For reprint orders, please contact reprints@expert-reviews.com

Vitamin D intake: what advice should be given to women of childbearing age?

Expert Rev. Obstet. Gynecol. 6(2), 115–118 (2011)

Adit A Ginde

Department of Emergency Medicine, University of Colorado School of Medicine, CO, USA
and
Department of Epidemiology, Colorado School of Public Health, Aurora, CO 80045, USA
Tel.: +1 720 848 6777
Fax: +1 720 848 7374
adit.ginde@ucdenver.edu

"…sometimes inaction can also cause substantial harm by withholding potentially beneficial treatment."

Vitamin D has been traditionally associated with calcium metabolism and skeletal outcomes, such as rickets and osteoporosis [1]. For women of a childbearing age, vitamin D supplementation through multivitamins and fortification of dairy and cereal products had essentially eradicated these known effects associated with vitamin D deficiency. However, a recent resurgence of rickets in infants [2] and increasing evidence supporting the impact of vitamin D deficiency on maternal, fetal and infant health [3–5] have challenged this dogma and the recommendations for women of childbearing age. The recently updated dietary reference intakes (DRIs) for calcium and vitamin D proposed conservative guidelines for vitamin D intake based only on what has been proven through large clinical trials [6]. These guidelines will be summarized in the context of emerging evidence suggesting that higher doses of vitamin D supplementation and target blood levels may be warranted.

Vitamin D physiology: the basics

Vitamin D is not technically a vitamin; rather, it is a fat-soluble prohormone that the body can generate, circulate, and activate to produce endocrine, paracrine and autocrine effects [7,8]. The two major forms of vitamin D are cholecalciferol (vitamin D_3), produced in human and animal skin, and ergocalciferol (vitamin D_2), produced by plants. Both forms are available as supplements, and because there is limited knowledge regarding which form is more effective in human health, they are typically collectively described as simply vitamin D. Vitamin D is produced in the skin by exposure to UVB radiation. It is metabolized in the liver to the major circulating form, 25-hydroxyvitamin D (25OHD), which crosses the placental barrier and is the most accurate blood measure of vitamin D status. The active form is 1,25-dihydroxyvitamin D (1,25OH_2D, or calcitriol), which can be formed systemically in the kidney and locally in most tissue (including the placenta). The vitamin D receptor binds calcitriol and is found through the body, regulating over 1000 human genes [9].

"Vitamin D is not technically a vitamin; rather, it is a fat-soluble prohormone…"

Defining vitamin D deficiency: how much is enough?

There has been significant debate in recent years surrounding what 25OHD serum levels constitute as deficient, relatively insufficient and optimal vitamin D status [10]. Culminating in the recent DRIs for vitamin D [6], there is growing consensus that people of all ages require serum 25OHD levels of at least 20 ng/ml (to convert to nmol/l, multiply by 2.497) to support skeletal health. While there are data to support higher target levels

Keywords: deficiency • diet • lactation • nutrition • pregnancy • prenatal • recommended daily allowance • supplement • vitamin D • women's health

 © 2011 Expert Reviews Ltd ISSN 1747-4108

for osteoporosis prevention, 25OHD levels ≥30 ng/ml are also associated with optimal nonskeletal outcomes [11]. Regardless of how vitamin D deficiency is classified, a large proportion of US women of childbearing age were assessed as deficient between 2001 and 2006; 42% had 25OHD levels of <20 ng/ml and 78% had <30 ng/ml [12]. During pregnancy, despite routine use of prenatal vitamins, 33% still had levels <20 ng/ml and 69% had <30 ng/ml. In addition, because most Americans derive vitamin D from sunlight exposure (vs diet and supplements), ambient UVB radiation, skin pigment and barriers all drive vitamin D status [13]. Thus, women who have to stay indoors, live at higher latitudes (especially in winter), have dark skin, regularly wear sunscreen and cover exposed skin with clothing are at an even higher risk of vitamin D deficiency.

Vitamin D & health outcomes in women of childbearing age

Comprehensive reviews on vitamin D and health have been recently published for the general population [8], and specifically on women of childbearing age [3–5]. Current knowledge of the impact of vitamin D on women and infant health from preconception to lactation will be briefly summarized and representative studies cited.

Women's health

Vitamin D has a potential role in fertility, although this has not been extensively investigated. In rodent models, vitamin D appears to have an important role in ovarian function and litter size [14]. In human studies, higher 25OHD levels were an independent predictor of successful pregnancy among IVF patients [15]. To date, no clinical trials of vitamin D supplementation and successful conception have been performed.

> "The major circulating form of vitamin D readily crosses the placenta, thus fetal and newborn vitamin D status is dependent almost entirely on the mother."

There are substantial epidemiologic data to support a beneficial effect of vitamin D on the incidence and severity of preeclampsia. Circumstantially, preeclampsia is more common in vitamin D-deficient populations, including in women with darker skin and those who live at higher latitudes during the winter season [16]. In several observational studies, lower material 25OHD levels were associated with an increased incidence of preeclampsia [17,18]. In addition, vitamin D supplementation appears to mitigate this increased risk [19], although larger trials are needed to confirm this effect, determine optimal doses and understand the role of vitamin D, independent of calcium supplementation.

Vitamin D metabolites are known to increase insulin production and sensitivity [7,8]. Cross-sectional studies have suggested a potential association between vitamin D status and gestational diabetes [20,21]. In addition, vitamin D regulates innate and adaptive immune function [7,8]. Accordingly, cross-sectional studies have shown an association between lower 25OHD levels and increased prevalence of bacterial vaginosis [22]. However, longitudinal studies and clinical trials for these outcomes have not yet been performed.

Infant health

The major circulating form of vitamin D readily crosses the placenta, thus fetal and newborn vitamin D status is dependent almost entirely on the mother [23]. As a result, low maternal 25OHD levels have long been associated with poor skeletal mineralization and bone development *in utero*, infantile rickets and reduced infant size in cross-sectional and longitudinal studies [24]. Maternal vitamin D supplementation to achieve serum 25OHD levels of >20 ng/ml have mitigated these adverse outcomes [25]. In addition, because vitamin D is excreted in very low concentrations in human milk, almost all cases of rickets occur in exclusively breastfed infants of vitamin D-deficient mothers [2].

> "...most foods have a relatively low vitamin D content, and the typical American diet contains limited vitamin D."

There is increasing evidence that vitamin D deficiency *in utero* and during early life is associated with nonskeletal health effects. Two prominent examples are Type 1 diabetes and wheezing/asthma. For both of these outcomes, lower maternal vitamin D intake and cord blood 25OHD levels have been associated with increased risk of disease [26,27]. In addition, vitamin D supplementation in the first year of life decreased the risk Type 1 diabetes in longitudinal cohorts [28]. Ongoing clinical trials will further clarify these associations.

Recommendations for vitamin D intake

Vitamin D is derived from three primary sources in humans:

- UVB radiation from sunlight;
- Food with natural or fortified vitamin D content;
- Supplements.

Ambient UVB radiation is the primary source of vitamin D for most humans. Although light-skinned adults can obtain 2000–3000 international units (IU) from 10–15 min of sunlight exposure on the arms and legs [8], sunlight is generally not recommended as a source of additional vitamin D owing to the risks of UV radiation. Sunscreen is effective at mitigating the risks of UV radiation, but also blocks up to 99% of vitamin D production in the skin [29].

Dietary sources include fatty fish and fortified dairy products. However, most foods have a relatively low vitamin D content, and the typical American diet contains limited vitamin D. Thus, supplements are the alternative way to improve vitamin D status.

Dietary reference intakes

The 1997 DRIs for calcium and vitamin D [30] were recently updated and the report provides recommendations for intake

from diet and supplements for the American and Canadian population, including a specific focus on pregnant and lactating women [6].

The appointed committee, composed of 14 Institute of Medicine scientists, was charged with establishing the Recommended Daily Allowance (RDA) for Vitamin D. The RDA is defined as meeting or exceeding the needs of 97.5% of the population, based on what has been established as a cause–effect relationship by large randomized controlled trials and meta-analyses. This is a rigorous standard, especially given that the field of vitamin D and nonskeletal outcomes is relatively new. Consequently, the recommendations of the committee were conservative.

The 2011 RDA for vitamin D was set at 600 IU per day for children and adults age 1–70 years (raised to 800 IU per day for those aged >70 years). These recommendations were based solely on proven benefit for skeletal health (e.g., rickets and osteoporosis prevention) to achieve target serum 25OHD levels of 20 ng/ml. The committee commented that most Americans receive this amount of vitamin D from diet and current supplements, since multivitamins (including prenatal vitamins) typically contain 400 IU of vitamin D. For pregnant and lactating women, the committee did not find sufficient randomized controlled trials to support a higher RDA, and thus the recommendation was also 600 IU per day.

Why might the 2011 DRIs be inadequate for women of childbearing age?

In the months following the release of the 2011 DRIs, there has been substantial criticism of the conservative RDAs for vitamin D [31]. In defense of the recommendations, the committee is tasked with making broad recommendations for the population rather than individuals, and thus maintains a high standard of evidence for proven efficacy and a lower standard of evidence of any potential toxicity. However, individual clinicians and patients can weigh existing evidence and make decisions on supplementation based on their assessments of the risks and benefits.

> **"In the months following the release of the 2011 dietary reference intakes, there has been substantial criticism of the conservative recommended daily allowances for vitamin D."**

Over two out of every five US women of childbearing age have 25OHD levels less than the conservative 20 ng/ml threshold (for skeletal health) and nearly four out of every five have levels less than 30 ng/ml (which appears to be a minimum target for nonskeletal health outcomes) [12]. These levels are in the context of many women taking multivitamins, which contain at least 400 IU of vitamin D. These data alone support a need for intake higher than 600 IU per day for many women. In addition, vitamin D toxicity (e.g., hypercalcemia and kidney stones) has not been observed below 10,000 IU per day of supplementation and serum 25OHD levels <88 ng/ml [32]. Owing to the lack of definitive evidence for a benefit of high-dose vitamin D supplementation and uncertainty regarding long-term effects, the Tolerable Upper Intake Level (UL) of supplementation was set at 4000 IU per day for the population, including pregnant and lactating women. The UL was defined by the level above which risk may increase and below which is likely to cause no risk to almost all individuals in the population.

Accordingly, clinicians may choose to weigh the substantial potential for benefit (albeit not proven) of a higher dose vitamin D supplementation against the relatively minimal risk for women of childbearing age. With this in mind, a reasonable starting dose would be 1000 IU per day followed by measurement of serum 25OHD levels. Even if the target level is the conservative 20 ng/ml threshold, some women will need more than 1000 IU per day. To achieve 30 ng/ml, many more women will need higher doses of supplementation. This strategy recognizes the relatively large therapeutic window before any toxicity is observed. Because vitamin D is poorly excreted in human milk, women who are exclusively breastfeeding may need up to 4000 IU per day (or even higher) to provide adequate vitamin D to the infant, or provide vitamin D supplementation directly to the infant [33].

Conclusion

According to one Institute of Medicine committee member, "The onus is on the people who propose extra calcium and vitamin D to show it is safe before they push it on people" [101]. The committee argues that in the absence of definitive proof for efficacy, we should observe the maxim 'primum non nocere' (first, do no harm). While I fully support this principle, sometimes inaction can also cause substantial harm by withholding potentially beneficial treatment. If all of the promising data for potential benefit of higher dose vitamin D supplementation on skeletal and nonskeletal health are proven inaccurate, the committee's recommendations will be lauded for their foresight. However, if even some of the evidence is substantiated by large clinical trials, we will have missed an opportunity to improve the health of women of childbearing age and their children. Over the next decade, until large clinical trials are resulted and the next DRIs for vitamin D are provided, the high potential for benefit and minimal risk for harm suggests that judiciously higher amounts of vitamin D supplementation, with serum 25OHD measurement when considering doses >1000–2000 IU per day, may be the best course to improve women's health while minimizing potential risk.

Financial & competing interests disclosure

Adit A Ginde is supported by the Colorado Clinical and Translational Sciences Institute through NIH grant KL2 RR025779. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

1 Holick MF. Resurrection of vitamin D deficiency and rickets. *J. Clin. Invest*. 116, 2062–2072 (2006).

2 Weisberg P, Scanlon K, Li R, Cogswell ME. Vitamin D and health in the 21st century: bone and beyond. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. *Am. J. Clin. Nutr.* 80, 1697S–1705S (2004).

3 Mulligan ML, Felton SK, Riek AE, Bernal-Mizrachi C. Implications of vitamin D deficiency in pregnancy and lactation. *Am. J. Obstet. Gynecol.* 202, 429.e1–9 (2010).

4 Barrett H, McElduff A. Vitamin D and pregnancy: an old problem revisited. *Best Pract. Res. Clin. Endocrinol. Metab.* 24, 527–539 (2010).

5 Lewis S, Lucas RM, Halliday J, Ponsonby A. Vitamin D deficiency and pregnancy: from preconception to birth. *Mol. Nutr. Food Res.* 54, 1092–1102 (2010).

6 Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D.* The National Academies, Washington, DC, USA (2011).

7 Lips P. Vitamin D physiology. *Prog. Biophys. Mol. Biol.* 92, 4–8 (2006).

8 Holick MF. Vitamin D deficiency. *N. Engl. J. Med.* 357, 266–281 (2007).

9 Tavera-Mendoza LE, White JH. Cell defenses and the sunshine vitamin. *Sci. Am.* 297(5), 62–65, 68–70, 72 (2007).

10 Vieth R, Bischoff-Ferrari HA, Boucher BJ *et al.* The urgent need to recommend an intake of vitamin D that is effective. *Am. J. Clin. Nutr.* 85, 649–650 (2007).

11 Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am. J. Clin. Nutr.* 84, 18–28 (2006).

12 Ginde AA, Sullivan AF, Mansbach JM, Camargo CA Jr. Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. *Am. J. Obstet. Gynecol.* 202(5), 436.e1–e8 (2010).

13 Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988–2004. *Arch. Intern. Med.* 169, 626–632 (2009).

14 Halloran BP, DeLuca HF. Effect of vitamin D deficiency on fertility and reproductive capacity in the female rat. *J. Nutr.* 110, 1573–1580 (1980).

15 Ozkan S, Jindal S, Greenseid K *et al*. Replete vitamin D stores predict reproductive success following *in vitro* fertilization. *Fertil. Steril.* 94, 1314–1319 (2010).

16 Mostello D, Catlin TK, Roman L *et al.* Preeclampsia in the parous woman: who is at risk? *Am. J. Obstet. Gynecol.* 287, 425–429 (2002).

17 Bodnar LM, Catov JM, Simhan HN *et al.* Maternal vitamin D deficiency increases the risk of preeclampsia. *J. Clin. Endocrinol. Metab.* 92, 3517–3522 (2007).

18 Robinson CJ, Alanis MC, Wagner CL, Hollis BW, Johnson DD. Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. *Am. J. Obstet. Gynecol.* 203(4), 366.e1–e6 (2010).

19 Haugen M, Brantsaeter AL, Trogstad L *et al.* Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology* 20, 720–726 (2009).

20 Zhang C, Qui C, Hu F *et al.* Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *PLoS One* 3, e3753 (2008).

21 Soheilykhah S, Mojibian M, Rashidi M *et al.* Maternal vitamin D status in gestational diabetes mellitus. *Nutr. Clin. Pract.* 25, 524–527 (2010).

22 Hensel KJ, Randis TM, Gelber SE, Ratner AJ. Pregnancy-specific association of vitamin D deficiency and bacterial vaginosis. *Am. J. Obstet. Gynecol.* 204(1), 41.e1–e9 (2011).

23 Hollis BW, Wagner CL. Nutritional vitamin D status during pregnancy: reasons for concern. *CMAJ* 174, 1287–1290 (2006).

24 Greer FR. 25-hydroxyvitamin D: functional outcomes in infants and young children. *Am. J. Clin. Nutr.* 88, 529S–533S (2008).

25 Kovacs C. Vitamin D in pregnancy and lactation: maternal, fetal, and neonatal outcomes from human and animal studies. *Am. J. Clin. Nutr.* 88, 520S–528S (2008).

26 Podar T, Solntsev A, Karvonen M *et al.* Increasing incidence of childhood-onset Type 1 diabetes in 3 Baltic countries and Finland 1983–1998. *Diabetologia* 44, B17–B20 (2001).

27 Camargo CA Jr, Ingham T, Wickens K *et al.* Cord-blood 25-hydroxyvitamin D levels and risk of respiratory infection, wheezing, and asthma. *Pediatrics* 127, e180–e187 (2011).

28 Hypponen E, Laara E, Reunanen A *et al.* Intake of vitamin D and risk of Type 1 diabetes: a birth cohort study. *Lancet* 358, 1500–1503 (2001).

29 Matsuoka LY, Ide L, Wortsman J, MacLaughlin JA, Holick MF. Sunscreens suppress cutaneous vitamin D3 synthesis. *J. Clin. Endocrinol. Metab.* 64, 1165–1168 (1987).

30 Standing Committee on the Scientific Evaluation of Dietary Reference Intakes Food and Nutrition Board, Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride.* The National Academies Press, Washington, DC, USA (1997).

31 Heaney RP, Holick MF. Why the IOM recommendations for vitamin D are deficient. *J. Bone Miner. Res*. DOI: 10.1002/jbmr.328 (2011) (Epub ahead of print).

32 Hathcock JN, Shao A, Vieth R, Heaney RP. Risk assessment for vitamin D. *Am. J. Clin. Nutr.* 85, 6–18 (2007).

33 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.* 80, 1752S–1758S (2004).

Website

101 Kolata G. Report questions need for two diet supplements. *New York Times*, 29 November (2010) www.nytimes.com/2010/11/30/health/30vitamin.html?_r=1 (Accessed 16 January 2011)