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Mini Review

Vitamin D and Influence on Reproduction

Alba Jiménez Guerrero*

MSc Biochemist and Embryologist, University of Granada, Spain

***Corresponding Author**: Alba Jiménez Guerrero, MSc Biochemist and Embryologist, University of Granada, Spain.

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Abstract

There is increasing evidence that vitamin D plays an important role in regulating both male and female fertility. The vitamin D and the vitamin D receptor status can influence reproductive processes throughout development. For example, it influences gametogenesis, fertilization, the preimplantation phase, and the final phases of organ development. Low fertility rates have been attributed to low vitamin D levels in the serum of males. These results have been checked with some research with rats. There was a large decrease in fertility when female rats were inseminated by sperm taken from males that were deficient in vitamin D.

Keywords: *Vitamin D; Male Infertility; Testis; Semen Quality*

Introduction

The term vitamin D refers to a group of liposoluble vitamins, with a biochemical structure similar to steroid hormones, whose main function is the regulation of calcium and phosphorus homeostasis [1]. The male reproductive tract is one of the sites where vitamin D is metabolizes. VitD has been suggested to play a role in male fertility, based on the evidence of the expression of vitamin D receptor in various reproductive tissues like smooth muscles of the epididymis, spermatogonia, Sertoli cells and sperms, especially mid piece and nucleus [2].

Vitamin D and infertility

The relevant role of VitD in male fertility is supported by the expression of VDR in male reproductive system of animals and humans. The vitamin D receptor (VDR) belongs to the steroid hormones nuclear receptor family. It is a transcription factor and its three domains are firstly the DNA bonding domain, secondly the ligand binding domain and thirdly the hinge region connecting the two. VDR polymorphism is present in only 1% of the population. VDR polymorphism can lead to its malfunctioning, leading to various diseases. For example, in Knockout male mice, VDR null mutant were found to have gonadal insufficiency [3].

The role of VitD on male fertility seems to depend predominantly on the effect on testis function. Testis function comprises two interconnected and complementary processes, hormone production and spermatogenesis, which, in coordination with the action of accessory glands, ensure proper potential of male fertility [4]. Moreover, the VDR expression in the testis suggests that the locally produced VitD might exert autocrine and paracrine action, possibly displaying a role in the regulation of testis function, therefore influencing male fertility. The role of vitamin D in the modulation of testis functions, including hormone production and spermatogenesis, has been investigated in animals and humans. Experimental studies support a beneficial effect of vitamin D on male fertility, by modulating hormone production through genomic and non-genomic actions, and, particularly, by improving semen quality essentially through non-

genomic actions. Indeed, vitamin D seems to contribute to the modulation of the bioavailable rather than total testosterone. In humans, the relationship between vitamin D status and testosterone production or prevalence of hypogonadism is even more controversial. The majority of clinical studies in men from the general population did not find association between vitamin D status and circulating testosterone levels, but some studies showed a positive association between vitamin D status and circulating SHBG levels, supporting the hypothesis that VitD might contribute to the modulation of the bioavailable testosterone. Animal and human studies demonstrated that VitD exerts a beneficial effect on semen quality, particularly on sperm motility, which is probably driven by the modulation of factors involved in spermatozoa function, namely, calcium homeostasis, in animals, and by direct non-genomic VitD actions on spermatozoa, in humans. In human spermatozoa, non-genomic actions of VitD included the modulation of intracellular calcium levels and of spermatozoa lipid metabolism, with consequent improvement of sperm motility, sperm capacitation, and acrosome reaction [5].

VitD has also been shown to modulate a wide number of cancer-related molecular pathways, by interfering with cancer cell proliferation, differentiation, and apoptosis, as well as angiogenesis and epithelial-to-mesenchymal transition, which are events involved in cancer progression. Testis cancer can arise from the entire series of cell populations of the testis, but the majority originate from a pre-invasive precursor lesion, derived from germ cells, and named carcinoma *in situ* (CIS) and are referred to as germ cell tumours (GCT), which most commonly affect young men and represent a risk for fertility.

It also plays a role in promoting the function of the endometrium during implantation [6]. Low vitamin D levels have been linked to preeclampsia, pregnancy loss, and infants who are small for gestational age [7]. A deficiency in vitamin D has also been linked to the infertility that is associated with polycystic ovary syndrome, diabetes mellitus and endometriosis. The ability of vitamin D to prevent endometriosis may depend on its ability to prevent inflammation [8]. Vitamin D deficiency may also be responsible for early-onset neonatal sepsis in term infants [9]. There is evidence that vitamin D deficiency reduces the chances of success when undergoing assisted reproductive technology [10]. One of the actions of vitamin D is to induce the expression of Anti-Müllerian hormone (AMH), which is generated in both the Sertoli cells in the testes and the granulosa cells in the ovaries [11]. AMH acts as a paracrine factor to control testicular function in males and fertility in females. The level of AMH is an important predictive marker for the success of *in vitro* fertilization (IVF) treatment [12].

Neurodevelopment diseases

Vitamin D is an essential hormone that acts to maintain the phenotypic stability of cell signalling systems, particularly the Ca^{2+} and redox pathways. Alterations in these pathways during development can account for both infertility and neurodevelopmental diseases. Vitamin D deficiency results in an increase in the resting levels of both Ca^{2+} and reactive oxygen species (ROS), which means that the Ca^{2+} signals that are generated during the course of development will be markedly altered and will result in changes in early development and implantation, leading to infertility. Later in development, when organs are differentiating, such Ca^{2+} dysregulation induced by vitamin D deficiency will seriously interfere with how cells organize their relationships to each other; this is particularly relevant to brain development and results in neurodevelopmental diseases such as autism spectrum disorders (ASD), schizophrenia and attention deficit hyperactivity disorder (ADHD). There is evidence that such changes occur in pregnant women that are deficient in vitamin D and result in the children having these neurodevelopmental diseases [13].

Conclusions

Vitamin D and its receptor present in the male and female reproductive organs have a very important role in fertility. Not only do they contribute to the normal functioning of the hormonal and cellular production of the testis, but it also influences the implantation, gestation and subsequent neuronal development of the embryo. Therefore, serum vitamin D levels in both men and women could be used to predict success in IVF.

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