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Review Article

Role of sunshine vitamin “D” sufficiency in male and female infertility

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ABSTRACT

Infertility is a complex disorder which affects about 15% of couple. Animal and human studies suggest that vitamin D deficiency is involved in both male and female infertility. The expression levels of vitamin D receptors and CYP24A1 in human spermatozoa serve as positive predictive markers of semen quality. In women, vitamin D status has been associated with better IVF outcomes, anti Mullerian hormone production and maintenance of ovarian reserve. Serum [25(OH)] D levels have a direct relationship with clinical pregnancy outcomes in women undergoing IVF. Women with sufficient levels of vitamin D show higher implantation rates, higher rates of clinical pregnancy in IVF and ET cycles. In women undergoing IVF, higher vitamin levels in their serum and follicular fluid are more likely to achieve clinical pregnancy. Its most important role in reproduction may be at the endometrial level.

Keywords: Vitamin D [25(OH)] D, Female infertility, Male infertility, AMH, IVF-ET

INTRODUCTION

Infertility is defined as inability to conceive after twelve months of unprotected intercourse under 35 years, and for six months after 35 years. Causes of infertility may be related to female or male factors or both together. In female, causes for infertility are ovulatory dysfunction (15%), tubal pathology 35%, cervical and others 5%, unexplained 10%. Ovulatory dysfunction may be due to poly cystic ovary syndrome, hyperprolactenemia, premature and age related ovarian failure, hypothalamic anovulation, and luteal phase defect.

Male factors contribute nearly 35% of causes. These may be due to reversible conditions like varicocele, obstructive azoospermia, and non-reversible but with viable available sperm like ejaculatory dysfunction, inoperable obstructive azoospermia, and non-reversible no viable sperm as in conditions like hypogonadism, genetic abnormalities, testicular or pituitary cancer. Infertility is a complex disorder with significant medical, psychological, and economic aspects, which affects about

15% of couple.¹ Although several causes are responsible for infertility in both genders, as discussed above some recent studies show relevance of vitamin D in reproductive physiology.²

Long known for its role in bone health, vitamin D is a steroid hormone that is emerging as a factor in fertility. Animal studies have shown that the hormone, which is produced in the skin as a result of sun exposure as well as absorbed from some fortified foods, affects fertility in many mammals. Vitamin D is an essential vitamin required by the body for the proper absorption of calcium, bone development, control of cell growth, neuromuscular functioning, proper immune functioning, and alleviation of inflammation. A deficiency in vitamin D can lead to rickets, a disease in which bones fail to properly develop. Further, inadequate levels of vitamin D can lead to a weakened immune system, increased cancer risk, poor hair growth, and osteomalacia, a condition of weakened muscles and bones. Conversely, excess vitamin D can cause the body to absorb too much calcium, leading to increased risk of heart attack and kidney

stones. The current U.S. daily value for vitamin D is 600 IU (international units) and the toxicity threshold for vitamin D is thought to be 10000 to 40000 IU/day. Sometimes vitamin D values are given in micrograms (mcg, µg), and when this is the case remember that 1µg = 40IU for vitamin D. 1,25-dihydroxyvitamin D₃ 24-hydroxylase, a mitochondrial enzyme in humans is encoded by the CYP24A1 gene. This mitochondrial protein initiates the degradation of 1,25-dihydroxyvitamin D₃, the physiologically active form of vitamin D₃, by hydroxylation of the side chain to form calcitric acid. In regulating the level of vitamin D₃, this enzyme plays a role in calcium homeostasis and the vitamin D endocrine system. This gene encodes a member of the cytochrome P450 super family of enzymes. The cytochrome P450 proteins are mono oxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids. Vitamin D is an essential oil soluble vitamin which means one needs to eat fat to absorb it. Natural food sources of vitamin D include fish oils, fatty fish, and to a lesser extent beef liver, cheese, egg yolks, and certain mushrooms. Vitamin D is also naturally made by the body when one exposes the skin to the sun, and thus, is called the sun-shine vitamin. In addition, vitamin D is widely added to many foods such as milk and orange juice, and can also simply be consumed as a supplement. Vitamin D is essential for strong bones, because it helps the body use calcium from the diet. Traditionally, vitamin D deficiency has been associated with rickets, a disease in which the bone tissue doesn't properly mineralize, leading to soft bones and skeletal deformities. But increasingly, research is revealing the importance of vitamin D in protecting against a host of health problems.

Other benefits of vitamin D: Research suggests that vitamin D could play a role in the prevention and treatment of a number of different conditions, including type 1 and type 2 diabetes, hypertension, glucose intolerance, and multiple sclerosis. Because the body makes vitamin D when ones skin is exposed to sunlight, one may be at risk of deficiency if homebound, live in northern latitudes, wear long robes or head coverings for religious reasons, or have an occupation that prevents sun exposure. The pigment melanin reduces the skin's ability to make vitamin D in response to sunlight exposure. Some studies show that older adults with darker skin are at high risk of vitamin D deficiency.

According to the European food safety authority, the tolerable upper intake levels are:³

- 0-12 months: 25 µg/day (1000 IU)
- 1-10 years: 50 µg/day (2000 IU)
- 11-17 years: 100 µg/day (4000 IU)
- 17+: 100 µg/day (4000 IU)

- Pregnant/lactating women: 100 µg/day (4000 IU)

SYNTHESIS OF VITAMIN D

The active vitamin D metabolite calcitriol mediates its biological effects by binding to the Vitamin D Receptor (VDR), which is principally located in the nuclei of target cells.⁴ The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins, which are involved in calcium absorption in the intestine.⁵ The vitamin D receptor belongs to the nuclear receptor super family of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood and to the maintenance of bone content.⁶ One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body.⁷ Thus, although it may initially appear paradoxical, vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption.⁸ The VDR is known to be involved in cell proliferation and differentiation, and affects the immune system. VDRs are expressed in several white blood cells, including monocytes and activated T and B cells.⁹ Vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells. It also is involved in the biosynthesis of neurotrophic factors, synthesis of nitric oxide synthase, and increased glutathione levels.¹⁰

An important role of vitamin D is, its function as a natural inhibitor of signal transduction by hedgehog (a hormone involved in morphogenesis).^{11,12}

Human and animal data suggests that low vitamin D status is associated with impaired infertility, endometriosis, and polycystic ovary syndrome.¹³ Recent data on vitamin D provides new insights in the complex pathogenesis and treatment of infertility. Several animal and human studies suggests that vitamin D is involved in many functions of the reproductive system in both genders.¹⁴ The importance of vitamin D for the reproductive biology is supported by several animal studies.

However, an appreciation that vitamin D signaling may be relevant for the reproductive health in humans is relatively recent (Table 1).²

Table 1: Vitamin D and reproduction.²

Parameter	Experimental models	Human studies
Folliculogenesis	+	±
Spermatogenesis	+	+
Steroidogenesis	+	--
Implantation	+	+
Relevance in pregnancy	+	+
Relevance in progeny	+	+

+ Evidence for involvement; -- No evidence for involvement; ± Contradictory evidence

VITAMIN D AND MALE INFERTILITY

The specific mechanism by which vitamin D influences male reproduction remain unclear. Vitamin D Receptors (VDR) are detected in human sperm, with binding sites in the nucleus and the mid piece of the sperm.¹ More recently, vitamin D metabolizing enzymes are described in the human testis, the ejaculatory tract, mature spermatozoa, and in Leydig cells.² The expression levels of vitamin D receptors and CYP24A1 in human spermatozoa serve as positive predictive markers of semen quality, and VDR mediates a non-genomic increase in intracellular calcium concentration that induces sperm motility. VDR elicits a rapid increase in intracellular Ca^{2+} concentration through inositol triphosphate (IP_3)-mediated Ca^{2+} release from intracellular IP_3 -receptor-gated calcium store in the neck of human spermatozoa (Figure 1).

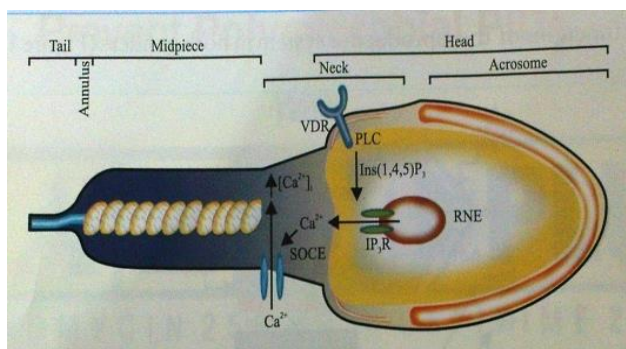


Figure 1: Proposed mechanism for the non-genomic effect of VDR in human spermatozoa.

[Ca^{2+}]_i: Intra cellular concentration of calcium ions; PLC: Phospholipase C; RNE: Redundant nuclear envelope; SOCE: Store-operated calcium entry; VDR: Vitamin D receptor.

Results from human association studies are in line with those in animal models, as men with vitamin sufficiency have a higher percentage of motile spermatozoa than men with vitamin deficiency. Overall, vitamin D signaling has a positive effect on sperm quality and increases estrogen responsiveness. The different reproductive effects of vitamin D in men is depicted in Table 2.¹⁵

Table 2: Reproductive effects of vitamin D.¹⁵

Reproductive function	Species		
	Mouse	Rat	Human
Fertility			
Conception	↑↑	↑↑	↑
Time to pregnancy	↑	↑	ND
Litter size	↑↑	↑↑	NA
Sperm quality			
Concentration	↑↑	↑↑	→→
Motility	↑↑	↑↑	↑↑
morphology	ND	ND	↑
Reproductive hormones			
Testosterone	→→	↑	→
Estradiol	↑	↑	→
AMH	→	ND	↑↑
Inhibin B	→	ND	→

↑ Increase; → No effect; AMH: Anti Mullarian hormone; ND: Not determined; NA: Not available

ERECTILE DYSFUNCTION

A 2014 study published in the journal of sexual Medicine found that men with severe Erectile Dysfunction (ED) had significantly lower vitamin D levels than men with mild ED. Endothelial dysfunction has been demonstrated to play an important role in pathogenesis of Erectile Dysfunction (ED) and vitamin D deficiency is deemed to promote endothelial dysfunctions.¹⁶

VITAMIN D AND FEMALE INFERTILITY

Vitamin D has a biologically plausible role in female reproduction.¹ In women, vitamin D deficiency may also be involved in the pathogenesis of infertility, menstrual dysfunction, and menstrual abnormalities.¹⁷ Vitamin D has been shown to be involved in the pathophysiology of some disorders of women in child bearing age among women undergoing *In Vitro* Fertilization (IVF) procedures. Studies have shown that vitamin D deficiency is highly prevalent among women undergoing Controlled Ovarian Stimulation (COS) in Assisted Reproductive Technology (ART) procedures.¹⁸ In women, vitamin D deficiency status has been associated with less IVF outcome, features of PCOS, and endometriosis.⁴ Vitamin D has direct effect on Anti Mullarian Hormone (AMH) production, and thus increases longer maintenance of ovarian reserve in the patients with its higher concentration.¹⁹ Further evidence supporting an association between vitamin D and reproduction comes from studies of vitamin D receptors. Vitamin D receptors are found in various reproductive tissues, including ovarian and uterine tissue. Vitamin D has also been shown to regulate expression of Homeobox (HOX) gene in the uterus. The HOX proteins which they encode are master regulators of embryonic development.^{20,21}

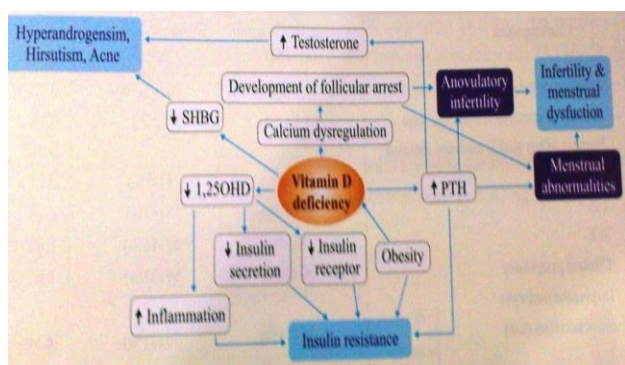


Figure 2: Role of vitamin D sufficiency in female infertility.

The national institute of health recommends that most adults should get about 600 IUs (International Units) of vitamin D daily, if one's blood level is above 45 ng/ml and for maintenance, recommended dose is 2000-4000 IU daily depending on age, weight, season, how much time a person spent outdoors, where one lives, skin color and obviously blood levels. In other words if one is older, larger, living in the Northern latitudes during the winter, are not getting sun and have dark skin, recommended maintenance dose is 5000 IU of vitamin D₃ per day for 3 months if blood level is 35-45 ng/ml, under supervision and then to recheck blood levels. Recommended dose of vitamin D₃ is 10000 IU/day, if blood level is <than 35 ng/ml under a doctor's supervision and then recheck blood levels after 3 months. It takes a good six months usually to optimize one's vitamin D levels if person is deficient of vitamin D. Once this occurs, one can lower the dose to the maintenance dose of 2000-4000 IU a day.

Vitamin D deficiency has been shown to play a role in almost every major disease. This includes:

- Osteoporosis and osteopenia
- 17 varieties of cancer (including breast, prostate and colon)
- Heart disease
- High blood pressure
- Obesity
- Metabolic syndrome and diabetes
- Autoimmune diseases
- Multiple sclerosis
- Rheumatoid arthritis
- Osteoarthritis

- Bursitis
- Gout
- Infertility and PMS
- Parkinson's disease
- Depression and seasonal affective disorder
- Alzheimer's disease
- Chronic fatigue syndrome
- Fibromyalgia
- Chronic Pain
- Periodontal disease
- Psoriasis

The current ranges for "normal" are 20 to 55 ng/ml. This level is enough to prevent rickets or osteomalacia, but not for optimal health. The ideal range for optimal health is 50-80 ng/ml.

CLINICAL EFFICIENCY OF VITAMIN D IN FEMALE INFERTILITY

Vitamin D is an emerging factor influencing female infertility and IVF outcome.

A prospective, cross sectional study investigated the IVF outcome in women with deficient 25-hydroxy vitamin D [25(OH) D] with serum levels (<20 ng/ml). The number of recruited women with serum [25(OH) D] (<20 ng/ml) and (≥20 ng/ml) was 154 and 181 respectively. Eligible women provided a serum sample for [25(OH) D] measurement at the time of cycle preparation. The main outcome measure in the study was clinical pregnancy rate.

The results showed that the clinical pregnancy rates were 20% in (<20 ng/ml) and 31% in (≥20 ng/ml). i.e. P = 0.02). The adjusted odds ratio for clinical pregnancy in women with vitamin D (≥20 ng/ml) was 2.15. Sub group analysis showed that the group of women with highest serum levels (>30 ng/ml) had highest chances of pregnancy.

'Alessio Paffoni' found that women who had sufficient levels of vitamin D were more likely to produce high-quality embryos and more likely to become pregnant than women who were deficient in vitamin D. Since vitamin D supplementation is an inexpensive and simple intervention, with few relevant side effects, additional study in this area has the potential to markedly influence the way infertility is treated. The researchers concluded

that vitamin D is an emerging factor influencing female fertility and IVF outcome.²² Women with sufficient levels of vitamin D are significantly more likely to achieve clinical pregnancy following IVF.

Previous studies, such as one published in the Journal of Nutrition, also found that although vitamin-D-deficient female rats were capable of reproduction, it reduced fertility by an astounding 75 percent, diminished litter sizes by 30 percent, and impaired neonatal growth.²

Interestingly, another study published in November 2009 confirmed that human sperm contain a vitamin D receptor.³

Analysis indicated that vitamin D is produced locally in the sperm, which suggests that vitamin D may be involved in the signaling between cells in the reproductive system. According to the authors, the study revealed “an unexpected significance of this hormone (vitamin D) in the acquisition of fertilizing ability,” and the results imply that vitamin D is involved in a variety of sperm signaling pathways.

As ‘Iva Keene’, author of the Natural Fertility Prescription, stated. “This is an imperative step to add vitamin D for anyone planning a pregnancy, not only for increasing the rate of conception but also for the benefits it offers during pregnancy”.

Vitamin D deficiency is currently at epidemic proportions in the United States and many other regions around the world, including South Asia largely because people do not spend enough time in the Sun to facilitate this important process of vitamin D production.

To ensure whether one is receiving all the benefits of vitamin D is to find out the blood levels of vitamin D by using a 25(OH) D test, also called 25-hydroxyvitamin D test.

There are two vitamin D tests - 1,25(OH) D and 25(OH) D - but 25(OH) D is the better marker of overall D status. It is this marker that is most strongly associated with overall health, and it is the one, physician should recommend for.

Be sure one is maintaining a therapeutic level of vitamin D in the blood. More recently the optimal vitamin D level has been raised to 50-70 ng/ml.

A study by Garbedian et al., investigated, whether vitamin D levels were predictive of implantation and clinical pregnancy rates in 173 infertile women following IVF. Serum [25(OH)] D samples were collected within one week before oocyte retrieval. The study results showed that women with sufficient levels of [25(OH)] D had higher rates of clinical pregnancy (52.5%) compared with women with insufficient levels (34.7%).²⁰

Table 3: *In vitro* fertilization cycle parameters for 173 women by vitamin D status.

Characters	Vitamin D status No. and %		P value
	Insufficient or deficient	Sufficient	
Implantation rate	25.6%	34.5%	0.6
Clinical pregnancy rate	34.7%	52.5%	<0.001
Clinical pregnancy rate for embryo transfer	37.9%	54.7%	<0.001

Studies have shown that vitamin D works synergistically with other vitamins. It may not be too much vitamin D that's the problem, but a deficiency in other nutrients. Either way, a good place to start for supplementation would be 1000 IU of D₃ per day for every 25 lbs of body weight, as per the vitamin D council's recommendations.

“A higher clinical pregnancy rate per embryo transfer performed among women in the vitamin D sufficient group than among women in insufficient group was also observed”. Although the implantation rate was higher in sufficient group than the insufficient group, this difference is not statistically significant. The study findings suggested that women with sufficient levels of vitamin D were more likely to achieve clinical pregnancy following IVF. The researchers opined that vitamin D supplementation could provide an easy and cost effective way of improving pregnancy rates. Women with higher vitamin D level in their serum and follicular fluid are more likely to achieve clinical pregnancy following IVF-embryo transfer. Vitamin D has also may increase fertility rates by six percent.²⁰ If one want to supplement vitamin more accurately, test and re-test blood vitamin D levels.

A prospective study was conducted in 84 infertile women undergoing IVF to determine if [25(OH)] D levels in the follicular fluid of infertile women undergoing IVF, demonstrated a relationship with IVF cycle parameters and outcome. Clinical pregnancy (defined as evidence of intrauterine gestational sac on USG) following IVF was the main outcome measure in the study. The study results showed that women with higher vitamin D level in their serum and follicular fluid were more likely to achieve clinical pregnancy following IVF embryo transfer. There was a significant increase in implantation and clinical pregnancy rates. Each ng/ml increase in follicular fluid [25(OH)] D increased the likely hood for achieving CP by 6%.²³ As the researchers reported in the European Journal of Endocrinology: this is not the first time the “sunshine vitamin” has been linked to infertility.

In 2008, Australian fertility specialist Dr. Anne Clark found almost one-third of the 800 infertile men included in her study had lower than normal levels of vitamin D.¹

“Vitamin D and folate deficiency are known to be associated with infertility in women, but the outcomes of the screening among men in the study group came as a

complete surprise. Men in the study group who agreed to make lifestyle changes and take dietary supplements had surprisingly good fertility outcomes”.¹

In fact, of the 100 men who agreed to make and maintain certain lifestyle changes (quitting smoking, minimizing intake of caffeine and alcohol, weight reduction, along with a course of vitamins and antioxidants) for three months prior to fertility treatment, 11 of them went on to achieve pregnancy naturally, without IVF treatment.

Published data has shown that obese women, those with insulin resistance and small ovarian reserve and in men with oligo and asthenozoospermia (with vitamin D concentration <20 ng/ml) should receive treatment with vitamin D.¹⁹ women who had sufficient levels of vitamin D were more likely to produce high-quality embryos and more likely to become pregnant than women who were deficient in vitamin D. “Since vitamin D supplementation is an inexpensive and simple intervention with few relevant side effects, additional study in this area has the potential to markedly influence the way infertility is treated”.

CONCLUSION

An epidemic of vitamin D deficiency has been emerging over the last decade among all racial groups in US and south Asia. Among women of reproductive age, more than 40 percent are insufficient in vitamin D.²⁴ In humans, the vitamin D receptors are present in many female organs, including the ovary, uterus, and placenta.²⁵ 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 endometrium produces calcitriol in response to the embryo as it enters the uterine cavity, shortly before implantation. Calcitriol controls several genes involved in implantation. Once a woman becomes pregnant, the uterus and 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. Infertility can be a challenging condition with multiple contributing factors, but one has nothing to lose and everything to gain by optimizing one’s vitamin D levels. A new report has shown that exposure to sunlight boosts fertility in both men and women by increasing their levels of vitamin D, a benefit that appears to work on multiple levels. Simple advice for sun exposure and vitamin D₃ supplementation can have a profound impact on patient’s health, even if trying to conceive naturally.

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Abbreviations

- [25(OH)] D: 25 hydroxy vitamin D
- CYP24A1: Gene cytochrome P 450, family 24, sub family A, polypeptide
- AMH: Anti-Mullerian Hormone
- IVF-ET: *In vitro* fertilization and embryo transfer.
- VDR: Vitamin D receptor
- COS: Controlled ovarian hyper stimulation
- ART: Assisted reproductive technology
- HOX gene: Homeobox gene

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