

Research Progress on the Relationship between Vitamin D and Female Reproduction

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ABSTRACT

Background: Vitamin D is a steroid hormone playing canonical roles in calcium metabolism and bone modeling. In recent years there has been a growing body of literature presenting associations between vitamin D levels and a variety of disease processes, including metabolic disorders, autoimmune conditions and reproductive system diseases.

Main Body: In females, there also has been many research exploring the role of vitamin D deficiency in polycystic ovary syndrome, in-vitro fertilization, pregnancy outcomes and so on. However, the results and studies evaluating the effects of replacing vitamin D have shown variable results. Therefore, we wrote this review to summarize the research progress about the potential role of vitamin D in female reproductive function and provide a perspective view for the following research.

Short Conclusion: There are controversial results of the studies. High quality RCTs and reliable fundamental studies are still needed to reach definitive conclusions.

List of Abbreviations: VDR: Vitamin D Receptor; PCOS: Polycystic Ovary Syndrome; AMH: Anti-Mullerian Hormone; IVF-ET: In-Vitro Fertilization-Embryo Transfer; ART: Assisted Reproductive Therapy; GDM: Gestational Diabetes; LGA: Large for Gestational Age

Introduction

Vitamin D is an essential steroid hormone playing crucial roles in human body with the main active forms of 25-(OH) D₃, 1,25-(OH)₂D₃, 24,25-(OH)₂D₃ [1,2]. Clinically, the serum 25-(OH) D₃ concentration is usually measured to predict the vitamin D level. Vitamin D deficiency means a serum concentration of 25-(OH) D₃ less than 20 ng/mL, and vitamin D insufficiency means a 25-(OH) D₃ level between 21ng/mL and 29 ng/ml [2]. The classical role of Vitamin D is maintaining the balance of calcium and phosphate

homeostasis in intestines, bone, and the parathyroid glands. In recent years, Vitamin D receptor (VDR) expression has been confirmed in the other tissues besides the above classic target organs, such as immune cells, the pancreas, the cardiac system, the skeletal muscle. Moreover, VDR has been found in the female reproductive tract, such as ovary, uterus, fallopian tubes, placenta, etc. More recently there has been increasing interest in the role of vitamin D in reproductive function.

Vitamin D deficiency is common in both the developed and developing countries [2]. In the United States, 20%–90% of reproductive-aged women have vitamin D deficient despite prenatal vitamin intake [2]. Numerous studies have explored the influences of vitamin D deficiency in polycystic ovary syndrome (PCOS), in-vitro fertilization, pregnancy outcomes and so on. However, the results and the effects of supplying vitamin D are still under debating. Therefore, we wrote this review to summarize the research progress about the potential role of vitamin D in female reproductive function and provide a perspective view for the following research.

Vitamin D and AMH

Anti-Mullerian hormone (AMH) is considered as an important marker of ovarian reserve used in clinical widely. One function of AMH is inhibiting recruitment of primordial follicles into folliculogenesis [3,4]. Epidemiology studies have shown an intricate correlation between vitamin D and AMH. One study enrolling thirty-three infertile women with normal ovarian reserve shown vitamin D altered AMH signaling and steroidogenesis in human cumulus GCs [5]. Another study recruiting 33 premenopausal women showed supplying vitamin D was able to reverse the seasonal decrease of AMH [6]. However, a retrospective cohort study reported that vitamin D levels were not associated with ovarian reserve in 457 infertile women (age: 21-50) with a high prevalence of diminished ovarian reserve [7].

And, a cross-sectional study in 73 healthy nonobese women of reproductive age without history of infertility did not find the correlation between vitamin D level and AMH too [8]. Moreover, a recent study demonstrated that patients with hereditary 1,25-(OH)₂D-resistant rickets who had a nonfunctioning VDR appeared to have a normal reproductive history, suggesting that partial effects of vitamin D on the reproductive system might be not direct [9]. Summarizing the above results suggests that there needs more prospective study with a large group as well as participants with similar backgrounds to confirm the correlation between vitamin D and AMH.

Vitamin D and PCOS

Polycystic ovary syndrome (PCOS) is the common endocrine disorder in women of reproductive age, and its prevalence is about 6–10% in general population. Moreover, PCOS is the major cause of anovulatory infertility, and is associated with insulin resistance (IR), hyperinsulinemia, dyslipidemia, and central obesity [10-13]. It is estimated 67%–85% of women with PCOS have vitamin D deficiency [14]. And there are plenty of studies related to vitamin D and PCOS. Studies suggested that there was an association between vitamin D status and hormonal as well as metabolic dysfunctions in PCOS [14], and they found that the active VDR complex regulated genes important for glucose and lipid metabolism [15]. However, some other studies did not support the results [16-21]. One study

reported that Tehran women with and without PCOS had the similar vitamin D levels. Moreover, some intervention trials had been carried out to explore the effect of vitamin D supplementation.

Thys-Jacobs et al. [22] and Rashidi B et al. [23] found an improvement in menstrual regularity after vitamin D supplementation in women with PCOS. Selimoglu et al. [24] and Majid Dastorani et al. [25] observed a significant decrease in IR after the vitamin D supplementation, whereas the others failed to find a positive effect of vitamin D supplementation on IR [26-31]. Other than these above, some studies explored the correlation between VDR gene polymorphisms and PCOS. Ranjzad et al. found that the CASR 'TG' polymorphism was associated with IR [32]; Mahmoudi T found that the variants of VDR were associated with an increase in insulin levels and IR [33]; Wehr E et al. found that the VDR Apa-I genotype was associated with the prevalence of PCOS [34]. Nevertheless, Lin et al. [35], Zadeh-Vakili et al. [36] and Ranjzad F et al. [37] found no difference in VDR gene polymorphisms between PCOS and control women. Therefore, it is difficult to draw a definite conclusion for the relationship between vitamin D status and PCOS due to the heterogeneity of the studies. Well-designed prospective randomized clinical trials are still needed to investigate the relationship.

Vitamin D and In-vitro Fertilization

Whether vitamin D played a role in the process of in vitro fertilization are still elusive. Sebiha Ozkan et al. found that women with higher vitamin D level in serum and follicle fluid were more likely to achieve clinical pregnancy following in-vitro fertilization-embryo transfer (IVF-ET) [38]. A systematic review showed that there was a positive association between vitamin D status and assisted reproductive therapy (ART) outcomes and suggested vitamin D deficiency and insufficiency should be treated in women considering ARTs [39]. However, the majority of studies did not find a significant correlation between vitamin D level and IVF outcomes [40-42]. A meta-analysis concluded that there was not sufficient evidence supporting the necessary of vitamin D supplementation during IVF [43]. Thence, it still needs further analysis and exploration.

Vitamin D and Pregnancy Outcomes

Cumulative studies suggested that vitamin D deficiency related to adverse pregnancy outcomes, e.g. gestational diabetes (GDM), preeclampsia, pre-term birth and so on [44-49]. Recently, a systematic review indicated that pregnant women with low vitamin D level had an increased risk for GDM, and GDM could ameliorate after vitamin D supplementation [50]. A cohort study found that higher vitamin D (≥ 30 nmol/L) in early pregnancy was associated with lower blood glucose both in early and throughout pregnancy, but higher vitamin D in late pregnancy was associated with higher risk of large for gestational age (LGA) at birth [51]. Interestingly, a recent research found that high vitamin D at 15 ± 1 weeks' gestation

was shown to be protective against the development of GDM and they also found that the correlation between vitamin D status and pregnancy complication might be affected by fetal sex [52]. Mehri Jamilian et al. demonstrated that magnesium-zinc-calcium-vitamin D co-supplementation to women with GDM might reduce biomarkers of inflammation and oxidative stress [53].

Sunni L Mumford and colleagues [54] presented increased rates of pregnancy and livebirth in women with sufficient serum concentrations of vitamin D preconception. Clinical trials about the effect of vitamin D supplementation during pregnancy shown conflicting results. Raden Tina Dewi Judistiani et al. suggested that sufficient maternal vitamin D was an important factor to improve fetal growth and development [55]. Hashemipour S et al., Roth DE et al. and Hossain N et al. found that treatment of low vitamin D during pregnancy improved the obstetric and neonatal outcomes [56-59]. Hornsby et al. demonstrated supplying vitamin D during pregnancy was beneficial for respiratory health in early life [60]. Urrutia-Pereira and Solé also reported low maternal vitamin D increased the risk for the later development of asthma and chronic obstructive pulmonary disease [61]. A post hoc analysis from RCT recommended regular exercise during pregnancy due to its positive influence on vitamin D level [62].

But Pérez-López FR et al. found that Vitamin D supplementation during pregnancy was not associated with maternal outcomes [63], and Moniek Looman et al. found vitamin D level or supplementation were not associated with glucose homeostasis in 105 women aged 18–40 years [64]. Some research explored the relationship between vitamin D level and postpartum depression, and the results were also perplexed [65-67]. Considering the heterogeneity of the above studies and the differences in vitamin D levels during pregnancy, non-pregnancy and different periods of pregnancy, larger, better-designed RCTs evaluating clinically relevant outcomes are necessary to reach a definitive conclusion.

Conclusion

The aim of this review was to present the findings of different kinds of studies on vitamin D and female reproduction. As presented, there are controversial results which could be due to the bias, inadequate power or other limitations of the studies. And the mechanisms are not clearly defined, whether vitamin D directly affecting female reproduction or via associated factors, such as AMH, hypocalcemia, insulin resistance, etc. playing indirect roles in reproductive outcomes is still confused. High quality RCTs are still needed to reach definitive conclusions, and reliable fundamental studies complement the mechanisms of vitamin D deficiency and supplementation in female reproduction ability and outcomes, ultimately set the appropriate vitamin D supplement doses for female.

Authors' Contributions

Xiaofei Xu was responsible for the search and selection of articles, extraction of data, and writing and revision of the

manuscript. Jie Qiao initiated the study, contributed to the study design, and revised the paper critically for important content. Yongxiu Hao revised the paper critically. All the authors were involved in the final approval of the version to be published.

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