



By Kristin Bendikson, MD, and Briana Rudick, MD

An epidemic of vitamin D deficiency has been emerging over the past decade among all racial groups in the United States. In fact, the prevalence of vitamin D insufficiency nearly doubled from 1994 to 2004.<sup>1</sup> Among women of reproductive age, more than 40 percent are insufficient in vitamin D.

Vitamin D's most important role in the human body is to keep bones healthy and strong by helping the body absorb calcium. Vitamin D deficiency therefore results in lower bone mineral density and an increased risk of osteoporosis and bone fracture. Recent research has pointed to additional ways that vitamin D deficiency factors into our overall health, including its role in chronic diseases like diabetes, obesity, autoimmune disease, cardiovascular disease, and cancer as well as an association with a higher risk of both overall and cancer mortality.<sup>2</sup>

In addition to affecting cells that live in the bone, vitamin D affects many different types of cells in different organs in the body by turning genes within that cell "on and off." In other words, vitamin D affects the way a cell carries out its function, and it can control the growth or the death of that cell.

Many recent studies have focused on the relationship of vitamin D levels to cancer. Vitamin D levels below 20 nanograms per millimeter (ng/mL) are associated with a 30 to 50 percent increased risk of colon, prostate, and breast cancer, including a higher risk of death from these cancers.<sup>3</sup> Indeed, the newly discovered roles of vitamin D in the body involving immunity and the ability to turn on or off certain genes provides a logical explanation for how vitamin D could contribute to cancer risk and mortality. Although these studies do show a *link* between vitamin D levels and cancer risk, they do not prove that low levels of vitamin D *cause* these cancers—and there have not yet been any studies that show a clear benefit of taking vitamin D. The Institute of Medicine recently released a consensus report stating that more evidence is needed before recommending vitamin D supplementation for any health benefit other than bone health and that levels of 20 ng/ml are sufficient to maintain good bone health.<sup>4</sup>

In the world of reproduction, the importance of vitamin D was initially shown in experiments with rats. Rats that either are deficient in vitamin D or lack the vitamin D receptor can demonstrate underdevelopment of the uterus and an inability to form normal mature eggs, resulting in infertility.<sup>5,6</sup> If pregnancy is achieved, the fetuses of these rats show impaired growth.<sup>7</sup> Reproduction is normalized in rats with vitamin D supplementation but not with calcium alone, suggesting that the role of vitamin D in female reproduction is not related to helping the body absorb calcium.<sup>8</sup>

In humans the vitamin D receptor is present in many female organs, including the ovary, uterus, and placenta.<sup>9</sup> The active form of vitamin D (calcitriol) has many roles in female reproduction. Bound to its receptor, calcitriol is able to control the genes involved in making estrogen. The uterine lining produces calcitriol in response to the embryo as it enters the uterine cavity, shortly before implantation.<sup>10</sup> Calcitriol controls several genes involved in embryo implantation.<sup>10</sup> Once a woman becomes pregnant, the uterus and the placenta continue to make calcitriol, which helps organize immune cells in the uterus so that infections can be fought without harming the pregnancy. Poor vitamin D status has been associated with certain pregnancy complications such as gestational hypertension and diabetes.<sup>11</sup>

Women about to undergo in vitro fertilization (IVF) can provide valuable insight into the role of vitamin D because it is possible to examine each aspect of reproduction, from egg development to implantation of the embryo. A recent study found that women with higher vitamin D levels were significantly more likely to achieve pregnancy from IVF compared with women with lower levels of vitamin D.<sup>12</sup> This study was repeated in another IVF center, which confirmed a fourfold difference in pregnancy rates between vitamin D replete and deficient women.<sup>13</sup> In another study looking at the recipients of donor eggs, vitamin D levels in the recipients were associated with clinical pregnancy, emphasizing that the critical role of vitamin D in pregnancy may be within the uterus.<sup>14</sup> Though more research is needed, it appears that vitamin D levels are associated with IVF success and that its most important role in reproduction may be at the uterine lining. No studies have yet evaluated whether vitamin D improves IVF outcomes, but the data that do exist suggest that there may be a role for vitamin D supplementation as a means of improving natural fertility among both fertile and infertile women. The research that implicates vitamin D deficiency as playing a role not only in fertility but in overall health is compelling, and it is backed by a sound physiologic hypothesis. Before broad treatment changes are instituted, however, further research needs to be completed to assess the health benefits of supplementing vitamin D to attain replete levels. Nevertheless, this is an exciting new field of research that could lead to simple and inexpensive approaches to improve health. Regardless of potential fertility benefits, patients should be counseled regarding appropriate vitamin D supplementation for overall health benefits, including bone health, pregnancy health, and chronic disease risk reduction.

#### References

1. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. *American Journal of Clinical Nutrition*. 2008;88(6):1519-27.
2. Michaelsson K, Baron JA, Snellman G et al. Plasma vitamin D and mortality in older men: a community-based prospective cohort study. *American Journal of Clinical Nutrition*. 2010;92(4):841-8.
3. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. *American Journal of Public Health*. 2006;96:252-61.
4. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: National Academies Press; 2011.
5. Kinuta K, Tanaka H, Moriwake T, Aya K, Kato S, Seino Y. Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. *Endocrinology*. 2000;141(4):1317-24.

6. Yoshizawa T, Handa Y, Uematsu Y, et al. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia and growth retardation after weaning. *Nature Genetics*. 1997;16(4):391-96.
7. Halloran BP, DeLuca HF. Effect of vitamin D deficiency on fertility and reproductive capacity in the female rat. *Journal of Nutrition*. 1980;110:1573-80.
8. Kwiecinski GG, Petrie GI, DeLuca HF. Vitamin D is necessary for reproductive functions of the male rat. *Journal of Nutrition*. 1989;119:741-74.
9. Johnson LE, DeLuca HF. Vitamin D receptor null mutant mice fed high levels of calcium are fertile. *Journal of Nutrition*. 2001;131:1787-91.
10. Viganò P, Lattuada D, Mangioni S, et al. Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. *Journal of Molecular Endocrinology*. 2006;36(3):415-24.
11. Bodnar LM, Catov JM, Simhan HN, Holick MF, Powers RW, Roberts JM. Maternal vitamin D deficiency increases the risk of preeclampsia. *Journal of Clinical Endocrinology and Metabolism*. 2007;92(9):3517-22.
12. Ozkan S, Jindal S, Greeneid K, et al. Replete vitamin D stores predict reproductive success following in vitro fertilization. *Fertility and Sterility*. 2010;94(4):1314-19.
13. Rudick B, Ingles SA, Stanczyk F, Chung K, Paulson R, Bendikson K. Characterizing the role of vitamin D levels on IVF outcomes: stimulation, embryo, or endometrium? Paper presented at: Annual Meeting of the American Society for Reproductive Medicine; October 23-27, 2010; Denver, CO. Abstract O-245.
14. Rudick B, Ingles SA, Stanczyk F, Chung K, Paulson R, Bendikson K. The role of vitamin D levels on IVF outcomes in donor-recipient cycles. Paper presented at: Annual Meeting of the Pacific Coast Reproductive Society; April 13-17, 2011; Rancho Mirage, CA. Abstract O-9.

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