Vitamin D requirements during pregnancy

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ABSTRACT

Adequate vitamin D concentrations during pregnancy are necessary to ensure appropriate maternal responses to the calcium demands of the fetus and neonatal handling of calcium. The purpose of this report is to review studies that investigated maternal and neonatal outcomes of vitamin D deficiency or supplementation during pregnancy. Most studies reported included women at high risk of vitamin D deficiency, because of low vitamin D and calcium intake or decreased ability to synthesize endogenous vitamin D (attributable to lack of sun exposure or to heavily pigmented skin). Overall, vitamin D supplementation in these populations leads to improved neonatal handling of calcium. Results concerning benefits for fetal growth and bone development are inconclusive. There is no evidence of a benefit of supplementation during pregnancy above amounts routinely required to prevent vitamin D deficiency. Am J Clin Nutr 2004;80(suppl):1740S–7S.

KEY WORDS Vitamin D, pregnancy, supplements, neonates, hypocalcemia, fetal growth

INTRODUCTION

Significant changes in maternal vitamin D and calcium metabolism occur during pregnancy, to provide the calcium needed for fetal bone mineral accretion. Approximately 25–30 g of calcium are transferred to the fetal skeleton during the last trimester, most of which is transferred during the last trimester. It has been estimated that the fetus accumulates up to 250 mg/d calcium during the third trimester (1). The 3 possible calcium sources that may supply the mother with the necessary calcium to support fetal growth include increased intestinal absorption from the diet, increased renal conservation, and increased bone mobilization.

Vitamin D is obtained either through photosynthesis in the skin with exposure to ultraviolet B radiation or through dietary sources. Vitamin D is then transported to the liver and hydroxylated to 25-hydroxyvitamin D [25(OH)D]. Additional hydroxylation of 25(OH)D occurs in the kidney and yields a wide variety of vitamin D metabolites, including 1,25-dihydroxyvitamin D [1,25(OH)2D]. The active metabolite of vitamin D, 1,25(OH)2D, increases the efficiency of intestinal calcium absorption, decreases renal calcium excretion, and, in conjunction with parathyroid hormone (PTH), mobilizes calcium from bone. Serum 25(OH)D concentrations are often used as an indicator of vitamin D status; although 25(OH)D is present in serum in nanogram amounts and 1,25(OH)2D is present in picogram amounts, prolonged vitamin D deficiency can result in increased PTH concentrations and decreased serum 1,25(OH)2D concentrations, leading to osteomalacia.

There are few natural food sources of vitamin D (fatty fish and eggs). In the United States, fluid milk is typically fortified with vitamin D. Maternal vitamin D deficiency is more likely to occur in the winter months, in countries that do not routinely fortify dairy products or other food products with vitamin D, among ethnic groups whose members cover most of their skin, and/or among individuals with heavily pigmented skin. Few randomized, nutritional vitamin D interventions have been conducted during pregnancy, and the importance of maternal vitamin D intake is best illustrated in observational studies of women with poor vitamin D status. Adequate maternal vitamin D status is necessary during pregnancy. To ensure appropriate maternal responses to the calcium demands attributable to the pregnancy and neonatal handling of calcium. Most studies that investigated the effects of vitamin D status on maternal and infant outcomes found effects primarily on neonatal calcium metabolism. A few studies showed that maternal vitamin D deficiency might affect maternal weight gain or fetal growth.

MATERNAL VITAMIN D AND CALCIUM HOMEOSTASIS DURING PREGNANCY

Increased intestinal calcium absorption appears to be the primary mechanism for obtaining extra calcium during pregnancy (2). Fractional calcium absorption increases from ~35% in the nonpregnant state to ~60% during the third trimester of pregnancy (3, 4). Serum concentrations of 1,25(OH)2D increase 50–100% over the nonpregnant state during the second trimester and by 100% during the third trimester (3, 4). Although serum concentrations of vitamin D-binding protein also increase during pregnancy, concentrations of 1,25(OH)2D continue to increase during the last trimester without an associated increase in binding protein concentrations, which leads to increases in free 1,25(OH)2D concentrations (5, 6). Although renal calcium conservation does not occur during pregnancy, calcium absorption has been found to be positively associated with serum 1,25(OH)2D concentrations in late human gestation (3, 4). The mechanism underlying the increased serum 1,25(OH)2D concentrations during pregnancy is not clear. PTH, which is usually

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considered the stimulus for increased renal hydroxylation of 25(OH)D to 1,25(OH)2D, has not been shown to be increased during pregnancy (3, 4, 7), and it has been speculated that the 1,25(OH)2D present in the maternal circulation may be of placental origin (8).

MATERNAL CHANGES IN BONE AND BONE MARKERS DURING PREGNANCY

Although there are case reports of pregnancy-associated osteoporosis, this appears to be a pathologic condition that occurs among women with preexisting bone disease or that results from inappropriate calcitropic hormonal responses during pregnancy (9, 10). Ensom et al (11) recently reviewed studies on bone changes that occur during normal pregnancies. Unfortunately, in many studies the final bone measurements were made up to 6 wk after the birth, when lactation-induced bone changes have already begun to occur. Although studies using biochemical markers of bone formation and bone resorption have been conducted to allow better understanding of bone turnover throughout pregnancy (4, 12–14), those studies are difficult to interpret because of changes in renal filtration, hemodilution, and the possibility that the markers are of fetal or placental origin.

Several longitudinal studies that included bone measurements before and after pregnancy showed bone density losses of 2–4%. Decreases in bone density were observed in the spine (12, 15, 16), hip (12, 17), and ultradistal radius (18, 19). One study reported an increase in bone density at cortical sites (16), whereas several other studies reported no changes during pregnancy (3, 4, 20, 21). The percentage postpartum bone gain among women who did not breast-feed their infants was of a magnitude similar to that of the observed bone loss (20, 22–24). Most of the postpartum studies of bone gain did not include nonpostpartum control subjects, and it is possible that the bone gain might be a normal, age-related gain. However, there is evidence that the bone changes observed in the postpartum period are not attributable to normal, age-related bone increases. Laskey et al (24) studied 11 nonlactating postpartum women and 22 nonpostpartum women of similar age and found a significant increase in bone mass among the postpartum women but no change among the nonpostpartum women.

EFFECTS OF MATERNAL VITAMIN D STATUS ON NEONATAL CALCIUM HOMEOSTASIS

In the early 1970s, Purvis et al (25) reported an association between the occurrence of neonatal tetany and the amount of sunlight exposure the mothers had received during the last trimester of pregnancy. Those authors, as well as others (26, 27), speculated that vitamin D-deficient mothers develop secondary hyperparathyroidism, which leads to transitory hypoparathyroidism and hypocalcemia among the neonates. Several investigators subsequently reported that infants of mothers with low vitamin D intake during pregnancy had low serum calcium concentrations in cord blood or during the first week of life (28–30).

Asian (subcontinent) immigrants to the United Kingdom are at increased risk of vitamin D deficiency. Okonofua et al (27) initially reported low serum 25(OH)D and calcium concentrations and higher PTH concentrations in maternal and cord samples obtained from 11 Asian mothers, compared with 10 white mothers, at delivery. These authors later reported the results of a similar but larger study involving 43 Asian women and 55 white women who were monitored throughout their pregnancies. They found that PTH concentrations among both Asian and white mothers increased throughout pregnancy (31). Serum PTH concentrations were inversely associated with serum 25(OH)D concentrations, and Asian mothers had lower 25(OH)D concentrations and higher PTH concentrations than did white mothers. The second study replicated the previous findings of lower serum 25(OH)D concentrations and higher PTH concentrations in cord samples obtained from Asian neonates, compared with white neonates.

Datta et al (32) recently screened 160 pregnant women from ethnic minority groups in South Wales and found that 50% had low serum 25(OH)D concentrations. In contrast to the findings of Okonofua et al (27, 31), Datta et al (32) found PTH concentrations to be within the normal range for 81% of the women with low 25(OH)D concentrations. The women were instructed to begin vitamin D supplementation at 800 IU/d and were rechecked at 36 wk of gestation. If serum 25(OH)D concentrations were still low, then the women were instructed to take 1600 IU/d. Serum 25(OH)D concentrations increased, and 60% of the women who were rechecked at delivery exhibited 25(OH)D concentrations within the normal range. Despite the increase in serum 25(OH)D concentrations, serum PTH concentrations remained unchanged. The authors noted that, although vitamin D supplementation during pregnancy is recommended by the British Department of Health for all ethnic minorities, it is not widely practiced and compliance may be low.

Paunier et al (28) measured plasma 25(OH)D and calcium concentrations among 40 healthy Swiss mothers and their term infants at delivery, during the winter months. At the time of delivery, maternal vitamin D intake during the last trimester was estimated by recall, and maternal and cord blood concentrations of 25(OH)D and calcium were measured. Infant calcium concentrations were determined on day 4. Three groups were defined based on the maternal vitamin D intake, ie, 16 mothers did not receive vitamin supplements and had mean intakes of ≤150 IU/d, 8 mothers did not receive vitamin supplements and had mean vitamin D intakes from fortified milk of 150–500 IU/d, and 16 mothers received regular vitamin supplements and had mean intakes of 500–1500 IU/d. Cord 25(OH)D concentrations were
### Table 1
Summary of studies of the effects of varying doses of maternal vitamin D intake on pregnancy outcomes

<table>
<thead>
<tr>
<th>Reference</th>
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<tr>
<td>Purvis et al (25)</td>
<td>Observational</td>
<td>112 infants with neonatal tetany, 100 control infants from same ward</td>
<td>63 (56%) of infants with tetany developed enamel hypoplasia; lower calcium in those infants with most severe enamel hypoplasia; occurrence of tetany and enamel hypoplasia associated with hours of sunlight 3 mo earlier</td>
<td>Authors' conclusion: Tetany and enamel hypoplasia is a manifestation of maternal vit D deficiency during pregnancy and likely attributable to maternal secondary hyperparathyroidism</td>
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<td>Paunier et al (28)</td>
<td>Observational</td>
<td>40 Swiss mothers during winter: 16, vit D intake &lt; 150 IU/d; 8, vit D intake 150–500 IU/d; 16, vit D intake &gt; 500 IU/d</td>
<td>Infants of mothers with vit D &lt; 150 IU/d had lower Ca on day 4, compared with infants with mothers with vit D &gt; 500 IU/d; no differences in maternal or cord 25(OH)D</td>
<td>Vitamin D intake determined by interview during last trimester; 25(OH)D concentrations in infant on day 4 not measured</td>
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<tr>
<td>Congdon et al (29)</td>
<td>Observational</td>
<td>76 British mothers: 45 Asian descent, no vit D; 19 Asian descent, 1000 IU vit D/d; 12 white mothers</td>
<td>Higher 25(OH)D and Ca in cord from mothers receiving vit D; no differences in birth weight or alk phos; BMC by SPA and cranioembytes did not differ by group or correlate with 25(OH)D; BMC not associated with presence of cranioembytes</td>
<td>Authors' conclusion: Mineralization of fetal skeleton not impaired in maternal vit D deficiency; cranioembytes should not be used as an indicator of impairment of mineralization</td>
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<tr>
<td>Reif et al (38)</td>
<td>Case-control</td>
<td>22 term infants with cranioembytes and 22 control subjects</td>
<td>Maternal and neonatal 25(OH)D lower in infants with cranioembytes, compared with no cranioembytes; maternal and neonatal serum Ca, P, and alk phos similar between groups</td>
<td>Authors' conclusion: Low vit D status during pregnancy and subsequent incomplete fetal ossification might partially explain higher incidence of cranioembytes during winter months</td>
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<tr>
<td>Datta et al (32)</td>
<td>Observational/ intervention</td>
<td>160 pregnant women from ethnic minorities in South Wales were screened for vit D deficiency; if deficient, they were treated with vit D (800 IU/d)</td>
<td>50% of women were deficient in vit D; 25(OH)D increased by delivery, no change in PTH</td>
<td>If women still had low 25(OH)D, they were treated with 1600 IU/d; 81% of deficient women had PTH within normal range at baseline</td>
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<td>Cockburn et al (33)</td>
<td>Quasi-randomized trial</td>
<td>1,139 Scottish women from 2 clinics with different vit D: 506, 400 IU/d beginning at 12 wk of gestation; 633, placebo</td>
<td>25(OH)D in maternal, cord, and infant (days 3 and 6) higher with vit D, compared with placebo; 5 cases of symptomatic hypocalcemia, all in the placebo group</td>
<td>Hypocalcemia also dependent on infant feeding (greater in formula-fed, compared with human milk); mothers not receiving vit D had regular intakes &lt; 100 IU/d</td>
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<td>Brooke et al (34)</td>
<td>Randomized trial (double-blind)</td>
<td>126 Asian women in United Kingdom: 59, 1000 IU/d vit D from 28 to 32 wk; 67, placebo</td>
<td>Maternal Ca higher, cord Ca similar; neonatal Ca on days 3 and 6 higher with vit D, compared with placebo; symptomatic hypocalcemia in 5 placebo infants, compared with 0 vit D infants (P &lt; 0.01); SGA in 9 vit D infants (15.3%), compared with 19 placebo infants (28.6%, P &lt; 0.1); cranioembytes in 2 vit D infants, compared with 4 placebo infants (NS)</td>
<td>Mothers with vit D gained more weight compared with placebo in last trimester, possibly because of increased malaise among placebo mothers; also found an effect of infant feeding: Ca higher in breast-fed compared with formula-fed infants; no evidence of rickets in infants with symptomatic hypocalcemia or cranioembytes</td>
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<td>Marya et al (30)</td>
<td>Randomized trial</td>
<td>120 Asian mothers at delivery: 75, no vit D supplements; 25, 1200 IU/d vit D 3rd trimester; 20, 600 000 IU twice (7th and 8th mo)</td>
<td>Maternal and cord Ca higher and alk phos lower with 600 000 vit D compared with control, with no difference between 1,200 IU/d and control</td>
<td>Baseline vitamin D intake &lt; 30 IU/d; birth weight greater in both vit D groups, compared with control</td>
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<td>Marya et al (35)</td>
<td>Randomized trial</td>
<td>200 Asian-Indian women: 100, 600 000 oral vit D twice (7th and 8th mo of gestation); 100, no vit D</td>
<td>Maternal and cord Ca and P higher, and alk phos lower in vit D group, compared with control</td>
<td>Did not measure 25(OH)D; no difference in maternal weight gain; infant birth weight and size greater with vit D, compared with no vit D</td>
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(Continued)
correlated with maternal plasma concentrations. Cord and maternal 25(OH)D concentrations were not correlated with maternal vitamin D intake and did not differ among the groups defined on the basis of maternal vitamin D intake. Despite the lack of statistical significance in serum 25(OH)D concentrations, which the authors speculated was attributable to large variations in 25(OH)D concentrations, infant calcium concentrations on day 4 were significantly lower among infants whose mothers consumed < 150 IU/d, compared with infants whose mothers consumed > 500 IU/d.

Congdon et al (29) measured cord 25(OH)D and calcium concentrations among 45 Asian women who received no vitamin D supplements and 19 Asian women who received 1000 IU/d vitamin D during the last trimester. The authors found higher serum 25(OH)D and calcium concentrations and similar alkaline phosphatase concentrations among infants of mothers who received vitamin D, compared with those who did not. Infant forearm bone mineral content (BMC) results are presented below.

Several randomized trials of vitamin D supplementation during pregnancy have been conducted. In 1980, Cockburn et al (33) reported the results of a quasi-randomized trial of 1139 Scottish women who attended 2 different obstetric wards. Women from one ward were assigned to receive 400 IU/d vitamin D from 3rd trimester; ~15, 1000 IU/d vit D from 3rd trimester; ~15, no vit D

Mallet et al (37) Randomized trial 68 French women: 21, 1000 IU/d during last trimester; 27, 200,000 oral IU once during 7th mo; 29, no vit D

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<td>Delvin et al (36)</td>
<td>Randomized trial</td>
<td>34 French women (40 randomized): ~15, 1000 IU/d vit D from 3rd trimester; ~15, no vit D</td>
<td>Cord and day 4 25(OH)D higher in vit D compared with control, group; no difference in cord Ca, but day 4 Ca and iCa greater in vit D compared with control; no group differences in cord or day 4 PTH</td>
<td>Authors excluded 2 control women with high 25(OH)D because they were subsequently found to have sunlight exposure; cord 1.25(OH)D was lower with vit D supplements, but infant concentrations on day 4 were higher. Conducted in winter; mode of infant feeding not stated; if all were breast-fed, this might explain their lack of significant findings on neonatal Ca; birth weights similar among groups</td>
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<td>Mallet et al (37)</td>
<td>Randomized trial</td>
<td>68 French women: 21, 1000 IU/d during last trimester; 27, 200,000 oral IU once during 7th mo; 29, no vit D</td>
<td>Serum 25(OH)D similar in both vit D groups and greater than control; no group differences in 1.25(OH)D or Ca; neonatal serum Ca on days 2 and 6 were similar</td>
<td>Cord and day 4 25(OH)D higher in vit D compared with control, group; no difference in cord Ca, but day 4 Ca and iCa greater in vit D compared with control; no group differences in cord or day 4 PTH</td>
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1 Vit D, vitamin D; Ca, calcium; iCa, ionized calcium; P, phosphorus; alk phos, alkaline phosphatase; PTH, parathyroid hormone; SGA, small for gestational age; BMC, bone mineral content; SPA, single-proton absorptiometry; NS, not significant.
The results of another randomized vitamin D supplementation trial, involving 200 Asian Indian women, were reported by Marya et al (35) in 1988. Two hundred women were randomly assigned to receive either 600 000 IU of vitamin D twice during the last trimester (seventh and eighth months of gestation, n = 100) or no supplement (n = 100). Serum calcium concentrations were higher and alkaline phosphatase concentrations were lower for mothers who were treated with vitamin D, compared with those who were not. Similar findings were observed for cord samples. Infants of mothers who received vitamin D had greater intrauterine growth, with greater birth weight, crown-heel length, head circumference, arm circumference, and skinfold thickness, compared with infants of mothers who did not receive vitamin D.

Delvin et al (36) conducted a vitamin D supplementation trial with 34 French women who received minimal to no vitamin D from dietary sources. The supplement-treated women received 1000 IU/d vitamin D from the sixth month of gestation, whereas the other group served as a control group. Cord samples for the vitamin D-supplemented group demonstrated higher concentrations of both 25(OH)D and 1,25(OH)2D. At 4 d of age, serum 25(OH)D and 1,25(OH)2D concentrations were higher in the vitamin D-supplemented group, compared with the control group. All infants were breast-fed and, although there was no group difference in cord calcium concentrations, the decline in serum calcium and ionized calcium concentrations during the first 4 d of life was less among infants whose mothers received vitamin D, compared with those who did not. There were no

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significant group differences in either cord or infant serum PTH concentrations.

A randomized trial was conducted by Mallet et al (37) in northern France, to determine the effects of single-dose and daily vitamin D supplementation during the last trimester of a winter pregnancy. One group acted as a control group (n = 29), one group was treated with 1000 IU/d during the last 3 mo of pregnancy (n = 21), and one group was given a single oral dose of 200 000 IU of vitamin D during the seventh month of pregnancy (n = 27). Serum 25(OH)D concentrations in maternal and cord samples did not differ between the 2 supplementation groups but were higher than those in the control group. There were no group differences in maternal or cord serum 1,25(OH)_{2}D and calcium concentrations or neonatal serum calcium concentrations on days 2 and 6.

The studies described above, as well as one by Reif et al (38), are summarized in Tables 1 and 2. The effects of vitamin D supplementation, as either a daily dose or a single high dose, on maternal serum 25(OH)D and neonatal calcium concentrations are illustrated in Figures 2 and 3.
relationship between maternal vitamin D deficiency and impaired fetal bone ossification (42). Neonatal wrist ossification centers were less likely to be found among infants born in the spring than among those born in the fall (2 of 127 infants, compared with 10 of 129 infants; \( P = 0.05 \)). In addition, among infants born in the fall, 3.8% of those with 25(OH)D concentrations of \(< 11 \text{ng/mL} \) had wrist ossification centers, compared with 13.7% of those with 25(OH)D concentrations of \( > 11 \text{ng/mL} \) (\( P = 0.04 \)). There was no relationship between the presence of ossification centers and cord 25(OH)D concentrations among infants born in the spring, when only 2 of 127 infants (1.6%) had ossification centers. The authors speculated that maternal vitamin D status might affect fetal bone development and that the low rate of ossification centers in the spring might be attributable to maternal vitamin D deficiency in the preceding winter months. Despite a high rate of low 25(OH)D concentrations in cord blood (57%), no cases of neonatal rickets were observed. Only one study investigated the effect of vitamin D supplementation during pregnancy on neonatal bone mineralization. Congdon et al (29) measured forearm infant BMC values with single-photon absorptiometry and found that BMC values did not differ according to the history of vitamin D supplementation during pregnancy and were not correlated with cord serum 25(OH)D concentrations.

Maternal vitamin D status during pregnancy has been shown to be associated with neonatal calcium homeostasis. There are conflicting reports indicating possible effects of maternal vitamin D status on fetal growth and bone development.

CONCLUSIONS

Increased intestinal calcium absorption during pregnancy meets fetal calcium demands. In cases of severe maternal vitamin D deficiency, serum PTH concentrations are increased, 1,25(OH)\(_2\)D concentrations are decreased, and osteomalacia may occur. Observational studies and vitamin D supplementation trials among pregnant women at high risk of vitamin D deficiency showed improved neonatal handling of calcium with improved maternal vitamin D status. Results concerning the effects of vitamin D on maternal weight gain and fetal growth in these high-risk populations are conflicting and inconclusive. There is no evidence to indicate a beneficial effect of vitamin D intakes during pregnancy above amounts routinely required to prevent vitamin D deficiency among nonpregnant women.

REFERENCES


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