Vitamin D and Infertility

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Vitamin D plays a crucial role in calcium and phosphate homeostasis, by increasing intestinal calcium absorption and renal calcium reabsorption. For vitamin D, accumulating evidence from observational human studies suggests a key role for both male and female fertility.

Keywords: vitamin D; infertility; assisted reproductive technologies

1. Introduction

Vitamin D plays a crucial role in calcium and phosphate homeostasis, by increasing intestinal calcium absorption and renal calcium reabsorption. It is found in two major forms, D₃ (ergocalciferol) and D₂ (cholecalciferol). The former is produced by ergosterol upon irradiation in plants and fungi. The latter is produced by 7-dehydrocholesterol upon irradiation in the epidermis. After hydroxylation at carbon 25 producing 25-hydroxyvitamin D, 25(OH)D, it is transported to the kidney, where it is hydroxylated by 1α-hydroxylase (CYP27B1) at the carbon 1 of the A ring, producing 1,25-dihydroxy-vitamin D [1,25(OH)₂D], the active form of vitamin D. CYP27B1 is also present in extrarenal sites, such as macrophages, osteoblasts, epithelial, endocrine, placental and cancer cells. The mechanism of 1,25(OH)₂D action involves its binding to vitamin D receptor (VDR), a transcription factor, member of the steroid hormone nuclear receptor family. VDR and CYP27B1 are expressed in various cells, indicating that vitamin D is characterized by a plethora of extra-skeletal actions, such as those on the immune and cardiovascular system.

Vitamin D deficiency is defined as 25(OH)D concentrations <20 ng/mL (50 nmol/L), whereas vitamin D insufficiency as 25(OH)D concentrations 20–30 ng/mL (50–75 nmol/L). The prevalence of vitamin D deficiency ranges from 8 to 90% in Europe (reaching >50% in Western European populations) and from 14 to 89% in North America.

2. Vitamin D and Infertility

2.1. Vitamin D and Male Infertility (Observational Studies)

An accumulative body of evidence from observational studies suggests a potentially key role for vitamin D in male reproductive function, including semen quality and androgen status. This is indicated by a positive correlation between vitamin D concentrations and sperm motility and vitamin D concentrations and normal sperm morphology in infertile men. Particularly, a cross-sectional study including 300 men showed that men with severe vitamin D deficiency [25(OH)D <10 ng/mL] had a lower proportion of motile spermatozoa (62% vs. 70%; p = 0.027), progressive motile spermatozoa (56% vs. 64%; p = 0.035) and % of morphologically normal spermatozoa (6% vs. 8%; p = 0.044) compared with those with vitamin D sufficiency. Similar results were obtained from a subsequent prospective study including 1427 infertile men, which demonstrated higher sperm motility in men with 25(OH)D >30 ng/mL compared with those with 25(OH)D <10 ng/mL [45% (31–63%) vs. 34% (22–54%), respectively; p = 0.030]. However, no differences were observed regarding total sperm count, sperm concentration, sperm volume or sperm morphology. On the other hand, a cross-sectional study, including 170 men, showed a U-shaped correlation of vitamin D concentrations with semen parameters, supporting that not only low, but also high vitamin D concentrations are associated with impaired sperm quality. In detail, men with high vitamin D concentrations (≥50 ng had lower sperm concentration [46.7 (95% confidence interval (CI) 27.2 to 73.9)] vs. 84.0 (95% CI 70.3 to 99.3) million/mL; p < 0.05), progressive motile sperm [38.4% (95% CI 29.3 to 49.2) vs. 52.6% (95% CI 47.6 to 58.0); p < 0.05] and normal sperm morphology [18% (95% CI 12.1 to 25.6) vs. 27.4% (95% CI 23.8 to 31.3); p < 0.05] compared with those with 25(OH)D concentrations between 20 and 50 ng/mL.

Furthermore, serum 25(OH)D concentrations are associated not only with semen quality, but also with androgen status. Data from cross-sectional studies have shown a positive association between 25(OH)D and testosterone concentrations. In particular, a large cross-sectional study of 2299 men demonstrated higher total testosterone concentrations, free androgen index, and lower SHBG concentrations in vitamin D-sufficient compared with vitamin D-insufficient or -
deficient \((p < 0.05 \text{ for all})\) [21]. Likewise, results from another cross-sectional survey of 3369 men in eight European centers (the European Male Ageing Study) supported a linkage between vitamin D deficiency and secondary or compensated hypogonadism \([\text{relative risk ratio (RRR)} = 1.16, p = 0.05]\), as 25(OH)D concentrations were positively associated with total and free testosterone and negatively with estradiol and LH concentrations [22].

### 2.2. Vitamin D and Male Infertility (Interventional Studies)

Few interventional studies have assessed the effect of vitamin D supplementation on semen quality, male fertility and testosterone concentrations. In a recent triple-blinded, randomized clinical trial, 330 men with infertility and vitamin D insufficiency received either a single dose of 300,000 IU cholecalciferol (followed by 1400 IU/day, combined with calcium 500 mg/day for 150 days) or placebo. Although there was no difference in sperm concentration, the number of spontaneous pregnancies was higher in the vitamin D compared with the placebo group \((7.3\% \text{ vs. } 2.4\%; 95\% \text{ CI } −0.6\% \text{ to } +10.5\%)\) [23]. In another study, 86 infertile men with idiopathic oligoasthenospermia were randomized to oral cholecalciferol 200 IU/day with calcium 600 mg/day, or a combination of vitamin E 100 mg plus vitamin C 100 mg, t.i.d.

After three months, semen quality, especially the progressively motile sperm count per ejaculate and the proportion of progressively motile sperm were increased only in the vitamin D group. In particular, the mean count of progressively motile sperm per ejaculate was increased from \(9.8 \pm 3.7 \times 10^6\) to \(21.5 \pm 6.5 \times 10^6\) \((p < 0.05)\) in the vitamin D group, while it was increased from \(9.5 \pm 6.3 \times 10^6\) to \(12.4 \pm 4.4 \times 10^6\) \((p > 0.05)\) in the control group. The proportion of progressively motile sperm was also increased, from \(18.4 \pm 9.8\%\) to \(28.3 \pm 4.5\%\) \((p < 0.05)\) in the vitamin D group, while it did not increase in the control group \((17.8 \pm 5.3\% \text{ to } 21.4 \pm 2.4\%; p > 0.05)\). In addition, pregnancy rates were higher in the vitamin D group \((16.3\%)\) compared with the control group \((2.3\%)\) \((p < 0.05)\) [24].

Additional interventional studies assessed the association between vitamin D and androgen status. A randomized controlled trial (RCT) in vitamin D-deficient men evaluated the effect of vitamin D supplementation \((\text{cholecalciferol 3330 IU/day, } n = 31)\) on testosterone concentrations, compared with placebo \((n = 23)\) [25]. An increase in total \((10.7 \pm 3.9 \text{ to } 13.4 \pm 4.7 \text{ nmol/L; } p < 0.001)\), bioactive \((\text{from } 5.2 \pm 1.9 \text{ to } 6.3 \pm 2.0 \text{ nmol/L; } p < 0.001)\) and free testosterone concentrations \((\text{from } 0.22 \pm 0.08 \text{ nmol/L to } 0.27 \pm 0.09 \text{ nmol/L; } p < 0.001)\) was observed in the vitamin D supplemented group, while there was no change in the placebo group [18]. Similar results were demonstrated by a prospective study, including 102 men who received a single dose of ergocalciferol \((600,000 \text{ IU})\). Significant increase in serum total testosterone concentrations \((\text{from } 12.46 \pm 3.30 \text{ to } 15.99 \pm 1.84 \text{ nmol/L, } p < 0.01)\) and erectile function scores \((\text{from } 13.88 \pm 3.96 \text{ to } 20.25 \pm 3.24, p < 0.01)\) were observed after 12 months [25].

The aforementioned data suggest a potentially adverse effect of low vitamin D status on male fertility, although a U-shape is more representative of its association with infertility. Vitamin D supplementation may improve sperm quality and increase spontaneous pregnancy rates and testosterone concentrations. Thus, while there is no level 1 evidence, vitamin D supplementation, achieving sufficient but not high \((\text{i.e., } 30–50 \text{ ng/mL})\) 25(OH)D concentrations, may have a beneficial effect on male infertility [23].

### 2.3. Vitamin D and Female Infertility (Observational Studies)

Recently, research has focused on the role of vitamin D concentrations in women undergoing assisted reproductive technologies (ART). Based on data reported in a systematic review and meta-analysis of 11 cohort studies, including 2700 women, investigating the association between vitamin D status and ART outcome, higher live birth rates have been reported in vitamin D-sufficient compared with vitamin D-deficient and -insufficient women \([\text{odds ratio (OR): } 1.33 (95\% \text{ CI } 1.08 \text{ to } 1.65), \text{ seven studies}]\). Similar results were shown in another recently published meta-analysis of nine cohort studies, which supported the decreased live birth rates after in vitro fertilization \((\text{IVF)/intracytoplasmic sperm injection (ICSI)}) in women with vitamin D deficiency compared with those of sufficient vitamin D status \([\text{relative risk (RR): } 0.74 \text{ (95\% CI 0.58 to 0.90), three studies}]\).

Vitamin D has also been involved in the development of specific gynecological conditions affecting fertility, such as endometriosis and polycystic ovarian syndrome (PCOS). In particular, a cohort study of 49 women showed a significant linear correlation between 25(OH)D concentrations and the diameter of ovarian endometriomas \((r = −0.3, p = 0.03)\) [26]. Moreover, a prospective comparative study, evaluating 25(OH)D concentrations in 135 women with endometriosis and 90 controls, showed that the incidence of women with vitamin D deficiency/insufficiency was significantly higher in women with endometriosis compared with the control group \((80\% \text{ vs. } 33.3\%; p < 0.001)\) [26]. Moreover, the impact of vitamin D concentrations on reproductive outcomes, in women with PCOS undergoing ovulation induction, has been investigated in a retrospective cohort study \((n = 540)\). This study showed that vitamin D-deficient women were less likely to achieve ovulation compared with those with 25(OH)D >20 ng/mL \((\text{OR 0.43, 95\% CI 0.25 to 0.76, } p = 0.006)\). Furthermore, live birth rates after ovulation induction were increased by 2% for each 1 ng/mL increase in 25(OH)D concentrations \((\text{OR 1.02, 95\% CI 1.00 to 1.04), five studies}]\).
CI 1.00 to 1.04, \( p = 0.040 \) \[26\]. However, data are still insufficient in order to establish a possible causality between vitamin D and endometriosis or vitamin D and PCOS. Further studies are needed to confirm these associations.

2.4. Vitamin D and Female Infertility (Interventional Studies)

Few RCTs currently exist evaluating the effect of vitamin D supplementation on ART outcome, yielding inconclusive results. In a recent RCT \[27\], infertile women undergoing ICSI, using both fresh and frozen embryo transfers, were randomized to either cholecalciferol (50,000 IU/week) supplementation for six weeks \( (n = 42) \) or placebo \( (n = 43) \). Higher clinical pregnancy rates were shown in the vitamin D group compared with the placebo group \( (38.1\% \text{ vs. } 20.1\%, \ p = 0.019) \) \[27\]. On the other hand, another RCT including 128 infertile women with vitamin D insufficiency, who underwent frozen-thawed embryo transfer cycles after IVF/ICSI and were treated either with cholecalciferol (50,000 IU/week) for 6-8 weeks \( (n = 57) \) or with no intervention \( (n = 57) \) \[28\], did not show any difference in clinical pregnancy rates between the two groups \( (25.5\% \text{ vs. } 21.8\%, \ \text{respectively}; \ p = 0.810) \) \[28\]. Although safe conclusions cannot be drawn by these two studies \[of note, both were conducted in Iran, with baseline 25(OH)D concentrations of 12.7–15.8 ng/mL\] \[27\], one should underline some differences between them, which may have had an impact on this discrepancy. First, participants of the former study \[27\] were of normal body weight in contrast to those of the latter \( (\text{mean BMI} >26 \text{ kg/m}^2) \) \[28\]. Second, the type of fertilization and the method of embryo transfer \( (\text{i.e., fresh or frozen}) \) also differed between studies. Third, 25(OH)D concentrations achieved after vitamin D supplementation also differed between studies \( (37 \text{ ng/mL vs. } 47 \text{ ng/mL}) \) \[28\].

With respect to PCOS patients, there is evidence for a possible beneficial effect of vitamin D supplementation on fertility outcomes. Particularly, a recent meta-analysis of nine RCTs \( (502 \text{ PCOS women}) \) showed that vitamin D supplementation \( \text{(in different doses)} \) resulted in increased number of dominant follicles \( (>14 \text{ mm}) \) compared with placebo or metformin \( (1000–1500 \text{ mg/day}) \) \( (\text{OR: } 2.34, \text{ 95\% CI 1.39 to 3.92, four RCTs}) \) \[29\]. Moreover, the same meta-analysis showed that vitamin D supplementation especially combined with metformin in women with PCOS seems to regulate menstrual cycles compared with women treated with metformin only \( (\text{OR 1.85, 95\% CI 1.01 to 3.39, three RCTs}) \) \[29\]. In addition, a recent double-blinded RCT was conducted aiming to evaluate the role of vitamin D supplementation on ICSI outcomes in 105 PCOS infertile women. Patients were randomized either to treatment group \( \text{(vitamin E, 400 mg/day and vitamin D3, 50,000 IU every two weeks, } n = 52) \) or placebo group \( (n = 53) \) for eight weeks. A higher clinical pregnancy rate was observed in the treatment group compared with the placebo group \( (62.1\% \text{ vs. } 22.6\%; \ p = 0.002) \), suggesting thus a beneficial effect of combined supplementation of vitamin D and E on ICSI outcomes in PCOS patients \[30\].

Thus, accumulating evidence supports the notion that vitamin D may play an important role in female fertility. Observational studies associate vitamin D status with IVF outcome, endometriosis and reproductive success after ovulation induction in women with PCOS \[\text{(Table 1)}\]. However, RCTs have not yet established the effect of vitamin D supplementation on the success of ART. Hence, while there is no level 1 evidence, vitamin D sufficiency may be required for improving female fertility outcome.

Table 1. Vitamin D and infertility.

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<th>Male infertility</th>
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<tr>
<td>Linear or U-shaped correlation between vitamin D concentrations and sperm motility/morphology [11,12,13].</td>
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<td>Sufficient vitamin D concentrations associated with high testosterone concentrations [14,15,16].</td>
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<tr>
<td>Supplementation of vitamin D improved semen quality and pregnancy rates [17,18].</td>
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<td>Supplementation of vitamin D increased testosterone concentrations [19,20].</td>
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<th>Female infertility</th>
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<tr>
<td>Contradictory data on whether supplementation of vitamin D is associated with pregnancy rates [27,28].</td>
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<td>Higher live birth rates in vitamin D-sufficient women [28,29].</td>
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Endometriosis

Linear correlation between vitamin D concentrations and diameter of ovarian endometriomas [24].

Higher incidence of vitamin D deficiency/insufficiency in women with endometriosis [25].

PCOS

Linear correlation between vitamin D levels and reproductive success rates after ovulation induction in women with PCOS [26].

Abbreviations: ART: assisted reproductive techniques; PCOS: polycystic ovary syndrome.

References


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