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.

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 [1]. It is found in two major forms, D_2 (ergocalciferol) and D_3 (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 [2]. 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$(OH)_2$D], the active form of vitamin D [3]. CYP27B1 is also present in extrarenal sites, such as macrophages, osteoblasts, epithelial, endocrine, placental and cancer cells [4]. The mechanism of 1,25$(OH)_2$D action involves its binding to vitamin D receptor (VDR), a transcription factor, member of the steroid hormone nuclear receptor family [2]. 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 [5].

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) [6]. 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 [7].

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 [8][9][10] and vitamin D concentrations and normal sperm morphology in infertile men [11]. 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 [11]. 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 [12]. 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 [13]. 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 [13].

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 [14][15][16]. 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 men ($p < 0.05$ for all) [15]. 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 [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 [16].

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% vs. 2.4%; 95% CI −0.6% to +10.5%) [17]. 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 ± 9.8% to 28.3 ± 4.5% ($p < 0.05$) in the vitamin D group, while it did not increase in the control group (17.8 ± 5.3% to 21.4 ± 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%) ($p < 0.05$) [18].

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 (cholecalciferol 3330 IU/day, $n = 31$) on testosterone concentrations, compared with placebo ($n = 23$) [19]. An increase in total (10.7 ± 3.9 to 13.4 ± 4.7 nmol/L; $p < 0.001$), bioactive (from 5.2 ± 1.9 to 6.3 ± 2.0 nmol/L; $p < 0.001$) and free testosterone concentrations (from 0.22 ± 0.08 nmol/L to 0.27 ± 0.09 nmol/L; $p < 0.001$) was observed in the vitamin D supplemented group, while there was no change in the placebo group [19]. Similar results were demonstrated by a prospective study, including 102 men who received a single dose of ergocalciferol (600,000 IU). Significant increase in serum total testosterone concentrations (from 12.46 ± 3.30 to 15.99 ± 1.84 nmol/L, $p < 0.01$) and erectile function scores (from 13.88 ± 3.96 to 20.25 ± 3.24, $p < 0.01$) were observed after 12 months [20].

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 (i.e., 30–50 ng/mL) 25(OH)D concentrations, may have a beneficial effect on male infertility [21].

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 [odds ratio (OR): 1.33 (95% CI 1.08 to 1.65), seven studies] [22]. 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 (IVF)/intracytoplasmic sperm injection (ICSI) in women with vitamin D deficiency compared with those of sufficient vitamin D status [relative risk (RR): 0.74 (95% CI 0.58 to 0.90), three studies] [23].

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 ($r = -0.3$, $p = 0.03$) [24]. 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% vs. 33.3%; $p < 0.001$) [25]. 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 (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 (OR 1.02, 95% 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% 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% vs. 21.8%, 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], 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 (mean BMI >26 kg/m^2) [28]. Second, the type of fertilization and the method of embryo transfer (i.e., fresh or frozen) also differed between studies. Third, 25(OH)D concentrations achieved after vitamin D supplementation also differed between studies (37 ng [27] vs. 47 ng/mL [28], respectively).

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 PCOS women) showed that vitamin D supplementation (in different doses) resulted in increased number of dominant follicles (>14 mm) compared with placebo or metformin (1000–1500 mg/day) (OR: 2.34, 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 (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 (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% 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 (**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.

Male infertility

Linear or U-shaped correlation between vitamin D concentrations and sperm motility/morphology [8][9][10][11][12][13]. Sufficient vitamin D concentrations associated with high testosterone concentrations [14][15][16]. Supplementation of vitamin D improved semen quality and pregnancy rates [17][18]. Supplementation of vitamin D increased testosterone concentrations [19][20].
Female infertility Contradictory data on whether supplementation of vitamin D is associated with pregnancy rates [27][28].
ART Higher live birth rates in vitamin D-sufficient women [22][23].
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.

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