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Editorial

Vitamin D and polycystic ovary syndrome



Vitamin D interacting its cognate vitamin D receptor (VDR), belongs to the superfamily of nuclear steroid receptor that use the same heterodimer partner (RXR) on virtually all cells in the human body to form the highly structural and functionally complex vitamin D endocrine system, and regulates the transcription of near 3% of genes, with a broad spectrum of functional activities which determine the systemic and auto/paracrine endocrine action [1–3]. Vitamin D signaling mainly promotes calcium absorption in the gut and stabilizes and normalizes serum calcium and phosphate concentrations to maintain a healthy mineralized skeleton [1,2]. In addition to conventional skeletal effects, vitamin D signaling has polymorphic roles in the body, regulating multiple extra-skeletal physiological processes in organs and systems, such as neuromuscular, cardiovascular, and immune systems, to regulate cell growth as well as proliferation, and hormone secretion, xenobiotic metabolism, inflammation, and reproduction [1]. Recent studies showed that vitamin D signaling system is important for several non-skeletal outcomes, such as cardiovascular and respiratory disease, neuromuscular dysfunction, autoimmune diseases, metabolic disorders, cancers, and immune dysfunction, and vitamin D deficiency is associated with worse pregnancy outcome, increased risk of pregnancy induced diseases, such as preeclampsia, gestational diabetes, as well as subfertility [1–5], suggesting this issue is worthy of investigation, especially focusing on the relationship between vitamin D and women's health. It is very happy to introduce the recent publication in the July issue of *Taiwanese Journal of Obstetrics and Gynecology* (TJOG) which evaluated the follicular fluid vitamin D level on its impact on the fertility outcomes of patients with polycystic ovary syndrome (PCOS) [6].

Drs. Ozyurt and Karakus enrolled 30 PCOS infertile women comparing the non-PCOS infertile women with similar serum level of vitamin D who underwent the assisted reproductive technology (ART) by *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) to determine the relationship between follicular fluid vitamin D levels and fertility outcome [6]. The authors found vitamin D concentration of follicular fluid was statistically significantly lower than serum, regardless whether PCOS women or non-PCOS women are; however, there was no statistically significant difference of vitamin D in either follicular fluid or serum between PCOS and non-PCOS women, contributing to absence of correlation between follicular fluid vitamin D and ART outcomes in PCOS [6]. The current study is relatively interesting and worthy of discussion.

First, as shown by authors, follicular fluid vitamin D levels were statistically significantly positively correlated with the number of total oocyte and mature oocyte (MII oocyte) in the PCOS women, and by contrast, this correlation was not found in the healthy control group (non-PCOS women) [6]. Additionally, non-PCOS women had a

higher follicular fluid vitamin D levels than PCOS women did (13.3 versus 11.2 ng/mL), not reaching statistical significance ($p = 0.06$), but the number of total oocyte and MII oocyte in non-PCOS women were significantly lower than the PCOS women [6]. The aforementioned data makes us relatively confused, since the higher follicular fluid vitamin D levels are good for both quality and quantity of oocyte retrieval in the PCOS women, favoring the potential benefits of vitamin D on female reproduction—especially for folliculogenesis. By contrast, the non-PCOS women had higher follicular fluid vitamin D levels but both quality and quantity of oocytes retrieval were statistically significantly lower than PCOS women having lower follicular fluid vitamin D levels did (11.6 versus 18.2 for total number of oocytes and 7.1 versus 12.5 for total number of MII oocytes, respectively) [6]. All suggest that follicular fluid vitamin D levels may not influence the quality and quantity of oocytes in healthy controls (non-PCOS women). If the aforementioned finding is real, the value of vitamin D on female reproduction may only be limited to the diseased population, such as PCOS women. Therefore, the impact of vitamin D on female reproduction may face the biggest challenge. Therefore, we would like to introduce the recent evidence addressing vitamin D on female reproduction. The better understanding the pathophysiology of vitamin D signaling on its impact on female reproduction may help us improve the fertility outcomes of women with vitamin D deficiency.

Second, the targeted population of their study was PCOS women, who are characterized by chronic anovulation, hyperandrogenism, and polycystic ovaries in ultrasonography [7–11]. PCOS is common metabolic disorder frequently accompanied with infertility in women of reproductive age. A relationship between vitamin D and anovulation infertility can be found either by epidemiology study and *in vivo* and *in vitro* studies [11]. The study showed 70.3% of infertile PCOS women had serum levels of vitamin D < 20 ng/mL and more than 90% had levels < 30 ng/mL [11]. Furthermore, vitamin D deficiency in infertile PCOS women have significantly diminished rates of ovulation, lower pregnancy rate and reduced live birth rate [11]. Higher vitamin D levels improve the outcome of IVF, independently from age, body mass index, ethnicity and the number of embryo transfers [12]. Besides epidemiology data support, pathophysiologic mechanisms of vitamin D signaling pathway also demonstrated its impact on female reproduction, including (i) there is wide expression of VDR in follicle cells and reproductive organs, suggesting the vitamin D signaling may have a critical role during reproduction processes; (ii) vitamin D deficiency is associated with impaired folliculogenesis (ovulation dysfunction) mediated by disrupted reproductive hormone balance, decreased anti-oxidant defense effect, and accumulation of pro-inflammatory cytokines and overproduction of

reactive oxygen species (ROS) with a resultant occurrence of irregular menstrual cycle, decreased number of all detectable essential follicles (preantral, antral, mature follicle and corpora lutea), and increased atretic and cystic follicles [11], and by contrast, vitamin D ameliorates the insulin resistance status of PCOS women, increases the survival of the preantral follicle, sustains AMH production and enhances the growth of the antral follicle, as well as affects the length of telomeres and telomerase enzyme activity to decrease the aneuploid ratio as well as improve embryo quality—the number of high-quality embryos, and subsequently improve the efficacy of IVF treatment, such as success implantation and clinical pregnancy rates, and every nmol/L increase in the follicular fluid vitamin D level increases the probability of clinical pregnancy by 2.4% [12]. The latter can be partly explained by normalized glucocorticoid system, and immunomodulatory effects of vitamin D [12], which results in the Th2 (T helper 2 cell) cytokine dominance, decreased overproduction of inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6) and interferon- γ (IFN- γ) [12]. Since PCOS women seemed to have the similar above-mentioned pathophysiology pattern of low vitamin D, it is possible that both may further deteriorate the ovulation dysfunction either by additive effect or by synergistic effect on impaired fertility. It may partly explain why the quality and quantity of oocytes are better in PCOS women when follicular fluid vitamin D levels are higher by the current study.

However, there are still some studies showing the conflicted data about the positive correlation between follicular fluid vitamin D levels and the quality and quantity of oocytes retrieval during the IVF process [13,14]. One study showed women with decreased ovarian reserve (DOR), one of troublesome infertility problems [15–17], had a higher follicular fluid vitamin D level than those women with normal ovarian reserve did (24.1 versus 18.8 ng/mL) [13]. Additionally, Hosseinsadat et al. did not find any correlation between follicular fluid vitamin D level and ART outcomes [14]. All suggest that the role of vitamin D on the female reproduction, especially for ovulation induction is still uncertain; however, for those women with underlying diseases, such as metabolic syndrome as PCOS, the benefits of vitamin D may be worthy of further evaluation.

Conflicts of interest

All authors declare no conflict of interest.

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