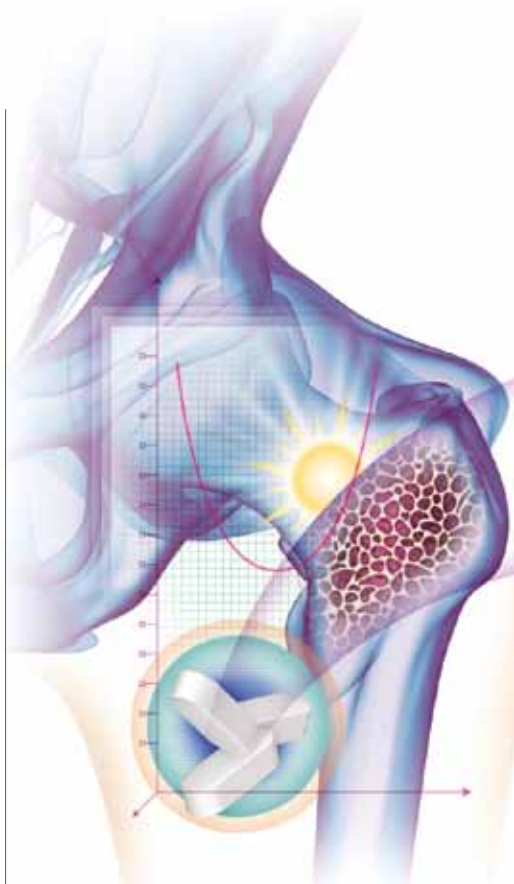


Vitamin D and pregnancy: 9 things you need to know

➔ Because the fetus derives vitamin D exclusively from maternal stores, a low level in a pregnant woman can have serious repercussions

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>> COMPANION ARTICLE

in the July 2011 issue of
OBG MANAGEMENT

“How much vitamin D should you recommend to your nonpregnant patients?”

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With all the publicity surrounding vitamin D lately, it's no surprise that you have lots of questions. Should you test your patients for deficiency? When? What numbers should you use? And how do you treat a low vitamin D level?

In pregnancy, these issues become critical because there are not one but two patients to consider. Despite the lack of clear guidelines, there is sufficient evidence to suggest that **you should at least consider monitoring the vitamin D status of your pregnant patients.**

Fetal needs for vitamin D increase during the latter half of pregnancy, when bone growth and ossification are most prominent. Vitamin D travels to the fetus by passive transfer, and the fetus is entirely dependent on maternal stores.¹ Therefore, maternal status is a direct reflection of fetal nutritional status.

The vitamin D level in breast milk also correlates with the maternal serum level, and a low vitamin D level in breast milk can exert a harmful effect on a newborn.

In this article, I address nine questions regarding vitamin D and pregnancy:

- Is vitamin D really a vitamin?
- Why do the numbers vary?
- Does the vitamin D level affect pregnancy outcomes?
- Can't people get enough vitamin D through their diet?

- What level signals deficiency?
- How many women are deficient?
- Should you test all pregnant patients?
- How should you treat vitamin D deficiency in pregnancy?
- Can a person get too much vitamin D?

1. Is vitamin D really a vitamin?

For years, vitamin D was discussed solely in relation to bone metabolism and absorption, and deficiency states were the purview of endocrinologists and gynecologists who treated menopausal patients at risk of osteoporosis. Recent studies demonstrate that vitamin D plays a role in multiple endocrine systems. Indeed, vitamin D may be more correctly considered a hormone because it is a substance produced by one organ (skin) that travels through the bloodstream to target end organs. Vitamin D receptors have been found in bone, breast, brain, colon, muscle, and pancreatic tissues. Not only does vitamin D affect bone metabolism, it also modulates immune responses and even glucose metabolism.² Vitamin D receptors have also been found in the placenta; their role in that organ remains to be elucidated.

2. Why do the numbers vary?

Some of the confusion surrounding vitamin D concerns the units used to measure and discuss it. Vitamin D can be measured in nanograms per milliliter (ng/mL) or in nanomoles per liter (nmol/L). A measurement of 1 ng/mL equals approximately 2.44 nmol/L. Therefore, deficiency in some articles is described as a vitamin D level below 20 ng/mL and in other articles as a level below 50 nmol/L. As for normal range, it may be listed as a level above 32 ng/mL or as a level above 75 nmol/L.

Compounding the confusion, vitamin D in supplement form can be written in two different measurements—using micrograms or international units. A measurement of 1 µg equals 40 IU, so a supplement of 150 µg/day is the same as one of 6,000 IU/day.

3. Does the vitamin D level affect pregnancy outcomes?

Vitamin D's role in pregnancy outcomes has yet to be fully described, making it an exciting field to explore. Research into vitamin D and its effects on pregnancy is still in its infancy, but many intriguing associations have been noted. For example, lower levels of vitamin D have been associated with increased rates of cesarean delivery,³ bacterial vaginosis,⁴ and preeclampsia,⁵ as well as less efficient glucose metabolism.⁶

There is biological plausibility for vitamin D to play a role in pregnancy outcomes, given the presence of receptors in gestational tissues. Vitamin D receptors in uterine muscle could affect contractile strength, and vitamin D has been shown to have immunomodulatory effects, thereby potentially protecting the host from infection.

As I mentioned, placental vitamin D receptors and their role need further exploration.

4. Can't people get enough vitamin D through their diet?

Very few foods contain a large amount of vitamin D, and the few that do (herring, cod liver oil) are not standard fare. Even fortified foods such as milk lack a substantial amount. **TABLE 1** (page 32) lists the amount of vitamin D in various foods.⁷

5. What level signals deficiency?

Experts disagree about the level of vitamin D that signals deficiency. Many labs report a reference range of 32 to 100 ng/mL as normal. However, in November 2010, the Institute of Medicine (IOM) weighed in on the matter. After examining the data, the IOM suggested that a vitamin D level of 20 ng/mL is sufficient to prevent bone loss and changes seen in rickets and osteoporosis.

This level is hotly contested by experts in other fields, who argue that, although 20 ng/mL may be considered the bare minimum level to prevent negative bone

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Lower levels of vitamin D in pregnancy have been associated with increased rates of cesarean delivery, bacterial vaginosis, and preeclampsia

resorption changes, it can hardly be construed as a normal level.

Nor did the IOM recommendation take pregnancy into consideration. Therefore, the IOM made no comment as to whether a level of 20 ng/mL is sufficient for a pregnant woman, given that the fetus will be actively soliciting maternal vitamin D for its own development. Indeed, some researchers have indicated that the actual daily recommended intake for pregnancy and lactation may be as high as 6,000 IU/day.⁸

6. How many women are deficient?

The rate of deficiency varies, but studies have documented rates as high as 97% in some pregnant populations; the rates vary by race and latitude.⁹⁻¹¹

The high prevalence of deficiency in the population is due, in large part, to vitamin D's mode of production and changes in human lifestyle and culture. Vitamin D is produced primarily through direct exposure of the skin to the sun. Over the past 50 years, as more and more people have come to spend their days in an office or factory instead of on a farm, the opportunity to produce vitamin D has greatly diminished.

Other entities or practices that reduce the production of vitamin D:

- **Sunscreen** SPF 50 may prevent skin cancer, but it also blocks vitamin D production.
- **Fat cells** Obese patients produce vitamin D less rapidly than patients of normal weight.
- **Melanin** Darker-skinned people produce vitamin D at a slower rate than those who have fair skin.

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Studies have documented a rate of vitamin D deficiency as high as 97% in some pregnant populations

TABLE 1 In food, the vitamin D level is generally low

Source	Amount of vitamin D (IU)
Egg yolk	25
Cereal, fortified with vitamin D, 1 cup	40–50
Cow's milk, fortified with vitamin D, 8 oz	98
Soy milk, fortified with vitamin D, 8 oz	100
Orange juice, fortified with vitamin D, 8 oz	100
Quaker Nutrition for Women instant oatmeal, 1 packet	154
Tuna, canned in oil, 3 oz	200
Sardines, canned, 3 oz	231
Mackerel, 3 oz	306
Most multivitamins	400
Tri-Vi-Sol infant supplements, 1 drop	400
Prenatal vitamins	400
Catfish, 3 oz	425
Pink salmon, canned, 3 oz	530
Cod liver oil, 1 tablespoon	1,360
Herring, 3 oz	1,383
Over-the-counter vitamin D ₃ supplements	2,000 (maximum)
Typical prescription of vitamin D ₂ for deficiency	50,000 (given weekly until replete)

TABLE 2 When (and with how much “D”) to treat pregnant patients

If the 25-OHD level is...	...then supplement with*
<20 ng/mL	50,000 IU oral vitamin D weekly for 12 weeks
20–32 ng/mL	2,000–4,000 IU oral vitamin D daily (~15,000–30,000 IU weekly)
>32 ng/mL	No action needed

*Assuming that the patient will continue taking a prenatal vitamin containing 400 IU/tablet.

- **Cultural practices** Some religious and cultural practices mandate full skin coverage in public, particularly for women, leading to minimal sun exposure.
- **Age** Older people also produce vitamin D more slowly. Among the population of reproductive age, however, the effect of age is minimal.
- **Latitude** Northern latitudes, with their longer winters and shorter summers, provide less opportunity for sun exposure.

Because vitamin D is, in essence, a “seasonal” vitamin, it makes evolutionary sense that the human body has developed a wide normal range to “store up” vitamin D when sunshine is plentiful and then use its stores during times of scarcity, such as winter. This seasonal variability is another reason why the rate of deficiency can vary, depending on the time and location of study.

Because vitamin D deficiency is clinically silent until severe events such as rickets occur, the best way to check for it is to measure total levels of the two forms of vitamin D found in the body—D₂ and D₃. The recommended test is total 25-hydroxy vitamin D (25-OHD). Measurement of the activated form of vitamin D—1,25-OHD—will not tell you whether a person’s overall stores are lacking, because the body maintains a normal 1,25-OHD level over a wide range until severe deficiency occurs.

7. Should you test all pregnant patients for deficiency?

ACOG does not recommend that vitamin D be measured routinely in pregnant women.¹² In a Committee Opinion published in July

2011, ACOG determined that “there is insufficient evidence to support a recommendation for screening all pregnant women for vitamin D deficiency.”¹²

Many experts disagree, however, citing the increased rate of rickets being found in the United States.^{6,8} Pediatricians in the United States have found such a high rate of deficiency in the neonatal population that the American Academy of Pediatrics now recommends that all exclusively breastfed babies be given a supplement of 400 IU of vitamin D daily, beginning in the first few days of life.¹³

ACOG acknowledged that, for pregnant patients “thought to be at increased risk, measurement of total levels can be considered with “high-risk groups” that have many of the risk factors cited earlier.¹²

If you want to test your patients, no single plan is recommended. A sample algorithm includes the following steps:

- Measure total 25-OHD at the time of prenatal registration labs
- Select a level of supplementation, based on the findings (see TABLE 2)
- Recheck the 25-OHD level after 3 months. For most patients, this would be around the time of a standard glucose screening test
- Adjust the supplementation level, as needed
- Measure 25-OHD at admission to labor and delivery.

8. How should you treat vitamin D deficiency in pregnancy?

Here, again, there is a lack of solid evidence. No guidelines exist for pregnant patients. In



ACOG does not recommend routine measurement of vitamin D in pregnant women, but it does acknowledge that measurement should be considered in “high-risk groups”

its Committee Opinion, ACOG points out that higher-dose regimens have not been studied in pregnancy, but cites studies using up to 4,000 IU daily.¹² The question becomes: Can guidelines that have been established for nonpregnant patients be used safely in pregnancy?

Although there is no evidence-based consensus, physiology and previous studies suggest that they can.

In one study, pregnant women were given doses as high as 200,000 IU in the third trimester to treat vitamin D deficiency.¹⁴ That investigation produced two key findings:

- There were no signs or symptoms of toxicity in patients or newborns, demonstrating that a single dose of a large amount of

vitamin D can be administered safely.

- Despite the treatment, many of the women in this study remained deficient, indicating that continued supplementation would be required beyond the initial dose.

Although the dosage administered in this study seems like a large amount, it should be viewed in context: a Caucasian female can produce 50,000 IU of vitamin D from 30 minutes of sun exposure at midday.¹⁴

The IOM acknowledged that it underestimated the amount of vitamin D that can be taken safely and increased its upper limit of normal to 4,000 IU daily. Note that this upper limit is for people who are presumed to have a normal level to begin with. Therefore, it would be expected that a deficiency would

NEWS FROM THE MEDICAL LITERATURE

Study finds vitamin D supplementation in pregnancy to be safe and effective

Daily 4,000-IU vitamin D supplementation from 12 to 16 weeks of gestation is safe and effective in achieving vitamin D sufficiency in pregnant women and their neonates, according to a study published in the July 2011 issue of the *Journal of Bone and Mineral Research*.

Bruce W. Hollis, PhD, from the Medical University of South Carolina in Charleston, and colleagues assessed the need, safety, and effectiveness of vitamin D supplementation in 350 women with singleton pregnancies at 12 to 16 weeks of gestation. Participants were randomly assigned to receive 400 IU, 2,000 IU, or 4,000 IU vitamin D₃ daily until delivery. The outcomes studied included maternal/neonatal circulating serum vitamin D (25-OHD) levels at delivery, achieving 25-OHD of 80 nmol/L or more, and achieving 25-OHD concentration for maximal 1,25-dihydroxycholecalciferol (1,25-OH₂D) production.

The investigators found that the percentage of participants who achieved vitamin D sufficiency was significantly different between

groups, with the 4,000-IU group having the highest percentage. Within 1 month of delivery, the relative risk (RR) of achieving 25-OHD of 80 nmol/L or more differed significantly between the 2,000-IU versus 400-IU groups and 4,000-IU versus 400-IU groups (RR, 1.52 and 1.60, respectively). There was no significant difference between the 2,000-IU and 4,000-IU groups. Circulatory 25-OHD directly influenced 1,25-OH₂D levels throughout pregnancy, with maximal production of 1,25-OH₂D in the 4,000-IU group. Vitamin D supplementation was not associated with adverse events, and safety measures were similar between the groups.

“A daily vitamin D dose of 4,000 IU was associated with improved vitamin D status throughout pregnancy, one month prior, and at delivery in both mother and neonate,” the authors write.

One of the study authors disclosed financial ties with the Diasorin Corporation.

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A Caucasian female can produce 50,000 IU of vitamin D from 30 minutes of sun exposure at midday

require a greater amount for treatment.

As for treatment, both daily and weekly regimens are acceptable. Because vitamin D is fat-soluble, a daily dose of 1,000 IU is equivalent to a weekly dose of 7,000 IU. Many patients prefer the convenience of weekly dosing, which can also improve compliance.

See **TABLE 2** for a proposed guideline on how to treat a pregnant patient, based on the 25-OHD level.

9. Can a person get too much vitamin D?

Vitamin D is fat-soluble. Should you worry about toxicity?

Because there is such a wide normal range for vitamin D, a person would have to be taking massive amounts of the nutrient for a substantial time before hypervitaminosis and a potential impact on calcium metabolism occur. Pharmacokinetic data demonstrate that toxicity may not occur until a vitamin D level of 300 ng/mL or higher is reached, which is three times the upper limit of normal for most reference ranges.¹⁵ A 2007 review found no cases of toxicity reported in the literature at a total serum level below 200 ng/mL (twice the normal limit) or a dose of less than 30,000 IU/day.¹⁶

Last words

Many questions and research opportunities remain regarding optimal vitamin D levels and supplementation in pregnancy, as well as the impact of vitamin D not only on pregnancy-related outcomes but on neonatal and infant health. One thing is certain: No one can argue that a nutritionally deficient state is preferred in pregnancy for maternal or fetal health. As advocates for women's health, it behooves us to address this situation for the benefit of our patients and their children. ☺

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How do you manage the vitamin D requirements of pregnant and nonpregnant patients?

Do you agree with the Institute of Medicine that a vitamin D level of 20 ng/mL is sufficient for most individuals? Do you routinely measure the vitamin D level of your patients? Do you recommend vitamin D supplementation in pregnancy?

Drop us a line at obg@qhc.com and let us know your opinion and clinical approach. We'll publish a selection of comments in an upcoming issue.