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# Association of Vitamin-D insufficiency and infertility: A Literature Review

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## Abstract

Vitamin D receptors are present in both male and female central neural system and reproductive system hence Vitamin D sufficiency or insufficiency affects fertility. The present review aims to determine a correlation between Vitamin D insufficiency and infertility. Regarding female infertility, it was found that Vitamin D insufficiency is associated with increased issues during conception and higher miscarriage rate. Furthermore, Vitamin D insufficiency is associated with lower FSH levels affecting follicle formation, maturation and ovulation. Regarding male infertility, Vitamin D and its Receptor have been identified in the prostate, seminal vesicles, epididymis, germ cells, spermatogonia, spermatocytes and Sertoli cells. The prevalence of Vitamin D insufficiency is higher among men with lower sperm count and lower motility. However, the relation between Vitamin D and testosterone levels remain unclear. The present review stresses the effects of Vitamin D insufficiency in both male and female infertility.

**Key words:** Vitamin D, insufficiency, supplementation, female infertility, male infertility

## Introduction

The link of vitamin D with fertility in men and women is formed because vitamin D receptors (VDRs) are located in the central and peripheral organs associated with reproduction, in tissues and in the cells of men and women. In addition, VDRs are found in the following: hypothalamus, pituitary gland, ovaries, granulosa cells, endometrium, placenta, testes and spermatogonia.<sup>1</sup>

## ***Association of Vitamin D insufficiency and female infertility***

Vitamin D sufficiency has been shown to improve female fertility, while lack of vitamin D has the opposite effect.<sup>2</sup> It is stated that the link between infertility in women and low vitamin D in the blood serum has now been substantiated, since a woman who has sufficient vitamin D is more likely to con-

ceive, enjoy a calmer time during pregnancy and also strengthen her body's defenses, since one of the most beneficial properties of vitamin D is that it contributes to a healthy musculoskeletal system. Subsequently, and after the woman gives birth to her child, if she already has issues relating to the aforementioned vitamin, this may have an impact on the production of breast milk which is fed to the child by the mother. It was found that in women with normal concentrations of vitamin D in their bodies, even the IVF process was successful.<sup>3</sup>

According to Dr. Sunni Mumford, from the Eunice Kennedy Shriver National Institute of Child Health and Human Development in Rockville, Maryland, vitamin D helps to protect the mother and the fetus during the pregnancy. According to a study conducted, women with a vitamin D deficiency have difficulty conceiving and often face a high risk of miscarriage. The study examined blood levels before pregnancy and after 8 weeks and the sample consisted of 1,200 women who had experienced a miscarriage and who were trying and hoping to conceive again, but this time with no complications. This study inferred that those who were not vitamin D deficient before they conceived were 15% more likely to give birth without the risk of miscarriage.<sup>4</sup>

When vitamin D levels are sufficient, chemical compounds and processes take place in the human body, such as an increase in the production of ovarian steroid hormones - progesterone, estradiol and oestrone, as well as in the ovarian follicle stimulating hormone (FSH) receptor genes. Furthermore, follicle maturation and sorting occurs.<sup>2</sup> On the other hand, when D levels are low to the point of deficiency, fertility is affected and the occurrence of diseases related to the female reproductive system is not improbable, most notably polycystic ovary syndrome (PCOS) in 67-85% of cases and endometriosis.<sup>5</sup> It also affects conditions related to the female reproductive system, such as ovulation disorder, uterine

leiomyomas, insulin resistance and hyperandrogenism. As to the consequences of vitamin D deficiency, it appears that the combination of this deficiency with the glucocorticoid system as a consequence causes adverse effects on the fetus, contributing to its poor development and causing placental dysfunction.

Another study showed that women who had at least 30 nanograms per milliliter or less (vitamin D levels) in their bodies were deficient, while those with higher levels increased their chances of conceiving by 10%, and it was also shown that increasing the levels of this vitamin before a woman conceived reduced the chance of miscarriage by 12%. Also, many studies have shown that vitamin D deficiency has a negative impact on the physiology of the female reproductive system. Among other things, impaired steroidogenesis in women without fertility problems, polycystic ovary syndrome (PCOS) and endometriosis were mentioned.<sup>6</sup> Moreover, vitamin D is also associated with some metabolic and reproductive aspects of PCOS and for this reason, its deficiency is thought to be a triggering factor for the pathogenesis of the syndrome.<sup>2</sup> Women with PCOS have lower levels of vitamin D compared to women who are perfectly healthy. Women who are overweight and have PCOS also have lower levels of vitamin D compared to those whose weight is balanced.<sup>2</sup> This implies that obesity is connected to the levels of this vitamin and that in short, its levels in the body are linked to body mass index, insulin levels and other factors responsible for PCOS. As for the relationship between vitamin D levels and endometriosis, the studies are not clear since many of them failed to detect any change in vitamin D levels in healthy women as well as in those suffering from endometriosis. A case in point is a study that found that low levels of vitamin D tested <30ng/ml were associated with individuals who were experiencing problems due to diagnosed endometriosis - a sample consisting of 49 women.<sup>7</sup> Experts recommend that along with the treatment to

recover her fertility, a woman should also take vitamin supplements. This is mainly for women suffering from polycystic ovary syndrome, insulin resistance or low levels of anti-Mullerian hormone.<sup>8</sup> It should be noted that while existing research has led to the conclusion that reduced vitamin D levels are indeed associated with the aforementioned diseases, these studies have not provided clear evidence regarding the beneficial properties of vitamin D supplements.<sup>1</sup> And while there is an improvement in vitamin D levels from supplement consumption, it has not yet been proven whether taking them leads to improved fertility. With regard to baby weight, pre-eclampsia and neonatal mortality, they are not related to the need for supplementation by a pregnant woman.<sup>9</sup>

#### ***Association of Vitamin D insufficiency and male infertility***

Research showed that male subjects whose vitamin D levels were at normal levels had better spermogram results compared to males who had vitamin D concentration problems i.e. people with vitamin D deficiency, whose levels were below 20 mg per ml. In this study, the more fertile men showed much higher levels of vitamin d  $21 \pm 10$  versus  $16 \pm 9$  mg ml.<sup>10</sup> As regards to men, it seems that vitamin D is age-dependent and thus has effects on testosterone. There is no mention about the association of testosterone and vitamin D in young adolescents. However, the study showed that in people of advanced age, a positive correlation between vitamin d and testosterone levels emerged. It seems that the intake of vitamins, and specifically vitamin D, by men has a crucial role in the metabolism of various enzymes and in enhancing fertility. As a result, and despite the thorough research that has been conducted, it is not clear whether vitamin D levels are linked to testosterone production. Numerous studies have demonstrated that VDR and vitamin D metabolic enzymes are expressed in mature human

spermatozoa as well as in testicular spermatozoa, so it appears that vitamin D, when detected at normal levels in the blood serum of the male, is associated with spermatogenesis as well as sperm motility and function. Based on the scientists, VDR and vitamin D show higher expressions in mature spermatozoa in those who are perfectly healthy. However, comparing vitamin D in terms of sperm of healthy men with those who have severe infertility problems, it is found that the former have higher expression in mature spermatozoa compared to the latter, which in itself means that vitamin D, when detected at high levels, has positive effects on the health of the male reproductive system and this means that it contributes to the high quality of the sperm.<sup>11</sup>

The notion of studying the potential role of vitamin D in male fertility belonged to Jensen and his associates. In a study conducted on the effect of vitamin D on fertility and infertility respectively, a sample of the population was selected, namely 13 men who had been affected by testicular or prostate cancer and who had undergone orchiectomy and prostatectomy respectively. The researchers drew some conclusions. In this particular sample, a strong expression of VDR and vitamin D was observed, which together metabolize enzymes in the testes, are associated with ejaculation and sperm production. All this led the researchers to conclude that vitamin D is indeed crucial for both spermatogenesis and the maturation process of male spermatozoa. Furthermore, as far as sperm motility problems and men suffering from infertility in general are concerned, it is reported that vitamin D supplements help men with oligospermia and asthenospermia. This means that supplementation of the vitamin, apart from its many benefits for one's health in general, also contributes to the strengthening and high quality of sperm.

In some studies, it was shown that excess body weight, vitamin D deficiency and male infertility are related. In a study, sperm and blood samples

were taken from 64 men who were divided into two categories, those who were overweight and those who were of normal weight for their height and general health. It was found that obese men had lower vitamin D levels than those who were of normal weight. In obese men, sperm motility was reduced and lower than in non-obese men. In terms of sperm count and morphology there were no major differences in these two groups, however, it appears that sperm viability in non-obese subjects was lower than in obese subjects. Furthermore, DNA integrity was higher in obese individuals than in non-obese individuals.<sup>12</sup>

Research has found that the somatic or germ cells of the testes are able to compose and degrade vitamin D locally, while the systematic vitamin D metabolism does not seem to affect the effect. In addition, it is reported that the expression of VDR in the testis demonstrates that vitamin D may exert both autocrine and paracrine effects and, thereby, affect male infertility. The importance of this vitamin has been studied not only in humans, but it has first been examined in studies using animals as a sample. With hindsight, the VDR protein was detected in the prostate, seminal vesicles, epididymis, germ cells, spermatogonia, spermatocytes and Sertoli cells.<sup>13</sup> Therefore, a clear conclusion based on a thorough analysis of the relationship between vitamin D deficiency and testosterone levels has not yet been drawn. Furthermore, in studies conducted in patients with hypogonadism the results were not clear as some of them had lower circulating 25-hydroxyvitamin D3 compared to normogonadal men. In addition, there were studies that did not present a link between hypogonadism and vitamin D deficiency.

It is estimated that 20 to 80% of Europe's elderly population is deficient in vitamin D. A recent study has also shown that vitamin D deficiency affects fertility and when its concentration increases it has a reproductive role, in that it enhances fertility in both

men and women.<sup>14</sup> In addition, a study reports that in Denmark the quality of men's sperm has declined drastically over the last 50 years. A study conducted, used a sample of 330 men with low vitamin D levels who had difficulty having children. As a result, half of the men were given a high dose of vitamin D and half were given a placebo, although only the quality of the sperm of the men who were vitamin D deficient was improved by the vitamin D supplementation.

### Conclusion

The present review of the literature aimed to investigate the effect of Vitamin D levels in both male and female fertility. Vitamin D insufficiency is correlated with disturbed spermatogenesis and oogenesis. Furthermore, obesity in both genders is a risk factor for decreased Vitamin D levels and worse reproductive outcomes. Vitamin D supplementation improves oogenesis but the positive effects of supplementation and dose selection requires further research to establish.

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