

# Calcium and Vitamin D for the Reproductive Female

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## ***Abstract***

*The importance of calcium as well as its interdependence upon vitamin D is well established. Vitamin D acts via the vitamin D receptor, which is found in 37 different human tissues. Because of its rather ubiquitous localization, vitamin D is the topic of a great deal of associative research. However, caution must be exercised in interpreting these initial studies until clear evidence for causality becomes available. The purpose of this article is to review some of the known vitamin D and calcium associations as well as the current guidelines for calcium and vitamin D supplementation in the reproductive female.*

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## **Introduction**

Calcium is essential for muscle contraction, second messenger formation, secretion of neurotransmitters and hormones, blood coagulation, and bone metabolism. Its availability for these essential functions is dependent upon dietary intake of calcium and vitamin D as well as gut absorption and bone metabolism. In particular, uptake of calcium requires prior vitamin D uptake and metabolism.

Vitamin D is not merely a vitamin but a highly regulated steroid hormone system with several derivatives and metabolites. Vitamin D<sub>2</sub> is a plant-derived molecule

that is ingested, whereas vitamin D<sub>3</sub> is a derivative of cholesterol that can also be ingested or formed in the skin via ultraviolet light. Vitamin D is then converted in the liver to 25-hydroxyvitamin D (25(OH)D), which is the precursor of the active metabolite. Final conversion to the active metabolite, 1,25-dihydroxyvitamin D occurs in the kidney. Vitamin D then acts via the vitamin D receptor (VDR). Because the VDR is found in 37 different human tissues, vitamin D is linked to a multitude of biological and pathological processes. However, caution must be exercised in interpreting these studies until clear evidence for causality becomes available. The purpose of this article is to review some of the known vitamin D and calcium associations with clinical condition as well as the current guidelines for calcium and vitamin D supplementation in women of reproductive age.

### **Defining calcium and vitamin D deficiency**

The levels of total calcium remain relatively stable throughout a women's reproductive life. During pregnancy, 25-30 grams of calcium are transferred to the fetus via active transport. Most of this transfer occurs in the 2<sup>nd</sup> and 3<sup>rd</sup> trimester when mineralization of the fetal skeleton occurs. Increased absorption in the gut allows this transfer while relatively preserving the maternal skeleton. This increased absorption is balanced not only by the fetal transfer but also by increased urinary excretion.

Vitamin D and its metabolites play an important role in calcium homeostasis and bone metabolism. Vitamin D is the only vitamin that can be derived in humans as well as ingested. In healthy adults, vitamin D levels are maintained by appropriate dietary intake as well as sun exposure.

Severe vitamin D deficiency is characterized by muscle weakness, bone pain, and fragility fractures. In assessing vitamin D deficiency, it is important to

measure 25(OH)D. While it is not the most active metabolite it does represent body stores. In the past, the level at which a patient was considered deficient was <10 ng/ml. Today, controversy exists as to what constitutes insufficiency. Most literature quotes levels < 30 ng/ml; however the Institute of Medicine defines insufficiency as  $\leq 20$  ng/ml. It should be noted that 97% of the population has levels of 20 ng/ml, which is generally considered to be adequate.

#### *Women are often insufficient in both calcium and vitamin D*

From a young age, women often do not have appropriate calcium intake, such that 13% of girls age 12-19 and 22% of women above the age of 20 are deficient in calcium. In a report from the 3<sup>rd</sup> National Health and Nutrition and Examination Survey, which used 30 ng/ml to define sufficiency, 69% of pregnant women and 78% of non-pregnant women age 13-44 were reported to have vitamin D insufficiency.<sup>1</sup>

Maternal insufficiency of calcium and vitamin D correlates with fetal insufficiency. In the 2010 study by Karim et al, a positive correlation between the level of vitamin D in maternal serum and cord blood was found, with a high prevalence of both insufficiency (20-29ng/ml) and deficiency (<20ng/ml) in the maternal sample population. Fetal Vitamin D levels were categorized as sufficient (>33ng/ml) or deficient (<33ng/dl). This study was conducted on 50 consecutive women presenting in labor with a singleton term pregnancy at a tertiary care center in Pakistan. Maternal blood taken prior to delivery was compared to cord blood at the time of delivery. Maternal deficiency was noted in 23 (46%) and insufficiency in 16 (32%) while fetal insufficiency was noted in 44 infants (88%). Maternal Vitamin D levels were significantly correlated to sunlight exposure and diet. ( $P<.0007$ ).<sup>2</sup>

#### *A little history of vitamin D*

The clinical presentation of rickets, which is caused by vitamin D deficiency, was first described in children in the mid-17<sup>th</sup> century. Vitamin D deficiency was noted to cause lifelong bone deformities in weight bearing bones including the pelvis. In the early 19<sup>th</sup> century in Glasgow, it was reported that one out of thirty deliveries required destruction of the fetal cranium because of a rachitic maternal pelvis.<sup>3</sup> In the British Medical Journal in 1890, Murdoch Cameron introduced c-sections into practice for women with a deformed pelvis.<sup>4</sup> An early 20<sup>th</sup> century public health campaign greatly reduced the prevalence of vitamin D deficiency. Unfortunately, rickets has started to re-emerge in the pediatric literature, potentially because of the current practice of avoiding ultraviolet light to decrease the incidence of skin cancer.

### **The significance of calcium and vitamin D: classic ideas**

Calcium is important for skeletal mineralization in the reproductive female. Sufficient maternal calcium intake is critical to maintain adequate circulating values and thereby avoid maternal skeletal depletion in pregnancy and lactation. Maternal calcium intake also affects circulating calcium levels in infants. Approximately 210 mg/day of calcium is secreted into the breast milk. The source of this maternal calcium is increased bone mineralization and decreased urinary excretion. Not surprisingly, a 2-5% loss in bone density occurs during pregnancy and lactation, but it rebounds with the resumption of menses. In addition to calcium, fat soluble vitamins (D, A, E) are also secreted into breast milk. Vitamin D levels in newborns (the first postnatal 6-8 weeks) are largely dependent upon pre-natal stores. Like with calcium, vitamin D levels in breast fed infants reflect maternal intake. Human breast milk has 20-60 IU/liter, which is 1.5-3% of the maternal levels of vitamin D. Therefore, it is recommended that all breast fed infants are supplemented with 400 IU of vitamin D daily. Another possible strategy to increase infant vitamin D intake is to increase maternal intake. In a

small study of 18 women, 4000 IU maternal supplementation substantially increased the vitamin D content of breast milk.<sup>5</sup> To attain the recommended daily allowance in formula fed infants, 400 IU/liter is added to all formula in the US.

## **Non Classical Associations**

### *Preconception*

Vitamin D is thought to be important in the preconception period. For example, animal studies demonstrate impaired fertility, likely attributed to abnormal ovulatory function, in vitamin D-deficient rats.<sup>6</sup> Mice devoid of  $\alpha$ 1-hydroxylase have hypoplastic reproductive organ development.<sup>7</sup> Finally, VDR null mice are infertile but develop normal fertility with a calcium-rich diet.<sup>8</sup> A prospective cohort study revealed that higher 25(OH)D levels in serum and follicular fluid predicted success of in vitro fertilization (IVF), even after adjustment for age, body mass index (BMI), ethnicity, and number of embryos.<sup>9</sup> Interestingly, there was no increase in ovulation, and the authors postulated that the increased levels of 25(OH)D improved receptivity and implantation.

### *Polycystic Ovarian Syndrome*

While no randomized control trials have examined the effect of vitamin D and/or calcium supplementation in women with polycystic ovarian syndrome (PCOS), several small trials have demonstrated some improvements in PCOS patients with vitamin D and calcium treatment. Thys-Jacobs et al demonstrated that calcium and vitamin D (1500mg supplement) treatment normalized menstrual cycles in 54% (7/13) of women with PCOS.<sup>10</sup> In another study of 15 PCOS patients, insulin secretion was improved with vitamin D treatment.<sup>11</sup> A pilot study in which women were treated with metformin, calcium, and vitamin D, improved number dominant follicles >14mm were observed.<sup>12</sup>

### *Pre-eclampsia*

The role of calcium in pre-eclampsia was first examined in the Calcium for Pre-Eclampsia Prevention Trial (CPEP) in 1997.<sup>13</sup> In this study, 4589 women at 13-21 weeks of gestation were randomized in a placebo-controlled double blinded trial to daily supplementation with 2000 mg calcium versus placebo for the remainder of pregnancy. Unfortunately, no difference was found in the development of gestational hypertension, pre-eclampsia, or adverse perinatal outcomes in healthy nulliparous women with or without calcium supplementation. In 2006, the World Health Organization reported results from a randomized placebo-controlled double blind trial of 8325 pregnant women with low calcium intake (< 600 mg/day) with calcium supplementation.<sup>14</sup> The subjects were enrolled prior to 20 gestational weeks and randomized to receive 1500 mg of calcium per day versus placebo for the duration of pregnancy. Supplementation did not prevent pre-eclampsia but it did reduce its severity, along with reducing maternal and neonatal morbidity. In a Cochrane database review of >15,000 women in 12 trials, supplementation with at least 1 gram of calcium daily during pregnancy compared to placebo reduced the risk of both gestational hypertension (RR 0.65) and pre-eclampsia (RR 0.45).<sup>15</sup> The women in a majority of the studies included in this meta-analysis could be categorized as having a low risk pregnancy as well as a low calcium diet.

Pre-eclampsia has been associated with low 1,25 dihydroxyvitamin D levels secondary to reduced expression and activity of  $\alpha$ 1-hydroxylase in the placenta. Interestingly, a study by Bodnar et al of 274 women found a significant association between low 25(OH)D concentrations in early pregnancy and the development of pre-eclampsia.<sup>16</sup> 25 (OH)D levels were measured at 16 weeks and then the patients were followed for the duration of pregnancy and outcomes measured. The 55 women who developed pre-eclampsia had significantly lower

levels of 25(OH)D than those that did not; however these women were not vitamin D deficient. Those who developed pre-eclampsia had a mean Vitamin D level of 45.4nmol/l (38.6-53.4 nmol/L) vs. 53.1nmol/L (47.1-59.9nmol/L). The authors concluded that vitamin D deficiency may be an independent risk factor for pre-eclampsia. Finally an epidemiologic study of 23,423 Norwegian women identified a 27% risk reduction for developing pre-eclampsia with vitamin D supplementation compared to no supplementation.<sup>17</sup>

### *Gestational Diabetes*

1,25 dihydroxyvitamin D is known to stimulate insulin production and improve insulin sensitivity; therefore investigators have tried to link vitamin D deficiency with gestational diabetes. No randomized control trials are available, but two cross sectional studies demonstrated lower 25 (OH) levels in gestational diabetes mellitus (GDM) when compared to controls.<sup>18,19</sup> A third cross sectional study of Indian mothers found no association.<sup>20</sup> One prospective case controlled study demonstrated that vitamin D deficiency (24.2 vs 30.1 ng/ml) at 16 weeks of gestation was associated with increased risk for GDM development. 33% of gestational diabetic cases had Vitamin D levels <20ng/ml compared with 14% of controls.<sup>21</sup>

### *Mode of delivery, preterm birth, and low birth weight*

To understand how vitamin D deficiency contributes to the mode of delivery, one study measured the maternal and neonatal 25(OH)D levels and found that women with deficiency in vitamin D were four times more likely to have a primary c-section.<sup>22</sup> The authors' explanation for this finding is related to the fact that skeletal muscle contains the vitamin D receptor such that vitamin D deficiency is associated with suboptimal muscle performance and strength.

With regards to birth weight, in the 1980's, the initial randomized controlled trial showed that vitamin D supplementation leads to fewer small for gestational age infants.<sup>23</sup> However, conflicting data from France reported no difference in birth weight between groups receiving 20,000 IU or 2000 IU vitamin D as compared to placebo.<sup>24</sup> However, maternal milk intake has been correlated with larger infants in two separate trials, one in Canada<sup>25</sup> and a larger cohort study in the Netherlands.<sup>26</sup> No randomized control trials of vitamin D replacement and preterm birth have been published until an abstract reported at the 2010 Pediatric Academic Societies Meeting.<sup>27</sup> In this study, 350 women were randomized to three different vitamin D supplemental regimens 400 IU, 2000 IU, and 4000IU. The authors conclude that vitamin D sufficiency correlated with decreased risk for preterm birth, infection, and co-morbidities of pregnancy with the greatest effect at 4000 IU/day. No adverse effects were noted with any treatment group.

### **A word of caution**

In 2011, the Institute of Medicine (IOM) reviewed its recommendations for calcium and vitamin D and made very few changes from previous years. Under these guidelines, women aged 14-50, regardless of pregnancy or lactation, need 1000 mg of calcium and 600 IU of vitamin D/day (Table 1). Women above 51 years of age require 1200 mg of calcium and 600 IU of vitamin D until the age of 71, when they should increase vitamin D intake to 800 IU. According to this report, "The data just aren't there to recommend people consume higher amounts of vitamin D or calcium." The upper limit of recommended intake is 2500 mg calcium and 4,000 IU vitamin D per day. The upper limit includes dietary intake, and most people get 600-900 mg of calcium from dietary sources. Of note, 5% of postmenopausal women are taking more than the daily recommended allowance, which increases the risk for kidney stones and possibly cardiovascular disease.<sup>30</sup> Controversy regarding optimal vitamin D supplementation exists. Many suggest that most individuals can benefit from a



supplement, especially in the winter months.<sup>28</sup>

**Table 1: Revised daily dietary allowance recommendations for calcium and vitamin D in reproductive female\***

Age (yrs)	Calcium			Vitamin D		
	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)	Estimated Average Requirement (mg/day)	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)
<b>14-19</b>	1100	1300	3000	400	600	4000
<b>19-50</b>	800	1000	2500	400	600	4000
<b>51-70</b>	1000	1200	2000	400	600	4000
<b>&gt;70†</b>	1000	1200	2000	400	800	4000
<b>14-18 pregnant/lactating</b>	1100	1300	3000	400	600	4000
<b>19-50 pregnant/lactating</b>	800	1000	2500	400	600	4000

*\*Adapted from the Institute of Medicine 2011 consensus report of dietary reference intakes for calcium and vitamin D*

***†denotes the only revised recommended dietary allowance***

## **Screening**

No formal screening guidelines exist. The IOM states we should not routinely screen, but take inventory and screen those at risk for deficiency based on diet and sun exposure, specifically habitation in the northern latitudes, regular sunscreen use, dark skin, obesity, aging, or malabsorptive syndromes. Interpretation of the results may be challenging, especially if the lab is not a reference lab. In May of 2010, Mulligan et al published a clinical opinion in the American Journal of Obstetrics and Gynecology. They stated that women with one or more risk factors should have vitamin D levels evaluated at the first prenatal visit and again mid-way through pregnancy.<sup>29</sup> According to these authors, caregivers should target a range between 32-100 ng/dl and treat with 2000-4000 IU to achieve it. It should be noted that the average vitamin D supplementation in prenatal vitamins is 400 IU.

## **Conclusions**

Calcium and vitamin D are important to the reproductive female. Deficiency leads to serious skeletal consequences (rickets), yet optimum levels or sufficiency is widely debated. Most literature and reference labs set 30 ng/ml as sufficient although the Institute of Medicine uses 20 ng/ml as the standard. Caution should be used in reviewing literature linking vitamin D to various disease states as very few randomized trial exists, and the findings have not been replicated. No formal screening guidelines exist for vitamin D deficiency, but given the variable sun exposure and level of obesity in Iowa, many of our patients have risk factors. Vitamin D levels should be measured by 25 (OH)D and only sent to reference laboratories to ensure a correct reading. Supplementation with up to 4000 IU/day is safe but not recommended by the Institute of Medicine. In short, further

research is needed.

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