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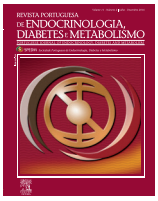

Artigo Original

Does Vitamin D Deficiency Have a Role in the Reduced Fertility?

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A B S T R A C T

Vitamin D is an emerging factor influencing fertility. The basis of this relationship lays on the presence of both vitamin D receptor and 1α-hydroxylase enzyme in reproductive organs. The widespread of vitamin D deficiency across all age groups and the published studies about the negative impact on overall health led to several investigations to assess the effect of vitamin D levels in human reproduction. Vitamin D status correlates to metabolic and hormonal dysfunctions in women with polycystic ovary syndrome and vitamin D deficiency is a negative predictor of ovulatory response in those women. Also, a positive correlation between vitamin D levels and anti-Müllerian hormone have been documented. Evidence suggests a link between lower vitamin D status, and endometriosis and vitamin supplementation has been associated with amelioration of dysmenorrhea. Studies in men revealed a positive correlation between circulating vitamin D levels and semen quality parameters. Vitamin D supplementation is being considered to improve semen quality in at least some of the idiopathic cases of male infertility. The relationship between vitamin D levels and assisted reproductive techniques outcomes have also been investigated, although the results are controversial.

This paper intends to review the latest knowledge concerning the role of vitamin D in human reproduction.

Será que a Deficiência de Vitamina D tem um Papel na Redução da Fertilidade?

Palavras-chave:
Deficiência da Vitamina D
Infertilidade
Vitamina D

R E S U M O

A vitamina D é um fator emergente que influencia a fertilidade. A base desta relação é fundamentada pela presença de recetores de vitamina D e da enzima 1α-hidroxilase em órgãos reprodutivos. A dispersão do défice de vitamina D em todas as faixas etárias e os estudos publicados sobre o seu impacto negativo na saúde incentivaram a várias investigações para avaliar os efeitos dos níveis de vitamina D na reprodução humana. A concentração de vitamina D correlaciona-se com disfunções metabólicas e hormonais em mulheres com síndrome do ovário policístico e a deficiência de vitamina D é um preditor negativo da resposta ovulatória nessas mulheres. Além disso, foi documentada uma correlação positiva entre os níveis de vitamina D e a hormona anti-mulleriana. A evidência sugere uma ligação entre níveis reduzidos de vitamina D e endometriose e a sua suplementação tem sido associada a melhoria da dismenorreia. Estudos em homens revelaram uma correlação positiva entre os níveis circulantes de vitamina D e parâmetros de qualidade do esperma e a sua suplementação de vitamina tem sido considerada para melhorar a qualidade do esperma em pelo menos alguns dos casos idiopáticos de infertilidade masculina. A relação entre os níveis de vitamina D e os resultados das técnicas de reprodução assistida também tem sido investigada, contudo os resultados são controversos.

Este artigo pretende rever a evidência mais recente sobre o papel da vitamina D na reprodução humana.

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Introduction

Vitamin D is a unique hormone as it can be synthesized by exposure of the skin to sunlight. In point of fact, the skin is the most important source of vitamin D, depending on the intensity of the ultraviolet irradiation, which in turn is dependent on season and latitude.[1]25-Dihydroxvitamin D3 [1,25(OH Vitamin D can also be obtained through the diet, although it represents less than 20% of the sources. With the exception of fatty fish and fortified foods, most foods contain little vitamin D.[1–3]

In the circulation, vitamin D is bound to the vitamin D-binding protein that transports it to the liver to be metabolized in 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D. However [25(OH)D] is biologically inactive and must be converted, predominantly in the kidneys, to its active form, 1,25-hydroxyvitamin D [1,25(OH)D], by the enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1).[4] The renal enzyme CYP27B1 is recognized as the principal determinant and as the rate-limiting enzyme in the production of the active 1,25(OH)D. The activity of CYP27B1 is stimulated by parathyroid hormone (PTH) and inhibited by fibroblast growth factor 23 (FDG-23).[5]

In the past years, the expression of CYP27B1 has been described in other tissues as ovaries, brain, breast, prostate, and colon suggesting the existence of local mechanisms that allows the production of the metabolically active form of vitamin D.[6]

The cellular effects of vitamin D and its metabolites are mediated mostly through the intranuclear vitamin D receptor (VDR), representing the final common pathway in which vitamin works on target tissues. This receptor is expressed in a variety of tissues such as the intestinal epithelium, the skeletal osteoblasts, the chondrocytes, the parathyroid glands, the pituitary gland, the hypothalamus, the reproductive tissue, the keratinocytes, the pancreas and the immune cells. This widespread distribution underlies the potential myriad of physiologic actions for vitamin D.[6–8]

The role of vitamin D in reproduction is an active area of investigation. The diverse presence of VDR in the ovary (particularly in granulosa cells), uterus, placenta, testis, hypothalamus, and pituitary suggests a potential role of vitamin D in reproductive physiology. The majority of the experimental data, either from diet-induced vitamin D-deficient rodent models or from transgenic VDR or CYP27B1 null mice, demonstrated a role for 1,25(OH)D in reproduction.[6]

Vitamin D deficiency

The best determinant of vitamin D status is the serum concentration of 25(OH)D. Besides the controversies, vitamin D deficiency is defined as a 25(OH)D level below 20 ng/mL, insufficiency when levels of 25(OH)D are between 21 and 29 ng/mL and sufficiency when concentration is superior to 30 ng/mL.[9] Accordingly, it is estimated that 1 billion people worldwide have vitamin D deficiency or insufficiency.[4] A recent study revealed that 13.0% of the 55 844 individuals had vitamin D deficiency, irrespective of age group, ethnics, and latitude of the study populations.[10]

Vitamin D and female reproduction

Several lines of evidence suggest that vitamin D deficiency disrupts female reproductive physiology including steroidogenesis in healthy women, pathogenesis of polycystic ovary syndrome (PCOS) and endometriosis and in vitro fertilization (IVF) outcomes.[6,11-13]An inverse association between serum 25(OH)D levels and insulin resistance, features of hyperandrogenism and circulating androgens in women with PCOS has been demonstrated.[6,14] Small interventional studies reported that supplementation with vitamin D improved insulin sensitivity, circulating androgens and parameters of ovarian folliculogenesis and ovulation.[15–18] A recent randomized controlled trial evaluated the relation of vitamin D status with ovulation induction (OI) outcomes in women with PCOS and demonstrated that the probability of achieving ovulation varied directly with vitamin status. Also, vitamin D deficient women were significantly less likely to achieve ovulation compared to those with 25(OH)D levels higher than 20 ng/mL. Moreover, on adjusted analyses, vitamin D deficiency was a negative predictor of ovulation response.[19]

Results from a meta-analysis confirmed a relationship between vitamin D status and metabolic and hormonal dysfunctions in women with PCOS. However, no significant improvement in metabolic and hormonal functions was found among those who were supplemented with vitamin D.[20] So far, vitamin D supplementation holds a promise of becoming a potential therapeutic adjunct for the ovulatory dysfunction and metabolic alterations observed in women with PCOS. Well-designed randomized controlled trials are needed to evaluate the direct effect of vitamin D supplementation on metabolic alterations and ovulatory dysfunction seen in vitamin D–deficient women with PCOS.

Some studies have demonstrated a positive correlation between vitamin D levels and anti-Müllerian hormone (AMH), a clinically useful marker of ovarian reserve. Vitamin D supplementation prevented the seasonal changes in serum AMH, indicating that AMH production in adults may be regulated by vitamin D.[21–23] Accordingly, the assessment of vitamin D status might be considered as part of the routine workup in infertile women and appropriate supplementation of patients with vitamin D deficiency might translate to better ovarian reserve markers and better ovarian follicular dynamics. However, most of the studies to date used markers of ovarian reserve and/or function rather than pregnancy as an outcome, which limits the translational significance of the findings.[7]

As vitamin D have anti-proliferative, anti-inflammatory and immune-modulatory properties, a possible association between endometriosis and vitamin D has been investigated. Although sparse and controversial, there is evidence suggesting a link between lower vitamin D status and endometriosis.[24,25] Also, vitamin D supplementation has been associated with amelioration of dysmenorrhea. However, larger and randomized control studies taking into consideration parameters such as seasonal variations, dietary intake of vitamin D, skin phototype and ultraviolet exposure are needed to clarify the possible favorable effects of vitamin D supplementation in women with endometriosis.[26]

Vitamin D and male reproduction

The VDR and the vitamin D metabolizing enzymes are expressed in fully mature human spermatozoa and in germ cells in testes from adults, indicating that local regulation of active vitamin D may be important for spermatogenesis and/or sperm function. It has been demonstrated that the VDR and the vitamin D metabolizing enzymes have higher expression in mature spermatozoa from normal men compared with spermatozoa from infertile men. This difference suggests a possible relationship between vitamin D and high semen quality and that vitamin D may play a functional role during the fertilization process.[27,28]

The 1,25(OH)D is a potent inducer of nongenomic effects in human spermatozoa as it induces a VDR-mediated increase in intracellular calcium concentration in the neck of spermatozoa. This increase leads to motility induction in both capacitated and uncapacitated sperm. Also, it improves sperm–egg binding *in vitro* and triggers the acrosome reaction, which is a prerequisite to oocyte fertilization.[29,30]

Studies with VDR-null mice and rodents demonstrated that those with vitamin D deficiency had impaired fertility due to compromised sperm motility and, occasionally, poor sperm morphology. Also, it has been demonstrated that the lower fertility rates can only partly be restored by calcium supplementation.[30]

A presumed link between vitamin D serum levels and semen quality has been evaluated in several human studies. A positive correlation between serum levels of vitamin D and sperm motility was found in studies both in young healthy and in infertile men.[31–33] Furthermore, sperm morphology and total sperm count has been positively associated with serum levels of vitamin D.[33–35] Although larger studies are needed, the existence of a relationship between vitamin D levels and successful conception has also been demonstrated.[36] Moreover, it has been suggested that both VDR and vitamin D metabolizing enzymes could be used as positive predictive markers to determine potential benefit from using media containing 1,25(OH)D during in vitro fertilization (IVF) or during sperm preparation for intrauterine insemination (IUI) or micro-insemination (ICSI). However, further studies are necessary to evaluate the effects on oocytes before it can be applied during routine assisted reproductive techniques (ART) procedures.[27]

The impact of vitamin D supplementation in semen quality, fertility and/or conception rate is currently unknown and new clinical studies are needed to address those questions.[37]

Although there is no currently evidence-based treatment for men with idiopathic infertility, the supplementation of vitamin D might improve semen quality in at least some of the idiopathic cases of male infertility in a safe and non-invasive manner. Data from small studies indicate that vitamin D supplementation may only be beneficial for men with vitamin D deficiency.[27]

Evidences from studies in assisted reproduction

The relationship between vitamin D levels and ART outcomes, particularly clinical pregnancy rates, has been inconsistent in the published literature.

Evidence from retrospective studies demonstrated contradictory facts. Rudick *et al* found that pregnancy rates and live births increased when recipients were vitamin D replete even after adjusting for potential confounding factors as embryo quality, recipient body mass index and race.[38] Although, it has also been demonstrated that vitamin D status was unrelated to the probability of pregnancy outcomes in recipients of donated oocytes and women undergoing euploid embryo transfer.[39,40]

Several prospective studies have demonstrated a positive correlation between vitamin D levels and ART outcomes. Higher pregnancy rates have been reported in women with higher levels of vitamin D and, after adjusting for age, body mass index and date of embryo transfer, vitamin D status was an independent predictor of pregnancy.[41–44] Abadi *et al* demonstrated that serum vitamin D concentrations were positively related to fertilization rate but unrelated to probability of pregnancy or live birth after ART.[45] In the study of Abdullah *et al*, a significant positive association of vitamin D levels and endometrial thickness was observed even after adjustment with age and body mass index. Also, they demonstrated higher pregnancy rates with higher vitamin D levels.[46]

In contrast, similarly conducted studies showed no significant relationship between vitamin D levels and pregnancy rates.[47–49] Curiously, in the study of Aleyasin *et al* the fertilization rate decreased significantly with increasing tertiles of vitamin D levels in follicular fluid.[49] Anifandis *et al* demonstrated a negative correlation between vitamin D levels in the follicular fluid and the quality of embryos. Also, higher values of vitamin D were associated with a lower possibility to achieve pregnancy.[50] Neville *et al* showed no correlation was found between vitamin D and total motility, progressive motility, count or morphology of sperm among men undergoing ART. Additionally, no association was found between vitamin D levels and anti-Müllerian hormone, number of collected and fertilized oocytes and pregnancy rates.[51]

Data from meta-analysis revealed no significant correlation between deficient vitamin D levels and lower clinical pregnancy rate in the infertile woman undergoing ART.[52,53] However, deficient vitamin D level was associated with the lower live birth rate.[53] Cost-benefit analyses suggested that screening and supplementing vitamin D prior to ART might be cost effective, but further evidence is needed.[54]

Despite a trend for a negative effect of vitamin D deficiency on ART outcomes, results are still controversial and further studies properly adjusting for confounders are required to assess the influence of vitamin D deficiency.

Conclusion

Although the large evidence supporting the role of vitamin D levels in several aspects of human reproduction, the influence of vitamin D supplementation to improve fertility remains uncertain. Currently, there is no unequivocal evidence to recommend routine vitamin D deficiency screening and supplementation prior to ART and more controlled prospective randomized trials are needed. However, the high prevalence of vitamin D deficiency and the beneficial role of vitamin D in overall health and human reproduction provide support for screening and supplementation when evaluating couples with infertility. Besides, vitamin D supplementation is safe, accessible and inexpensive.

Responsabilidades Éticas

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