

Controversies in the role of vitamin D in infertility

Abstract

The study that implicates vitamin D in playing a role in fertility is compelling, and it is backed up by sound hypothesis. Nevertheless, further research needs to be assess for the health benefits and reaching appropriate levels. This could represent a starting point of a new domain which could find simple approaches to improve health. Notwithstanding fertility benefits, patients should have vitamin D supplementation for health benefits, including pregnancy health, bone health and chronic disease risk reduction. This review is based on the results of clinical trials and studies published in medical journals and database from the moment it was first acknowledged until nowadays. We aim to present the evolution of the perspective on the subject and the new findings surrounding it. Vitamin D has its well-known function in calcium and phosphorus hemostasis, and its deficiency is predominant in high-risk populations, but the prevalence among healthy or asymptomatic adults is not well defined. Several theories and hypothesis have been launched over the last years regarding the etiology of vitamin D deficiency, none of them being flawless or able to explain the entire panel of symptoms. Taken into consideration the insufficiency of vitamin D which could have implications also in infertility, especially in young fertile women, the newest research could lead to new supplementation of vitamin D in the treatment of both women and male infertility management.

Keywords: vitamin D, fertility, reproduction, management

Introduction

The studies that implicates vitamin D in playing a role in fertility is compelling, and it is backed up by sound hypothesis. Nevertheless, further research needs to be completed in order to assess a higher level of vitamin D to reach appropriate levels. This represents a new research domain that could find simple approaches to improve health⁽¹⁾.

From the fertility benefits point of view, patients should have vitamin D supplementation for health benefits, including pregnancy health, bone health and disease prevention. Vitamin D is a well-known regulator both for metabolic disorders and reproduction. It is proven that vitamin D have an important role in regulation of sex hormones in women. Vitamin D has its well-known function in calcium and phosphorus hemostasis, and its deficiency is predominant in high-risk populations, but the prevalence among healthy or asymptomatic adults is not well defined. Several theories have been released in the last decades regarding the etiology of vitamin D deficiency, none of them being able to explain the mechanism by which the symptoms appear⁽²⁾.

Methods

We search the results of clinical trials and studies published in medical journals and database from the moment it was first acknowledged the role of vitamin D until nowadays. We aim to present the evolution of the perspective on the subject and the new findings surrounding it.

Results

Controversies in diagnosis

A widespread of vitamin D deficiency has been displayed for the last decade. In fact, the prevalence of vitamin D deficiency nearly doubled since 1994 to 2004. About women of reproductive age, more than 40% showed to have lower levels of vitamin D.

Vitamin D have an important role in the human organism, keeping bones healthy though the body's calcium levels. However, some studies have showed that new ways of how vitamin D deficiency factors affect our overall health, including its role in diabetes, obesity, autoimmune disease, or cardiovascular disease and cancer⁽¹⁾.

Instead of only affecting cells that reside in the bone, we may now understand that vitamin D affects many different types of cells in different organs. The method is by turning genes within that cell "on and off." In this way, vitamin D affects the function of the cell, having a role in initiating the growth or death state⁽³⁾.

Some research studies have showed that lower quantities of vitamin D could lead to 30-50% risk of colon or prostate cancer. It's immunity role was recent discovered especially in inducing the "turn on" of specific genes, leading to cancer risk. Whatsoever until present there were no other studies to sustain the connection between lower level of vitamin D and the appearance of cancer. In this context, no other studies have been developed to show the fact that the increased amount of vitamin D could lead to a lower cancer risk.

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Regarding the infertility mechanism, there only have been mice experiments with vitamin D supplementation, showing an abnormal growth of the uterus⁽²⁾. Some experiments showed that the supplementation of vitamin D, but not with calcium alone, are going to be normalized. In the uterus, there are present the vitamin D receptor⁽³⁾, knowing the fact that the active form (i.e. calcitriol) have an important role in reproduction. It seems that calcitriol controls the genes which are involved in forming the estrogen. The uterine cavity produces this active form especially for the new embryo. During pregnancy, the uterus continue to secrete calcitriol, together with immune system, protecting in this way the embryo from different infections. Therefore, lower quantities of active form has been associated with appearance of many complications such as gestational hypertension⁽⁴⁾. When women assess *in vitro* fertilization (IVF), can interfere with the amount of vitamin D, since it's role was seen from egg development to implantation.

Some studies showed that women with higher quantities of vitamin D who undergo IVF are more likely to lead the pregnancy in time. Another study have shown that the main role in pregnancy is attributed to the recipients of donor eggs, evaluating in this way the importance of vitamin D^(4,5). Interestingly, in the last decades the vitamin D have been showed a higher role in uterus developing and the rate of IVF success. Some data showed that the accumulation of vitamin D during pregnancy, improved natural fertility for both women and men⁽⁶⁾.

The methods most often used to predict fecundity are antral follicle count, cycle day 3-5 follicle stimulating hormone (FSH) level and change in FSH in response to the CC (clomiphene citrate) challenge test.

Before treatment changes are instituted, further researches are needed to assess the health benefits of supplementing vitamin D. In the same context, this is an exciting new field of research that could lead to simple and inexpensive approaches to improve health. Considering the potential benefits in fertility, patients should be encouraged regarding appropriate vitamin D supplementation⁽⁷⁾.

Controversies in treatment

Although the vitamin D was used for ages in the field of bone metabolism or calcium nutrients supplementation, more recently a new approach regarding *in vitro* and *in vivo* supplementation sustain the "noncalcemic" effects of the metabolites. Therefore, the metabolic pathways of the vitamin D could play an important role in the emerging of gynaecological and obstetric disease. The vitamin D levels could achieve a higher risk in different gynecological abnormalities, such as polycystic ovary syndrome, endometriosis, including ovarian cancer⁽⁸⁾. If we consider that the maternal-fetal unit is develop under the vitamin D metabolites, a rupture in its homeostasis could lead to infertility, preeclampsia or gestational diabetes mellitus. Therefore, few studies showed that the bond between vitamin D and gynecological diseases

must be sustained in further research being able to clarify the mechanism behind the benefit results^(9,10,11). In the future, the vitamin D serum level should be taken into consideration, especially in trials studies, elucidating in sich way the relationship between vitamin D metabolism and the hormonal pathway.

Discussion

In human natural conception, a seasonal distribution has been consistently established, showing a peak outset rate especially in northern countries with strong seasonal contrast in luminosity^(12,13). Experimental studies have confirmed that the ovary is a target structure for 1,25(OH)2D3 sustaining the theory that this active metabolite of vitamin D3 might play a role in controlling ovarian action⁽¹⁴⁾.

Trials investigating the implication for fertility and reproductive capacity, reveal that 25(OH)D3-deficient in rats has reduced fertility rates, compromised mating behavior⁽¹⁵⁾. The mice displayed hypergonadotropic hypogonadism with reduced aromatase activities in the ovary, and uterine hypoplasia⁽¹⁰⁾.

Ablation of 1 α -hydroxylase in female mice is accompanied by uncharacteristic uterine hypoplasia similar to the mice experiment^(16,17).

Similar studies showed that the infertility seen in 1,25(OH)2D3-deficient mice represent an secondary effect exacerbated by calcium and phosphorus and not a direct result of vitamin D deficiency^(18,19).

One of the first study which revealed the implication of vitamin D metabolites in IVF success was achieved on 10 healthy women in which it was found an association of higher oestradiol levels during gonadotrophin phase of ovarian stimulation and a increase of serum 1,25(OH)2D3^(20,21).

Ozkan et al. recently followed the implantation rates of 25(OH)D3 in follicular fluid of 84 infertile women undertaking IVF and proposed follicular fluid 25(OH)D3 levels as a self-governing predictor⁽²²⁾. Another two prospective studies achieved on 101 and 82 women were in contradictory^(23,24).

Furthermore, it wasn't seen any significant differences in pregnancy rates between patients with low (<50 nmol/l) and moderate (50-75 nmol/l) 25(OH)D3 follicular fluid levels^(23,24).

It was also shown that augmented follicular fluid 25(OH)D3 levels in combination with decreased follicular fluid glucose levels have an negative impact on embryo development and IVF management^(23,25).

Conclusions

While many experimental studies who assess the benefits of vitamin D were achieved only on animals and not on humans, the implementation of new *in vitro* and *in vivo* studies are still needed. Considering the higher infertility incidence in young women and men and the possible role of vitamin D in reproduction, new research could unravel other new strategies in the treatment of such disorders. ■

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