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THE IMPORTANCE OF VITAMIN COMPLEXES IN THE TREATMENT OF POLYCYSTIC OVARY SYNDROME: A REVIEW

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ABSTRACT

Polycystic ovary syndrome is a modern disease that affects 1 out of 5 women of reproductive age worldwide. The disease is accompanied by dysmenorrhea, hyperandrogenism, overweight, skin problems, etc. To date, it has been precisely established that polycystic ovary syndrome is a polygenic hormonal problem correlated with genetically determined determinants. There are exogenous factors that induce the development of pathology, which can be regulated and controlled. One of the exogenous factors that can have a serious impact on women's health and control of polycystic ovary syndrome is a balanced diet and elimination of deficiencies in the body, especially vitamin D and folic acid deficiency. The improvement of numerous health indicators through lifestyle modification, which includes nutrition and exercise, is among the suggested management techniques in the evidence-based international clinical guidelines. This systematic review seeks to offer a general idea regarding the state of know-how in this topic by summarising the actual findings from randomised controlled trials, systematic reviews, and meta-analyses.

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Introduction

Polycystic ovary syndrome is currently incurable and is a consequence of the complementation of hereditary determinants and environmental factors that collectively determine the clinical phenotype of the disease. As a rule, the phenotypes of the disease can replace each other throughout life [1]. It is believed that of the exogenous factors affecting the development and progression of polycystic ovary syndrome, food chemicals, and environmental toxins have the greatest weight. Strictly speaking, it is these factors that can be aggravated by improper unbalanced nutrition, physical inactivity, and subsequent increase in excess weight **(Figure 1)**.

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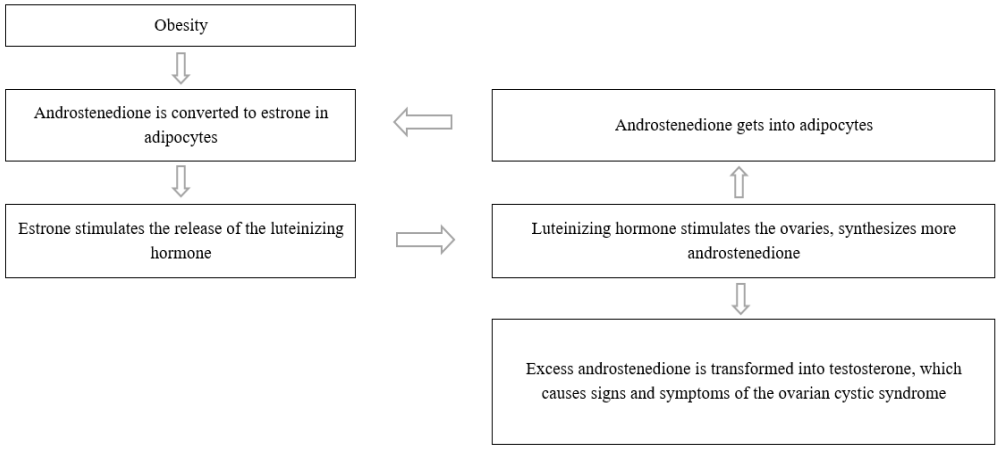

Figure 1. Simplified scheme of development of polycystic ovary syndrome

Almost 80% of women with polycystic ovary syndrome are overweight or obese, and about 25% of the general population are morbid [2, 3]. This negatively affects their reproductive and metabolic functions, and aggravates the psychological consequences of this disorder [4]. The residual consequences of polycystic ovary syndrome include type II diabetes mellitus, cardiovascular diseases, infertility, various types of dysmenorrhea, and mental disorders up to severe depressive episodes and bipolar disorder are distinguished [5]. However, almost all of these effects can be prevented or reduced.

There is information proving that complications and consequences of polycystic ovary syndrome are reversible when correcting lifestyle with diets or physical exercises [6]. This is an interesting fact that may indicate that polycystic ovary syndrome is indeed a disease of the XXI century.

The incurable, but for the most part controlled, the nature of polycystic ovary syndrome highlights the significance of creating novel symptom relief techniques, as they are currently the only methods accessible to enhance women's quality of life.

The data available to date indicate that certain vitamins (B12, B9, D, E, K, and inositols), vitamin-like substances (bioflavonoids and alpha-lipoic acid), some minerals (calcium, zinc, selenium, chromium) and other drugs (melatonin, ω-3 fatty acids, and others) may be directly useful in polycystic ovary syndrome [7]. But before these techniques can be incorporated into the regular practise of specialists, there are still important constraints and areas of uncertainty in clinical practise.

Vitamin Supplements in Complementary Therapy for Polycystic Ovary Syndrome

The proposed mechanism of action of vitamin complexes on polycystic ovary syndrome is as follows: individual nutrients, acting on key pathways of disease induction (for example, insulin signaling, lipid metabolism disorders), change the symptoms and severity of polycystic ovary syndrome, generally leveling the disease phenotype. The data that will be described below are taken from individual randomized clinical trials.

A steroid hormone called vitamin D is created mostly by sunshine and in small amounts by food sources (such fatty fish or fortified dairy products). In addition to being essential for calcium metabolism and bone homeostasis, vitamin D is also thought to have significant metabolic and endocrine effects [8]. A meta-analysis conducted several years ago [9], in which various doses of vitamin D supplements were studied for 30 weeks in females who have polycystic ovary syndrome, demonstrated an improvement in the HOMA-IR index ("Homeostasis model assessment of insulin resistance" - a calculation formula that takes into account the parameter of glucose and insulin in the blood) of the homeostatic model evaluation of pancreatic β-cell function, as well as improvement of total testosterone and low-density lipoprotein (LDL) cholesterol levels. However, no effect was found on body mass index, dehydroepiandrosterone sulfate, triglycerides, or high-density lipoproteins (HDL). Similarly, a meta-analysis involving 824 women reported a decrease in the HOMA-IR index, very low-density lipoprotein cholesterol (VLDL), glucose, and insulin in the fasting blood [10]. There was also an increase in the quantitative QUICKI index (checking insulin sensitivity) when taking vitamin D supplements compared to placebo. It was discovered that daily low dosages of vitamin D (as opposed to sporadic large doses) had more pronounced glycemic effects.

Vitamin D also improves the condition of the entire lipid panel, except HDL (no significant changes). Based on these findings, vitamin D supplements given daily to women with deficiencies may have a modestly positive impact on glycemic status in those with polycystic ovarian syndrome [11-13], Its influence on the lipid profile, inflammation, and hyperandrogenism, however, is still unknown.

Data from experimental and clinical studies demonstrate that vitamin D deficiency contributes to increased inflammation, dyslipidemia and decreased fertility in polycystic ovary syndrome. The studies suggest that vitamin D treatment in these patients reduces IR and hyperandrogenism. Due to its unique anti-inflammatory properties, vitamin D is thought to have a protective effect on cells when inflammation first begins. In addition, a change in the content of Ca^{2+} ions inside or outside the cell against the background of vitamin D deficiency has a negative effect on pancreatic β-cells and insulin secretion, leads to a violation of the activity of glucose transporters GLUT-4 and the development of insulin resistance. Insulin resistance

involving women with polycystic ovary syndrome with level 25(OH)D in blood serum <30 ng/ml showed more successful results in the regulation of the menstrual cycle in the case when vitamin D supplementation was performed along with metformin [14]. Systematic reviews indicate lower levels of 25(HE)D in females with polycystic ovary syndrome and on feedback between level 25(OH)D of blood and the severity of metabolic disorders in females who have polycystic ovary syndrome [15]. Meta-analyses of RCTs demonstrated the presence of a positive effect of vitamin D intake on follicle development and normalization of the menstrual cycle, but did not show an improvement in metabolic disorders [16], which justifies the expediency of combining vitamin D with myo-inositol.

Large studies also support the notion that polycystic ovarian syndrome severity and vitamin D insufficiency are related. Fertility indicators with vitamin inclusion are crucial since vitamin D deficiency is common and substantial in individuals with polycystic ovary syndrome, as well as in healthy women **(Table 1)** [17].

Table 1. Polycystic ovary syndrome and Vitamin D

Author's research	Type of Research	Focus group	The main conclusions about the correlation between vitamin D and polycystic ovary syndrome
Tavakoli *et al*. [18]	Cell line (human)	Endometrial samples (from females with repeated spontaneous abortion and a healthy control group)	When a woman experiences several miscarriages, vitamin D pills can be helpful. So, taking vitamin D supplements, the dominance of Th2 cytokines was seen with a decrease in the proliferation of inflammatory cytokines
Diaz *et al*. [19]	Cell line (human)	Full-term placenta samples (37-41 weeks of pregnancy with uncomplicated pregnancy)	Calcitriol supplements prevent the production of TNF-alpha, IL-6, and gamma-IFN - this is probably mediated by the vitamin D receptor apparatus (VDR)
Liu *et al*. [20]	Cell line (human)	Human trophoblastic cell lines from the collection of American-type tissue cultivation	In human trophoblast cells, vitamin D metabolites largely improve antibacterial reactions
Kuyucu *et al*.	Animal research	Prepubescent female rats, control group (n = 8), polycystic ovary syndrome group (n = 8) and polycystic ovary syndrome + D3 group (n = 8)	Treatment with vitamin D significantly reduced the thickness of the endometrium, epithelium, and stroma in patients with polycystic ovary syndrome, as well as pathological proliferation and apoptosis. Anti-Mullerian Hormone (AMH) was also reduced as a result of taking vitamin D supplements (this, however, did not reach the significance level)
Guo *et al*. [21]	Case-control study	Endometrial samples from women who underwent standardized IVF treatment (n = 16)	Increased expression of VDR in the endometrium contributes to the development of endometrial susceptibility (especially in the implantation window of the menstrual cycle) leads to pregnancy much more often
Zadeh-Vakili *et al*. [22]	Case-control study	Women with polycystic ovary syndrome (n = 260) and women with physiological cycles (n = 221)	The genetic variant of VDR is associated with the severity of clinical signs of polycystic ovary syndrome, but not with the risk of the disease itself
Aghadavod *et al*. [23]	Case-control study	Control group (n = 20 normal weights and n = 20 overweight); polycystic ovary syndrome group (n = 20 normal weight and n = 20 overweight)	Patients with overweight and polycystic ovarian syndrome had significantly reduced levels of vitamin D in their follicular fluid. The level of vitamin D in the follicular fluid strongly correlates with BMI. The expression of VDR in granulosa cells is significantly lower in patients with polycystic ovary syndrome/overweight than in those without polycystic ovary syndrome or with normal weight
Zhao *et al*. [24]	Case-control study	A total of 305 women were divided into four groups depending on the level of vitamin D in the blood serum	Optimal vitamin D levels raise clinical pregnancy rates and enhance the quality of the embryo
March *et al*. [25]	Retrospective cohort study	A total of 728 women who were born in the same maternity hospital in adulthood between 1973 and 1975 were tracked and interviewed (age = 27-34 years; n = 728)	Estimates of prevalence for Rotterdam and AES may be two times higher than those for NIH criteria: Many women with polycystic ovarian syndrome go undiagnosed or receive a late diagnosis
Pal *et al*. [26]	Retrospective cohort study (secondary analysis of randomized controlled trial data)	Participants of the randomized controlled trial "Pregnancy with polycystic ovary syndrome I" (n = 540) who met the diagnostic criteria of polycystic ovary syndrome of the National Institute of Health	In women with polycystic ovary syndrome, the level of vitamin D in the blood serum is an independent predictor of reproductive success after ovulation induction. The probability of ovulation correlates with the level of vitamin D in polycystic ovary syndrome. The reproductive threshold of serum vitamin D is higher than recommended for the non-pregnant population

Hahn *et al*. [27]	Prospective cohort study	Women with polycystic ovary syndrome (n = 120)	In polycystic ovary syndrome, insulin resistance negatively correlates with vitamin D levels
Pittas *et al*. [28]	Randomized controlled trial	Adult Caucasian women (n = 314)	Calcium and vitamin D supplementation may help older, healthy individuals with impaired fasting glucose (IFG) prevent the further development of insulin resistance

As for folic acid (vitamin B9), in several crucial metabolic processes required for the creation of DNA and RNA, it functions as a coenzyme. The methylation of homocysteine into the amino acid methionine requires vitamin B9 [29].
It is assumed that folic acid has antioxidant, antitumor, cardio- and neuroprotective features that may be useful in polycystic ovary syndrome, given the increased systemic oxidative stress in this cohort of women [29]. Moreover, folic acid supplementation can normalize the usually elevated homocysteine concentration seen in females who have polycystic ovary syndrome [30-32] and prevent the development of homocysteine, which positively affects the indicators of glycemic, inflammatory, and oxidative stress, as well as increase the overall antioxidant capacity of glutathione.

Conclusion

Polycystic ovary syndrome requires a multi-system approach in management. Polycystic ovary syndrome depends on many modifiable exogenous influences, including the correction of nutrition and elimination of deficiencies of micro- and macroelements in the body. This is especially true of vitamins such as D and B9, which have a very crucial role in metabolic reactions, the failure of which can induce the growth of polycystic ovary syndrome. It follows from this that a doctor and a patient with polycystic ovary syndrome should work together to control tests and eliminate deficiencies promptly.

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References

1. Patel S. Polycystic ovary syndrome (PCOS), an inflammatory, systemic, lifestyle endocrinopathy. J Steroid Biochem Mol Biol. 2018;182:27-36. doi:10.1016/j.jsbmb.2018.04.008
2. Glueck CJ, Goldenberg N. Characteristics of obesity in polycystic ovary syndrome: Etiology, treatment, and genetics. Metabolism. 2019;92:108-20. doi:10.1016/j.metabol.2018.11.002
3. Kataoka J, Larsson I, Björkman S, Eliasson B, Schmidt J, Stener-Victorin E. Prevalence of polycystic ovary syndrome in women with severe obesity - Effects of a structured weight loss programme. Clin Endocrinol (Oxf). 2019;91(6):750-8. doi:10.1111/cen.14098
4. Calcaterra V, Verduci E, Cena H, Magenes VC, Todisco CF, Tenuta E, et al. Polycystic Ovary Syndrome in Insulin-Resistant Adolescents with Obesity: The Role of Nutrition Therapy and Food Supplements as a Strategy to Protect Fertility. Nutrients. 2021;13(6):1848. doi:10.3390/nu13061848
5. Zhu T, Goodarzi MO. Causes and Consequences of Polycystic Ovary Syndrome: Insights from Mendelian Randomization. J Clin Endocrinol Metab. 2022;107(3):e899-e911. doi:10.1210/clinem/dgab757
6. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab. 2005;90(12):6364-9. doi:10.1210/jc.2005-1490
7. Szczuko M, Kikut J, Szczuko U, Szydłowska I, Nawrocka-Rutkowska J, Ziętek M, et al. Nutrition Strategy and Life Style in Polycystic Ovary Syndrome-Narrative Review. Nutrients. 2021;13(7):2452. doi:10.3390/nu13072452
8. Mu Y, Cheng D, Yin TL, Yang J. Vitamin D and Polycystic Ovary Syndrome: a Narrative Review. Reprod Sci. 2021;28(8):2110-7. doi:10.1007/s43032-020-00369-2
9. Miao CY, Fang XJ, Chen Y, Zhang Q. Effect of vitamin D supplementation on polycystic ovary syndrome: A meta-analysis. Exp Ther Med. 2020;19(4):2641-9. doi:10.3892/etm.2020.8525
10. Gao H, Li Y, Yan W, Gao F. The Effect of Vitamin D Supplementation on Blood Lipids in Patients with Polycystic Ovary Syndrome: A Meta-Analysis of Randomized Controlled Trials. Int J Endocrinol. 2021;2021:8849688. doi:10.1155/2021/8849688
11. Lee WL, Lee FK, Wang PH. Vitamin D and polycystic ovary syndrome. Taiwan J Obstet Gynecol. 2022;61(6):919-20. doi:10.1016/j.tjog.2022.06.010

12. Ostadmohammadi V, Jamilian M, Bahmani F, Asemi Z. Vitamin D and probiotic co-supplementation affects mental health, hormonal, inflammatory and oxidative stress parameters in women with polycystic ovary syndrome. J Ovarian Res. 2019;12(1):5. doi:10.1186/s13048-019-0480-x
13. Menichini D, Facchinetti F. Effects of vitamin D supplementation in women with polycystic ovary syndrome: a review. Gynecol Endocrinol. 2020;36(1):1-5. doi:10.1080/09513590.2019.1625881
14. Aldhafiri FK, Abdelgawad FE, Mohamed Bakri GM, Saber T. Insulin Resistance and Bone Metabolism Markers in Women with Polycystic Ovary Syndrome: A Cross-Sectional Study on Females from the Islamic University Medical Center. Medicina (Kaunas). 2023;59(3):593. doi:10.3390/medicina59030593
15. Zhang N, Liao Y, Zhao H, Chen T, Jia F, Yu Y, et al. Polycystic ovary syndrome and 25-hydroxyvitamin D: A bidirectional two-sample Mendelian randomization study. Front Endocrinol (Lausanne). 2023;14:1110341. doi:10.3389/fendo.2023.1110341
16. Moin ASM, Sathyapalan T, Butler AE, Atkin SL. Classical and alternate complement factor overexpression in non-obese weight matched women with polycystic ovary syndrome does not correlate with vitamin D. Front Endocrinol (Lausanne). 2022;13:935750. doi:10.3389/fendo.2022.935750
17. Várbíró S, Takács I, Tűű L, Nas K, Sziva RE, Hetthéssy JR, et al. Effects of Vitamin D on Fertility, Pregnancy and Polycystic Ovary Syndrome-A Review. Nutrients. 2022;14(8):1649. doi:10.3390/nu14081649
18. Tavakoli M, Jeddi-Tehrani M, Salek-Moghaddam A, Rajaei S, Mohammadzadeh A, Sheikhhasani S, et al. Effects of 1,25(OH)2 vitamin D3 on cytokine production by endometrial cells of women with recurrent spontaneous abortion. Fertil Steril. 2011;96(3):751-7. doi:10.1016/j.fertnstert.2011.06.075
19. Díaz L, Noyola-Martínez N, Barrera D, Hernández G, Avila E, Halhali A, et al. Calcitriol inhibits TNF-alpha-induced inflammatory cytokines in human trophoblasts. J Reprod Immunol. 2009;81(1):17-24. doi:10.1016/j.jri.2009.02.005
20. Liu N, Kaplan AT, Low J, Nguyen L, Liu GY, Equils O, et al. Vitamin D induces innate antibacterial responses in human trophoblasts via an intracrine pathway. Biol Reprod. 2009;80(3):398-406. doi:10.1095/biolreprod.108.073577
21. Kuyucu Y, Çelik LS, Kendirlinan Ö, Tap Ö, Mete UÖ. Investigation of the uterine structural changes in the experimental model with polycystic ovary syndrome and effects of vitamin D treatment: An ultrastructural and immunohistochemical study. Reprod Biol. 2018;18(1):53-9. doi:10.1016/j.repbio.2018.01.002
22. Guo J, Liu S, Wang P, Ren H, Li Y. Characterization of VDR and CYP27B1 expression in the endometrium during the menstrual cycle before embryo transfer: implications for endometrial receptivity. Reprod Biol Endocrinol. 2020;18(1):24. doi:10.1186/s12958-020-00579-y
23. Aghadavod E, Mollaei H, Nouri M, Hamishehkar H. Evaluation of Relationship between Body Mass Index with Vitamin D Receptor Gene Expression and Vitamin D Levels of Follicular Fluid in Overweight Patients with Polycystic Ovary Syndrome. Int J Fertil Steril. 2017;11(2):105-11. doi:10.22074/ijfs.2017.4704
24. Zhao J, Liu S, Wang Y, Wang P, Qu D, Liu M, et al. Vitamin D improves in-vitro fertilization outcomes in infertile women with polycystic ovary syndrome and insulin resistance. Minerva Med. 2019;110(3):199-208. doi:10.23736/S0026-4806.18.05946-3
25. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25(2):544-51. doi:10.1093/humrep/dep399
26. Pal L, Zhang H, Williams J, Santoro NF, Diamond MP, Schlaff WD, et al. Vitamin D Status Relates to Reproductive Outcome in Women with Polycystic Ovary Syndrome: Secondary Analysis of a Multicenter Randomized Controlled Trial. J Clin Endocrinol Metab. 2016;101(8):3027-35. doi:10.1210/jc.2015-4352
27. Hahn S, Haselhorst U, Tan S, Quadbeck B, Schmidt M, Roesler S, et al. Low serum 25-hydroxyvitamin D concentrations are associated with insulin resistance and obesity in women with polycystic ovary syndrome. Exp Clin Endocrinol Diabetes. 2006;114(10):577-83. doi:10.1055/s-2006-948308
28. Asbaghi O, Ashtary-Larky D, Bagheri R, Moosavian SP, Olyaei HP, Nazarian B, et al. Folic Acid Supplementation Improves Glycemic Control for Diabetes Prevention and Management: A Systematic Review and Dose-Response Meta-Analysis of Randomized Controlled Trials. Nutrients. 2021;13(7):2355. doi:10.3390/nu13072355
29. Alesi S, Ee C, Moran LJ, Rao V, Mousa A. Nutritional Supplements and Complementary Therapies in Polycystic Ovary Syndrome. Adv Nutr. 2022;13(4):1243-66. doi:10.1093/advances/nmab141
30. Kamrul-Hasan A, Aalpona FTZ. Comparison of Serum Vitamin B12 Levels Among Drug-Naïve and Metformin-Treated Patients With Polycystic Ovary Syndrome. Cureus. 2022;14(10):e30447. doi:10.7759/cureus.30447
31. Ku CW, Ku CO, Tay LPC, Xing HK, Cheung YB, Godfrey KM, et al. Dietary Supplement Intake and Fecundability in a Singapore Preconception Cohort Study. Nutrients. 2022;14(23):5110. doi:10.3390/nu14235110
32. Cowan S, Lim S, Alycia C, Pirotta S, Thomson R, Gibson-Helm M, et al. Lifestyle management in polycystic ovary syndrome - beyond diet and physical activity. BMC Endocr Disord. 2023;23(1):14. doi:10.1186/s12902-022-01208-y