

Poly Cystic Ovarian Syndrome and Vit D Correlation with Fertility: Review Article

Marah Mohammed Alzaidi¹, Hassan Hamza A Almir², Afraa Qasim Ibrahim Khormi³,
Yassmeen Mohammed Alltaleb⁴, Zahra Mohamed A Al Muwais², Rehab Abdul Rahman Alsaleh⁵,
Nora Faisal Alsaud⁴, Lama Mohammed Alomar⁶, Lara Saleh Alkuhaimi⁴, Fatimah Radi Slais⁷,
Alhanouf Abdullah Alyahya⁶, Reema Adnan Shabkah⁸, Abdulrahman Hassan Khormi⁹, Reyhana Safi⁵

Department of Obstetrics and Gynecology

¹Taif University, Taif, ²Imam Abdulrahman bin Faisal university, Dammam, ³Jazan University, Jazan,
⁴Alfaisal University, Riyadh, ⁵Ibn Sina National College, Jeddah, ⁶Almaarefa College for Science and
Technology, Riyadh, ⁷Al Amal complex for Mental Health, Dammam, ⁸King Abdulaziz University, Jeddah,
⁹King Fahd Central Hospital, Jazan, Saudi Arabia

Corresponding Author: Marah Mohammed Alzaidi, email: dr.mara7-alzaidi@hotmail.com, mobile:+966564999166

ABSTRACT

Over the past few decades, vitamin D was proposed to be highly influential on female fertility and reproductive health. Its role was extensively studied and evaluated specifically in females with polycystic ovarian syndrome. **Objectives:** the aim of this research was to study the correlation between vitamin D and fertility in general, and in polycystic ovarian syndrome-associated infertility in particular. **Methods:** we searched Cochrane Library and PubMed for articles addressing the impact and role of vitamin D in fertility issues in females with polycystic ovary disease. Specifically-related topics were carefully reviewed and analyzed to summarize their conclusive results. **Results and Discussion:** Vitamin D was lower in females with PCOS and vitamin D administration had increased its level, improved metabolic disturbance and shortened inter-menstrual intervals in those patients. Patients with high vitamin D levels had a better success rate of *in-vitro* fertilization. However, it did not affect the time to pregnancy in PCOS women. **Conclusion:** Vitamin D is beneficial for improving metabolic as well as reproductive functions in women with PCOS. It is also essential for successful *in-vitro* fertilization, and it is probably protective against endometriosis. However, results from different studies are contradictory, and still there is no solid evidence that there is a cause-effect relationship between vitamin D and fertility.

Keywords: Polycystic ovary, PCO, Vitamin D, Fertility.

INTRODUCTION

Vitamin D is one of the fat-soluble vitamins that can be exogenously taken, via certain types of food, or endogenously formed, through skin exposure to ultraviolet sun rays. The main well-established role of vitamin D is related to calcium metabolism, mineralization, and bone health. However, it was found that it is also implicated in the pathogenesis and risk amplification in certain medical diseases. Vitamin D deficiency or disturbed metabolism is encountered in many disorders such as cancer, autoimmune, infectious, endocrinal, as well as cardiovascular diseases⁽¹⁾.

Polycystic ovarian syndrome, on the other side, is one of the most common endocrinopathies, it affects 6-10% of females in the reproductive age worldwide. Patients with polycystic ovarian syndrome (PCO) present with menstrual irregularities and signs of hyperandrogenism⁽¹⁾. Infertility, diabetes, obesity, and metabolic syndrome are not uncommon among those patients⁽²⁾. The pathophysiology of PCOS is

complex; excessive pituitary gland secretion of luteinizing hormone (LH) that subsequently stimulate ovarian thecal cells for overproduction of androgens is one of the common proposed mechanisms⁽³⁾. PCOS is closely correlated with obesity, insulin resistance, and hyperinsulinemia which may augment the gonadotropin hormonal effect on ovaries⁽⁴⁾.

Study rationale and objectives:

Many researches had proposed a role of vitamin D in polycystic ovarian syndrome management, and eventually various studies had intensively focused on this point of research. The aim of this research article was to review the literature studies addressing the correlation between vitamin D and fertility in general, and Vitamin D in PCOS-associated fertility in particular.

METHODS

To achieve the review article objective, we conducted a systematic search of medical database,

namely PubMed and Cochrane Library for articles addressing the correlation between fertility, polycystic ovary and vitamin D. The search results were closely inspected to select those with appropriately-related significant data. We selected studies and review articles specifying the role of vitamin D in females with polycystic ovary syndrome, the relationship between vitamin D and fertility, the association of vitamin D with polycystic ovary, and the impact of vitamin D administration on fertility for females with polycystic ovary syndrome. Data from selected results were analyzed carefully, organized, and summarized to reach conclusive remarks.

The study was approved by the Ethics Board of Taif University.

RESULTS

Literature studies showed contradictory results about the association of vitamin D and polycystic ovarian syndrome (PCOS) and/or fertility. **Fang *et al.***⁽⁵⁾ in their meta-analysis of 9 studies including 502 women with polycystic

ovarian syndrome (PCOS) stated that there was a significant enhancing effect of vitamin D supplementation on reproductive functions through improving follicular development and increasing numbers of dominant follicles (OR 2.34). Vitamin D administration had also increased the regulation of menstrual cycles in females with PCOS on metformin in comparison to giving metformin alone (OR 1.85). Additionally, **Nick *et al.***⁽¹⁾ in their review article in May 2015 indicated that vitamin D was significantly associated with fertility; it prevented endometriosis and ameliorated the reproductive dysfunction in patients with polycystic ovarian syndrome. On the contrary, **Ming-Wei *et al.***⁽⁶⁾ reported that in spite of the presence of many studies suggesting the association between vitamin D receptor (VDR) gene (one of the genes involved in vitamin D metabolism) and polycystic ovarian syndrome, no consistent conclusion could be made that vitamin D has a significant role in neither the pathophysiology nor the outcome of polycystic ovarian syndrome⁽⁶⁾.

Table (1): Literature survey of vitamin D correlation with PCOS and infertility

Author	Year	Patients number	Type	Conclusive remarks
<i>Fang et al.</i> ⁽⁵⁾	2017	502	Meta-analysis	Vit D supplement significantly improved follicular development in PCOS
<i>Elida et al.</i> ⁽⁷⁾	2016	23 patients 23 controls	Cross-sectional	Vit D level is lower in PCOS and lower in obese PCOS
<i>Nick et al.</i> ⁽¹⁾	2015	NA	Review article	Vit D was associated with fertility Vit D ameliorated reproductive dysfunction in females with PCOS.
<i>Ming-Wei et al.</i> ⁽⁶⁾	2015	NA	Review article	Polymorphism in VDR gene is associated with PCOS, but the role of Vit. D is still debatable
<i>Dipanshu et al.</i> ⁽⁸⁾	2015	NA	Review article	Increase vit D deficiency in PCOS Vit D deficiency was associated with insulin resistance, fertility problems, and hyperandrogenism signs and symptoms.
<i>Irani et al.</i> ⁽⁹⁾	2015	68	prospective, randomized, placebo-controlled trial	Vit D supplementation improved vit D deficiency and TGF-β1 bioavailability in PCOS, and decreased the interval between menstrual cycles and triglycerides levels.
<i>Kim et al.</i> ⁽¹⁰⁾	2014	38 patients 109 controls	Case-control	No difference in vit D levels between PCOS and controls
<i>Lerchbaum et al.</i> ⁽¹¹⁾	2014	NA	Review article	High vit D level is necessary for successful IVF, protective against endometriosis, and decrease metabolic parameters in PCOS
<i>Rainer et al.</i> ⁽¹²⁾	2012	53	Retrospective	Increase vit D deficiency among PCOS patients No association between vit D deficiency and time to pregnancy

NA: not applicable, Vit: Vitamin, PCOS: polycystic ovarian syndrome, VDR: Vitamin D Receptor, TGF-β: Transforming growth factor beta, IVF: in-vitro fertilization

Irani et al.⁽⁹⁾ conducted a prospective randomized placebo-controlled trial on 68 women with PCOS to determine the effect of Vitamin D supplementation versus placebo on the disease outcome. Results from their study showed that vitamin D supplementation had significantly normalized vitamin D levels from 16.3 ± 0.9 to 43.2 ± 2.4 ng/mL ($p < 0.01$). It had also decreased the interval between menstrual cycles from 80 ± 9 to 60 ± 6 ($p = 0.4$) and triglyceride level from 138 ± 22 to 117 ± 22 mg/dl ($p = 0.3$).

Kim et al.⁽¹⁰⁾ in their case-control study on Korean women with polycystic ovarian syndrome found that there was no statistically significant difference between 25-hydroxy vitamin D levels among PCOS patients (19.6 ± 6.6 ng/mL) and controls (20.1 ± 7.4 ng/mL) with a p value of 0.696. Similarly, there was no significant difference in the overall prevalence of vitamin D deficiency among patients (57.9%) and controls (56.5%) ($p = 0.88$). In disagreement with this study, **Rainer et al.**⁽¹²⁾ reported a high prevalence of vitamin D deficiency among patients with PCOS, however, there was no significant association between vitamin D deficiency and the number of cycles to pregnancy [HR $\frac{1}{4} 1.4$ (95% CI 0.3-8.5)]. **Dipanshu et al.**⁽⁸⁾ also reported a high prevalence of vitamin D deficiency among females with PCOS with a figure ranging from 67-85%. The average serum concentration of 25-hydroxy Vitamin d was < 20 ng/ml. Lower levels of vitamin D were associated with insulin resistance, low pregnancy rates, and menstrual irregularities, and signs of hyperandrogenism. Similarly, results from cross-sectional study conducted by **Elida et al.**⁽⁷⁾ indicated that PCOS patients had significantly lower vitamin D levels when compared to controls, and obese PCOS ladies had even much lower level of vitamin D specifically those with waist-hip ratio of > 0.85 .

Studying the effect of vitamin D supplementation on fertility in general, **Lerchbaum et al.**⁽¹¹⁾ noticed that females with vitamin D levels of > 30 ng/mL had a higher success rate of their *in-vitro* fertilization (IVF) than their counterparts. This was attributed to the vitamin D effects on uterine endometrium. Vitamin D supplementation was also reported to be beneficial for women with PCOS in diminishing different metabolic diameters such as

lipid profile; and it decreased incidence of endometriosis in animal models.

DISCUSSION

Although the main well-known role of vitamin D is the regulation of mineralization, calcium metabolism, and bone health, another key function of the vitamin is regulation of cell growth. And because it is a fat-soluble seco-steroid chemical, it is vital for production of sex hormones inside the body. Additionally, it plays a considerable role in reproductive functions mainly through altering the signaling of anti-müllerian hormone, the sensitivity of follicle-stimulating hormone, and production of progesterone in human granulosa cells which subsequently affect ovarian follicle luteinization⁽¹³⁾. This is proposed due to the presence of Vitamin D receptors (VDR) in the placenta, ovary and uterine endometrium. Furthermore, a probable role of vitamin D in insulin resistance is hypothesized by the observation of an element for vitamin D response on the insulin gene promoter as well as the presence of vitamin D receptor (VDR) in β -Langerhans cells of the pancreas⁽¹⁴⁾.

Over the past few decades, the correlation between vitamin D and fertility in general – or PCOS in particular – had become a matter of interest. The effect and role of vitamin D in improving infertility has been intensively researched. Although results from different studies were contradictory, there is a promising finding that propose a beneficial effect of vitamin D on improving fertility problems. For instance, reports of **Lerchbaum et al.**⁽¹¹⁾ indicated that females with vitamin D levels of > 30 ng/mL had a higher success rate of their *in-vitro* fertilization (IVF) emphasize the vital role of vitamin D for maintain the integrity and health of the uterine endometrium. Findings by other researchers had stated that patients with vitamin D deficiency did not respond well to Clomid ovarian stimulation or to *in-vitro* fertilization (IVF)⁽¹⁵⁾.

As regards the association of vitamin D and polycystic ovarian syndrome, many researchers had observed a significantly lower vitamin D level among PCOS women^(8,9,11,12), it was even lower in obese PCOS⁽⁷⁾. Data indicated that vitamin D supplementation for those patient had improved their follicular development and increased the

number of dominant follicles⁽⁵⁾. It has also decreased the interval between menstrual cycles in one study⁽⁹⁾. However, it did not seem to decrease the time or number of cycles to pregnancy⁽¹²⁾. Results from **Irani *et al.***⁽⁹⁾ study provided a new possible role of vitamin D supplementation on the pathophysiology of PCOS by acting on TGF- β . Other studies^(7,8) assumed a probable role of vitamin D in insulin resistance. It seemed that vitamin D deficiency might aggravate insulin resistance and its correction might help control of the condition.

The findings reported by **Kim *et al.***⁽¹⁰⁾ indicated that there was no statistically significant difference in neither the vitamin D level nor the prevalence of vitamin D deficiency between patients and controls signifying that the role of vitamin D in the pathogenesis of PCOS remains elusive.

In conclusion, there may be an evidence that Vitamin D supplementation to females with polycystic ovarian syndrome (PCOS) may improve their menstrual irregularities, insulin resistance, as well as pregnancy success rates. However, the contradictory results stated through different studies make this evidence limited and/or inadequate. The reviewed studies indicated that vitamin D administration induced significantly improved polycystic ovarian syndrome-associated fertility problems.

Vitamin D was also reported to enhance fertility on other aspects rather than PCOS, it was noted that it improves the success of *in-vitro* fertilization⁽¹²⁾, and protect against endometriosis⁽¹⁶⁻²⁰⁾. While vitamin D impact on fertility and reproductive health is promising, data available are still inadequate and are not sufficient to establish a solid causal-effect relationship between fertility problems and vitamin D administration or deficiency. Further longitudinal multi-centric studies are still recommended to establish this hypothesis and to generate a consensus for usage of vitamin D in infertile patients.

CONCLUSION

Vitamin D is beneficial for improving metabolic as well as reproductive functions in women with PCOS. It is also essential for successful *in-vitro* fertilization, and it is probably protective against endometriosis. However, results from different studies are contradictory, and still

there is no solid evidence that there is a cause-effect relationship between vitamin D and fertility.

REFERENCES

1. **Voulgaris N, Papanastasiou L, Piaditis G, Angelousi A, Kaltsas G, Mastorakos G *et al.* (2017):** Vitamin D and aspects of female fertility. *Hormones* (Athens, Greece),16(1):5-21.
2. **Richard Scott Lucidi (2017):** Polycystic Ovarian Syndrome: Practice Essentials, Background, Etiology [Internet]. Available from: <https://emedicine.medscape.com/article/256806-overview#a1>
3. **Diamanti-Kandarakis E, Argyrakopoulou G, Economou F, Kandaraki E, Koutsilieris M *et al.* (2008):** Defects in insulin signaling pathways in ovarian steroidogenesis and other tissues in polycystic ovary syndrome (PCOS). *J Steroid Biochem Mol Biol.*,109(3-5):242-6.
4. **Sam S. (2007):** Obesity and Polycystic Ovarian Syndrome. *Obes Manag.*,3(2):69-73.
5. **Fang F, Ni K, Cai Y, Shang J, Zhang X, Xiong C *et al.* (2017):** Effect of vitamin D supplementation on polycystic ovary syndrome: A systematic review and meta-analysis of randomized controlled trials. *Complementary Therapies in Clinical Practice*. [cited 2017 Oct 16] Available from: <http://www.sciencedirect.com/science/article/pii/S174438811630130X>
6. **Lin M-W, Wu M-H (2015):** The role of vitamin D in polycystic ovary syndrome. *Indian J Med Res.*,142(3):238-40.
7. **Sidabutar E, Halim B, Siregar MFG, Lutan D, Adenin I, Kaban Y *et al.* (2016):** Vitamin D Levels in Women with Polycystic Ovary Syndrome. *KnE Med.*,1(1):125-32.
8. **Ratnabali Chakravorty DS, Chakravorty R (2015):** The Relationship between Vitamin D, Insulin Resistance and Infertility in PCOS Women. *Gynecol Obstet. OMICS International*. Available from: <https://www.omicsonline.org/open-access/the-relationship-between-vitamin-d-insulin-resistance-and-infertility-in-pcoswomen-2161-0932-1000294.php?aid=52835>
9. **Irani M, Seifer DB, Grazi R V., Julka N, Bhatt D, Kalgi B *et al.* (2015):** Vitamin D supplementation decreases TGF- β 1 bioavailability in PCOS: A randomized placebo-controlled trial. *The Journal of Clinical Endocrinology and Metabolism*,100(11):4307-14.
10. **Kim JJ, Choi YM, Chae SJ, Hwang KR, Yoon SH, Kim MJ *et al.* (2014):** Vitamin D deficiency in women with polycystic ovary syndrome. *Clin Exp Reprod Med. Korean Society for Reproductive Medicine*, 41(2):80-5.
11. **Lerchbaum E, Rabe T (2014):** Vitamin D and

- female fertility. *Curr Opin Obstet Gynecol.*,26(3):145–50.
12. **Rainer D, Davis E, Peck J, Hansen KR, Craig LB et al. (2012)** : Vitamin D Deficiency and Time to Pregnancy in Women With Polycystic Ovary Syndrome. *Fertil Steril.*,97(3):S22.
 13. **Irani M, Merhi Z (2014)**:Role of vitamin D in ovarian physiology and its implication in reproduction: A systematic review. *Fertil Steril.*,102(2).
 14. **Alvarez JA, Ashraf A (2010)**:Role of Vitamin D in Insulin Secretion and Insulin Sensitivity for Glucose Homeostasis. *Int J Endocrinol.*,1-18:351385.
 15. **Rebecca L. Thomson; Simon Spedding; Jonathan D. Buckley et al. (2017)**: Vitamin D in the Etiology and Management of PCOS. Available from: <https://www.medscape.com/viewarticle/769614>
 16. **Laganà AS, Vitale SG, Ban Frangež H, Vrtačnik-Bokal E, D’Anna R et al. (2017)**:Vitamin D in human reproduction: the more, the better? An evidence-based critical appraisal. *Eur Rev Med Pharmacol Sci.*,21(18):4243–51.
 17. **Lata I, Tiwari S, Gupta A, Yadav S, Yadav S et al. (2017)**:To study the vitamin D levels in infertile females and correlation of Vitamin D deficiency with AMH levels in comparison to fertile females. *J Hum Reprod Sci.*,10(2):86.
 18. **Akhavizadegan H, Karbakhsh M (2017)**:Comparison of serum vitamin D between fertile and infertile men in a vitamin D deficient endemic area: a case-control study. *Riv Urol.*, Available from: <http://www.ncbi.nlm.nih.gov/pubmed/28665459>
 19. **Fabris AM, Cruz M, Iglesias C, Pacheco A, Patel A, Patel J et al. (2017)**:Impact of vitamin D levels on ovarian reserve and ovarian response to ovarian stimulation in oocyte donors. *Reprod Biomed Online*,35(2):139–44.
 20. **Fung JL, Hartman TJ, Schleicher RL, Goldman MB et al. (2017)**:Association of vitamin D intake and serum levels with fertility: results from the Lifestyle and Fertility Study. *Fertil Steril.*,108(2):302–11.