PMA and at 3 months’ CA. A small but possibly significant risk of vitamin D excess underscores the need to monitor serum vitamin D levels in neonates receiving high doses of vitamin D daily. Moreover, the clinical significance of maintaining sufficient vitamin D levels in the absence of any demonstrable effect on bone mineralization needs to be studied in trials with a larger sample size.

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