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Vitamin D and female reproductive health

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SUMMARY

The conventional mechanism of vitamin D bioactivity involves its impact on calcium–phosphate metabolism. Homeostasis in the levels of these two elements warrants undisturbed functioning of the nervous system and normal mineral bone density. Results of numerous investigations have confirmed that vitamin D affects reproductive processes in both males and females. The fact that the number of pregnancies, also those after IVF, is strictly correlated with a season of the year supports this claim. Also, high-latitude countries are characterized by lower ovulation parameters and higher incidence of endometriosis. Moreover, the concentration of calcitriol impacts the clinical course of polycystic ovary syndrome and the development of gestational diseases, i.e. gestational diabetes mellitus or pre-eclampsia. Moreover, an appropriate level of vitamin D has an influence of the regulation of the respiratory system: regular cycles and oocyte maturation. By reinforcing the action of gonadotropin, a hormone that regulates ovarian function, vitamin D3 has a direct effect on enhancing fertility.

Key words: vitamin D, reproductive health, women

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INTRODUCTION

Vitamin D has undoubtedly become the most "trendy" vitamin of the past decade. Is this rightly so? Its action and effects of deficiency raise more and more scientific interest. Numerous studies suggest that this deficiency affects bones, but can also constitute a significant factor in the development of infections, autoimmune cardiac diseases, neurological and mental conditions, and cancer. More and more reports are appearing concerning substantial importance of vitamin D in male and female reproductive health.

Vitamin D is a group of organic compounds whose precursors are cholecalciferol (vitamin D3) in animals and ergocalciferol in plants and fungi (vitamin D2). Provitamin D3 (7-dehydrocholesterol) is present in epidermal keratinocytes and dermal fibroblasts [1]. Provitamin D3 undergoes photochemical reactions under ultraviolet B radiation, the product of which is cholecalciferol [2]. It has been determined that the intensity of this process depends on geographical latitude, duration and degree of radiation exposure, time of the day and year, exposed body area, race and type of complexion as well as the level of air pollution and the degree of cloud cover [3,4]. Moreover, anthropometric parameters, such as body weight or the amount of fat tissue, are also significant. Leptin, produced in the adipose tissue, may contribute to a decrease in the intensity of vitamin D transformation to its biologically active metabolites [5,6].

The biological activity of vitamin D begins with its double hydroxylation in the liver and kidneys. Cholecalciferol and ergocalciferol are transported to the liver where they undergo the first reaction to bind hydroxyl groups. This leads to the production of 25-hydroxycholecalciferol (25(OH)D3, calcidiol). 25-hydroxylase dependent upon cytochrome P450 (CYP27A1) is a catalyst of this process. The intensity of the reaction also depends on the vitamin D intake in diet and with therapeutic agents, thus being

a biochemical marker of vitamin D requirement. The biological activity of calcidiol is still low, i.e. approximately 1.5 times higher than that of cholecalciferol [7–9]. The final activity is conferred through renal hydroxylation stimulated by calcium and phosphate concentrations, and thus by parathyroid hormone and CYP27B1 [10]. The reaction is inhibited by hydroxylation products. One of them, 1á,25 dihydroxycholecalciferol (1α,25(OH)2D3, calcitriol), exerts biological activity that is almost a thousand times higher than that of calcidiol with a short half-life (4–6 hours) [11–14].

The biological activity of calcitriol directly results from the interaction of this compound with nuclear vitamin D receptors (VDRs) and retonoid X receptors (RXRs). In the receptor mechanism, vitamin D also regulates the expression of numerous (over 200) genes, the products of which are responsible essentially for calcium and phosphate regulation. These include osteopontin, calcium-binding proteins, such as calbindin or vanilloid receptor, which is a channel that removes calcium from cells, osteoblastogenesis-promoting lipoprotein receptor-related protein 5 and receptor activator for nuclear factor κ B ligand that has a positive influence on bone resorption through osteoclastogenesis [15]. Moreover, the process of 1α-hydroxylation occurs not only in the kidneys, but also in macrophages, keratinocytes, placenta, parathyroid glands, vascular smooth muscle or cancer cells. Vitamin D receptors are distributed also beyond the target tissues. This makes vitamin D affect various physiological processes in the human body [2,11,13,14,16–19]. It has been proven that calcitriol is a cell proliferation mediator and immune response modulator [20]. The results of various studies have confirmed that vitamin D deficiency, which is encountered especially in people living farther from the equator, is associated with higher incidence of autoimmune conditions, cancers and cardiovascular diseases [21–23].

Serum 25(OH)D levels should range from 30 to 40 ng/mL, which is optimal. The concentration below 20 ng/mL signifies a deficiency, while levels below 10 ng/mL indicate substantial vitamin D deficiency [24].

MULTIDIRECTIONAL VITAMIN D ACTION

The conventional mechanism of vitamin D bioactivity involves its impact on calcium–phosphate metabolism. Homeostasis in the levels of these two elements warrants undisturbed functioning of the nervous system and normal mineral bone density. Vitamin D is essential for calcium absorption in the bowel and for osteoclast stimulation. It also mobilizes bone calcium when the dietary intake of this element is insufficient. Furthermore, it has positive effects on calcium reabsorption in the kidneys, bone calcium mobilization and calcitriol synthesis, and negative effects on phosphate reabsorption [12,25–29].

Vitamin D has an influence on proliferation and differentiation of immune cells and on endothelial function [30]. VDRs are present on activated T and B cells, neutrophils, macrophages and dendritic cells [11]. The expression of the cytochrome p450 gene, CYP27B1, has been confirmed on monocytes and macrophages [20]. It has also been proven that the activity of the enzyme that it encodes is not dependent on calcium, but on an inflammatory response-triggering stimulus [31].

In vitro studies have revealed that vitamin D inhibits cytokine Th1 production, but promotes Th2 cytokine synthesis. Additionally, calcitriol limits the expression of the gene that encodes interleukin-17, which is produced by these cells. As Hewinson states [32], vitamin D directly acts on B cells, having an inhibitory effects on plasma cells, immunoglobulin class switching and differentiation into memory cells. On the other hand, there is a positive relationship between vitamin D levels and the number and activity of TREG cells that restrict excessive inflammatory responses in patients with renal disease and multiple sclerosis [32]. Hypovitaminosis D is also associated with the risk of other autoimmune diseases, such as type 1 diabetes mellitus, rheumatoid arthritis or primary sclerosing cholangitis [33]. The literature also contains reports corroborating the contribution of vitamin D to the shaping of innate immunity, mainly by acting through toll-like receptors (TLR). It has been shown that vitamin D stimulates TLR2 of monocytes, thereby leading to interleukin-15 production, CYP27B1 induction, vitamin D receptor expression and transcription of the *LL37* gene that encodes antibacterial protein [34].

FEMALE RESPIRATORY SYSTEM

In the 1980s, it was noticed that vitamin D deficiency in female animals reduces fertility and restricts desired mating behaviors [35]. Also, women at risk of hypovitaminosis D have few-

er children, and the risk of ovulation disorders and endometriosis increases [36]. Vitamin D receptors are found in tissues composing female reproductive structures. It has been confirmed that VDRs are present in ovaries (granulosa cells of the cumulus oophorus), endometrium and tubal epithelial cells, and their expression increases during pregnancy [37–40]. VDRs have also been found in the pituitary gland [30]. VDR gene knockout mice displayed hypergonadotropic hypogonadism, ovulation disorders and uterine hypoplasia [38]. Similar observations have been derived from studies on CYP27B1 -/- animal models [41]. In both cases, changes were partially reversible upon implementation of diet that secured calcium and phosphorus ions, thus restoring the function of the hypothalamic–pituitary–gonadal axis. Wojtusik and Johnson [42] recount that calciferol stimulates the production of steroid hormones (progesterone, estradiol and estrone) in the ovary. As in the male reproductive system, this is linked with the effects of vitamin D on aromatase activity and intracellular calcium concentration [43]. At the same time, experimental studies have demonstrated that vitamin D induces, via the receptor mechanism, the transcription of dehydroepiandrosterone sulphotransferase (DHEAS), an enzyme that participates in the conjugation of endogenous hydroxysteroids with sulfuric acid, which results in DHEAS formation [44].

Both VDR and CYP27B1 activity has been observed *in vitro* in syncytiotrophoblast tissue cultures [45]. It has been shown that 1,25(OH)2D3, through its immunosuppressive properties, co-participates in the formation and maintenance of the fetal–placental unit. Vitamin D regulates *HOXA10* expression, the product of which is critical for the development of the uterus and endometrium as well as further implantation processes [46]. It has also been noticed that pregnancy is dominated by the regulatory action of vitamin D on lactogen synthesis in the placenta, production and release of human chorionic gonadotropin, placental calcium ion transport and endometrial decidualization [47]. In studies conducted in the group of women undergoing IVF, it has been demonstrated that the serum calcitriol level is strongly correlated with the estradiol concentration during ovarian stimulation [48]. Similar vitamin D levels in the follicular fluid, particularly low and moderate (20 and 21–30 ng/mL, respectively), may be markers of IVF success.

CLINICAL IMPLICATIONS OF VITAMIN D METABOLISM DISORDERS IN THE FEMALE REPRODUCTIVE SYSTEM

Vitamin D shows pleiotropic effects in the human body. Also, its impact on the reproductive system is unquestionable. The results of various studies have shown that calcitriol metabolism disorders are involved in the etiopathogenesis and clinical course of gynecologic and obstetric conditions [49].

ENDOMETRIOSIS

Endometriosis is one of the main endocrine diseases. It affects up to 10% of women of childbearing age. The inflammatory factor is thought to play the main role in this condition [36]. Indeed, immune system dysfunction associated with a defect in the detection and elimination of fragments of the endometrium beyond the peritoneal cavity is one of the etiopathogenic factors of the disease [50]. The literature states that vitamin D may exert anti-inflammatory action by being a mediator of immune processes in the presence of nuclear factor-?? or mitogen-activated protein kinase (MAPK), thus inhibiting the production of proinflammatory cytokines. In activated CD4+ and CD8+ cells as well as macrophages and dendritic cells, VDRs and vitamin D-activating and -metabolizing hydroxylases become active [51]. Additionally, as presented earlier, vitamin D receptors and 1á-hydroxylase are produced in endometrial cells [3,41,52]. Other authors believe that an abnormal vitamin D level in women with endometriosis has a negative effect on genome methylation and transcription repression [53].

The team of Agic et al. [38] demonstrated that women with endometriosis had enhanced (as compared with healthy women) activity of VDRs and vitamin D hydroxylase in the endometrium, even though the numbers of produced proteins showed no significant differences on the cellular level. Somigliana et al. [54] carried out a study involving 87 patients with endometriosis and 53 healthy women, and concluded that high vitamin D levels reduce the risk of the disease significantly. Besides, it was found that the 25(OH)D concentration increases with the advancement of the pathologic process. Vigano et al. [52] observed VDR and 1α-hydroxylase activity in both orthotopic and ectopic endometrium, and showed that the quantity of mRNA for the hydroxylating en-

zyme was significantly higher in patients with endometriosis. Harris et al. [55] reported that serum vitamin D levels above the highest quintile were linked with a 24% lower risk of endometriosis as compared with women displaying vitamin D levels in the lowest quintile. Faserl et al. [56] stated that the amount of vitamin D-binding protein (VDBP) more or less tripled in patients compared with healthy volunteers. Borkowski et al. [57] found that the total VDBP concentration in the serum and peritoneal fluid was not significantly different between patients and healthy women. However, the serum protein level was higher in women with more advanced forms of endometriosis. Ferrero et al. [58] determined that the concentration of protein E was higher in the peritoneal fluid of women with untreated endometriosis compared with healthy individuals. The scientists have also found that VDBP activity is independent of disease advancement and stage of the menstrual cycle. Moreover, there are studies that illustrate the effects of changes in genes coding vitamin D signaling pathway proteins on endometriosis. Vilarino et al. [59] recruited 132 women with infertility due to endometriosis, 62 patients with idiopathic infertility and 132 healthy women. The aim of their study was to assess the frequency of VDR Fok1 polymorphism. The authors did not note any significant changes in the distribution of this alteration. In the study already quoted above, Faserl et al. [56] showed that VDBP GC*2 polymorphism was more common in patients with endometriosis. This may be a consequence of the fact that carriers of this alteration are characterized by insufficient activity of the macrophage phagocytic function. Szczepańska et al. [60] evaluated the prevalence of the following polymorphisms in patients with endometriosis: VDBG rs1155563, rs2298849 and rs7041; RXRA rs10881578, rs10776909 irs749759; VDR BsmI rs1544410 and FokI rs2228570. They did not note any significant links between the carrier status of these changes and endometriosis, but found that the A-T haplotype of VDR rs1544410 and rs222857 was associated with over 1.6 times greater probability of endometriosis-associated infertility.

POLYCYSTIC OVARY SYNDROME

The results of various studies suggest that vitamin D may be involved in the etiopathogenesis and clinical course of PCOS. Although a study of Chavarro et al. [61], conducted among 18,555 married perimenopausal women who tried to get pregnant or were pregnant in the 8 years preceding the study, showed no association between exogenous vitamin D and infertility due to ovulation disorders, medical literature does include a list of examples linking vitamin D with the metabolic determinant of PCOS. Vitamin D is involved in autocrine insulin secretion, thereby playing a role in the pathogenesis of metabolic disturbances. These observations are valid both for women without gynecologic diseases and for PCOS patients. Moreover, there are studies that support the beneficial action of vitamin D on insulin receptor expression and thus on intensification of insulin response [62]. Wehr et al. [63] observed that exogenous vitamin D3 intake at a dose of 50,000 IU weekly for 24 weeks improved carbohydrate metabolism parameters and the course of the menstrual cycle.

UTERINE MYOMAS

Women with vitamin D levels in normal ranges are less prone to developing myomas. Animal studies have revealed that vitamin D3 reduces the size of uterine myomas by decreasing MMP expression [64, 65].

GESTATIONAL DIABETES MELLITUS

As has been mentioned above, vitamin D plays a role in the pathogenesis of type II diabetes mellitus. 1,25(OH)2D induces insulin secretion and decreases the degree of insulin resistance [66]. Maghbooli et al. [67] investigated 741 pregnant women and observed critically low vitamin D levels (<5 ng/mL) in women with GDM. The team demonstrated the existence of a strong negative correlation between serum vitamin D concentration and the HOMA index. Zhang et al. [68] also observed vitamin D deficiency in 1/3 of the studied GDM patients. They concluded that a decrease in the serum 25(OH)D level by each 5 ng/mL raises the risk of GDM by nearly 30%. Zuhur et al. [68] confirmed that vitamin D deficiencies are significantly linked with GDM, irrespective of the mother's age, race, positive history for diabetes and body mass index from before pregnancy.

PRE-ECLAMPSIA

Pre-eclampsia (PE) is a multiple organ disease manifested by hypertension and proteinuria after week 20 of gestation. PE concerns approximately 7% of pregnant women worldwide [69]. Vitamin D deficiency is a common find-

ing in pre-eclampsia patients. Its deficiencies have been confirmed in both the preconception period and during pregnancy, but less frequently in the sunny months. It has been found that vitamin D levels that are lower than 20 ng/mL double the risk of pre-eclampsia. Moreover, in the second half of pregnancy, there is a linear association between the disease and vitamin D concentration. According to Bodnar et al. [70], a low 25(OH)D concentration before week 22 of gestation is an evident risk factor for PE. Zehnder et al. [71] believe that intensive VDR and 1α-hydroxylase expression in the placenta can be observed especially in the first and second trimesters of pregnancy, and consequently hypovitaminosis D may play a role in the etiopathogenesis of preeclampsia of early onset. Exogenous vitamin D has a positive impact on the risk of PE. It has also been observed that intervention in women maintaining a diet to secure vitamin D reserves lowers the risk of eclampsia by over 30%. Pregnant women in Norway who used vitamin D supplementation of 400–600 IU daily had a risk lower by 27% [72].

CONCLUSION

The current investigations on the relevance of vitamin D in infertility associated with polycystic ovary syndrome, uterine myomas, lower semen parameters and IVF treatment as well as in pregnancy support its significant role in reproductive processes and underline the need to correct deficiencies in the preconception period. According to the recommendations, vitamin D levels should be maintained at a level of 30–50 ng/mL. These levels are needed for proper functioning of each of the systems as well as for maternal and fetal health.

REFERENCES

1. **Armas LA, Dowell S, Akhter M et al.** Ultraviolet-B radiation increases serum 25-hydroxyvitamin D levels: the effect of UVB dose and skin color. *J Am Acad Dermatol* 2007 Oct; 57(4):588-593. Epub 2007 Jul 16.
2. **Dittfeld A, Gwizdek K, Koszowska A, Fizia K.** Wielokierunkowe działanie witaminy D. *Ann Acad Med Siles* 2014;68(1):47–52.
3. **Grant WB, Holick MF.** Benefits and requirements of vitamin D for optimal health: A review. *Altern Med Rev* 2005 Jun;10(2):94-111.
4. **Cuomo RE, Garland CF, Gorham ED, Mohr SB.** Low Cloud Cover-Adjusted Ultraviolet B Irradiance Is Associated with High Incidence Rates of Leukemia: Study of 172 Countries. *PLoS One* 2015 Dec 4;10(12):e0144308. doi: 10.1371/journal.pone.0144308. eCollection 2015.
5. **Maetani M, Maskarinec G, Franke AA, Cooney RV.** Association of leptin, 25-hydroxyvitamin D, and parathyroid hormone in women. *Nutr Cancer* 2009;61(2):225-31. doi: 10.1080/01635580802455149.
6. **Karonova T, Belyaeva O, Jude EB et al.** Serum 25(OH)D and adipokines levels in people with abdominal obesity. *J Steroid Biochem Mol Biol* 2016 Sep 11. pii: S0960-0760(16)30241-2.
7. **Hollis BW.** Assessment and interpretation of circulating 25-hyÑdroxyvitamin D and 1,25-dihydroxyvitamin D in the clinical environment. *Rheum Dis Clin North Am* 2012 Feb;38(1):29-44. doi: 10.1016/j.rdc.2012.03.005. Epub 2012 Apr 12.
8. **Chung M, Balk EM, Brendel M et al.** VitaÑmin D and calcium: a systematic review of health outcomes. *Evid Rep Technol Assess* (Full Rep) 2009 Aug;(183):1-420.
9. **Cannell JJ, Hollis BW.** Use of vitamin D in clinical practice. *Altern Med Rev* 2008 Mar;13(1):6-20.
10. **Henry HL.** Regulation of vitamin D metabolism. *Best Pract Res Clin Endocrinol Metab* 2011;25:531–541.
11. **DeLuca HF**. Overview of general physiologic features and functions of vitamin D. *Am J Clin Nutr* 2004;80:1689S-1696S.
12. **Lips P.** Vitamin D physiology. *Prog Biophys Mol Biol* 2006;92:4–8.
13. **Bikle DD.** Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol 2014 Mar 20;21(3): 319-29. doi: 10.1016/j.chembiol.2013.12.016. Epub 2014 Feb 13.
14. **Grygiel-Górniak B, Puszczewicz M.** Witamina D- nowe spojrzenie w medycynie i reumatologii. *Postępy Hig Med Dosw* 2014;68:359-368.
15. **Haussler MR, Jurutka PW, Mizwicki M, Norman AW.** Vitamin D receptor (VDR)-mediated actions of 1a, 25(OH)2vitamin D3: genomic and non-genomic mechanisms. *Best Pract Res Clin Endocrinol Metab* 2011;25:543–559.
16. **Stumpf WE, Sar M, Reid FA et al.** Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidÑney, skin, pituitary, and parathyroid. *Science* 1979 Dec 7;206 (4423):1188-1190.
17. **Alpert PT, Shaikh U.** The effects of vitamin D deficiency and insufficiency on the endocrine and paracrine systems. *Biol Res Nurs* 2007;9:117-129.
18. **Olędzka R.** Witamina D w świetle badań ostatnich lat. *Bromat Chem Toksykol* 2013;XLVI, 2:121-131.
19. **Norman AW.** From vitamin D to hormone: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr* 2008;88:491S-499S.
20. **Bouillon R, Carmeliet G, Verlinden L et al.** Vitamin D and human health: lessons from vitamin D receptor null mice. *Endocr Rev* 2008;29:726-776.
21. **Yee YK, Chintalacharuvu SR, Lu J, Nagpal S.** Vitamin D reÑceptor modulators for inflammation and cancer. *Mini Rev Med Chem.* 2005 Aug;5(8):761-778.
22. **Ahn J, Peters U, Albanes D et al.** Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial Project Team. Serum vitamin D concentration and prostate cancer risk: a nested case-control study. *J Natl Cancer Inst.* 2008 Jun 4;100(11):796-804. doi: 10.1093/jnci/djn152.
23. **Myszka M, Klinger M.** Immunomodulacyjne działanie witaminy D. *Postępy Hig Med Dosw* 2014;68:865-878.
24. **Oszukowski P, Spaczyński M, Nowak-Markwitz E, Karowicz-Bilińska A, Opala T, Wielgoś M.** Recommendations of the Polish Gynecological Society concerning application of D-Vitum forte *Ginekol Pol.* 2014, 85, 968-970.
25. **Williams S, Seidner DL.** Metabolic bone disease in gastrointestinal illness. *Gastroenterol Clin North Am* 2007; 361:161–190.

26. **Murray R, Granner D, Rodwell V** (Eds). Biochemia Harpera ilustrowana. Wydawnictwo Lekarskie PZWL, Warszawa 2008.
27. **Lieben L, Carmeliet G, Masuyama R.** Calcemic actions of vitamin D: effects on the intestine, kidney and bone. *Best Pract Res Clin Endocrinol Metab* 11;25:561–572.
28. **Veldurthy V, Wei R, Oz L et al.** Vitamin D, calcium homeostasis and aging. *Bone Res* 2016 Oct 18;4:16041.
29. **Hansen KE, Johnson MG.** An update on vitamin D for clinicians *Curr Opin Endocrinol Diabetes Obes* 2016 Dec; 23(6):440-444.
30. **Pérez-Hernández N, Aptilon-Duque G, Nostroza-Hernández MC et al.** Vitamin D and its effects on cardiovascular diseases: a comprehensive review. *Korean J Intern Med* 2016 Nov;31(6):1018-1029. Epub 2016 Apr 27.
31. **Overbergh L, Stoffels K, Waer M et al.** Immune regulation of 25-hydroxyvitamin D-1á-hydroxylase in human monocytic THP1 cells: mechanisms of interferon-gmeÑdiated induction. *J Clin Endocrinol Metab.* 2006 Sep;91(9):3566-3574. Epub 2006 Jun 20.
32. **Hewison M.** An update on vitamin D and human immunity. Clin Endocrinol (Oxf) 2012;76:315–325.
33. **Rosen Y, Daich J, Soliman I et al.** Vitamin D and autoimmunity. *Scand J Rheumatol* 2016 Nov;45(6):439-447. Epub 2016 May 18.
34. **Bacchetta J, Salusky IB, Hewison M.** Beyond mineral metabolism, is there an interplay between FGF23 and vitamin D in innate immunity? *Pediatr Nephrol* 2013; 28:577–582.
35. **Halloran BP, DeLuca HF**: Effect of vitamin D deficiency on fertility and reproductive capacity in the female rat. *J Nutr* 1980;110(8):1573-1580.
36. **Anagnostis P, Karras S, Goulis DG.** Vitamin D in human reproduction: a narrative review. *Int J Clin Pract* 2013 Mar;67(3):225-235. doi: 10.1111/ijcp.12031. Epub 2013 Jan 7.
37. **Avila E, Dýaz L, Halhali A, Larrea F.** Regulation of 25-hydroxyvitamin D3 1alpha hydroxylase, 1,25-dihydroxyvitamin D3 24-hydroxylase and vitamin D receptor gene expression by 8-bromo cyclic AMP in cultured human syncytiotrophoblast cells. *J Steroid Biochem Mol Biol* 2004;89-90:115–119.
38. **Agic A, Xu H, Altgassen C et al.** Relative expression of 1,25-dihydroxyvitamin D3 receptor, vitamin D 1a-hydroxylase, vitamin D 24-hydroxylase, and vitamin D 25-hydroxylase in endometriosis and gynecologic cancers. *Reprod Sci* 2007;14:486–497. doi:10.1177/1933719107304565.
39. **Parikh G, Varadinova M, Suwandhi P et al.** Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. *Horm Metab Res* 2010;42:754–757.
40. **Zarnani AH, Shahbazi M, Salek-Moghaddam A.** Vitamin D3 receptor is expressed in the endometrium of cycling mice throughout the estrous cycle. *Fertil Steril* 2010; 93: 2738–2743.
41. **Lerchbaum E, Obermayer-Pietsch B.** Vitamin D and fertility: a systematic review. *Eur J Endocrinol* 2012 May;166(5):765-778. doi: 10.1530/EJE-11-0984. Epub 2012 Jan 24.
42. **Wojtusik J, Johnson PA.** Vitamin D regulates antimullerian hormone expression in granulosa cells of the hen. *Biol Reprod.* 2012 Mar 30;86(3):91. doi: 10.1095/biolreprod.111.094110. Print 2012 Mar.
43. **Kinuta K, Tanaka H, Moriwake T et al.** Vitamin D is an important factor in estrogen biosynthesis of both female and male gonads. *Endocrinology* 2000;141:1317- 1324. doi:10.1210/en.141.4.1317.
44. **Echchgadda I, Song CS, Roy AK, Chatterjee B.** Dehydroepiandrosterone sulfotransferase is a target for transcriptional induction by the vitamin D receptor. *Mol Pharmacol* 2004;65:720–729.
45. **Tuan RS, Moore CJ, Brittingham JW et al.** In vitro study of placental trophoblast calcium uptake using JEG-3 human choriocarcinoma cells. *J Cell Sci* 1991;98:333–342.
46. **Bagot CN, Troy PJ, Taylor HS.** Alteration of maternal Hoxa10 expression by in vivo gene transfection affects implantation. *Gene Ther* 2000;7:1378–1384. doi:10.1038/sj.gt.3301245.
47. **Barrera D, Avila E, Hernandez G et al.** Calcitriol affects hCG gene transcription in cultured human syncytiotrophoblasts. *Reprod Biol Endocrinol* 2008;6:3.
48. **Wehr E, Pilz S, Boehm** BO **et al.** Association of vitamin D status with serum androgen levels in men. *Clin Endocrinol (Oxf)* 2010;73(2):243-248.
49. **Colonese F, Laganà AS, Colonese E et al.** The pleiotropic effects of vitamin D in Gynaecological and obstetric diseases: an overview on a Hot topic. *Biomed Res Int* 2015;2015:986281. doi: 10.1155/2015/986281. Epub 2015 Apr 27.
50. **Sturlese E, Salmeri FM, Retto G et al.** Dysregulation of the Fas/FasL system in mononuclear cells recovered from peritoneal fluid of women with endometriosis. *J Reprod Immunol* 2011 Dec;92(1-2):74-81. doi: 10.1016/j.jri.2011.08.005. Epub 2011 Oct 5.
51. **Baeke F, Etten EV, Overbergh L, Mathieu C.** Vitamin D3 and the immune system: maintaining the balance in health and disease. *Nutr Res Rev* 2007 Jun;20(1):106-118. doi: 10.1017/S0954422407742713.
52. **Vigano P, Lattuada D, Mangioni S et al.** Cycling and early pregnant endometrium as a site of regulated expression of the vitamin D system. *J Mol Endocrinol* 2006; 36: 415–425.
53. **Zelenko Z, Aghajanova L, Irwin JC, Giudice LC.** Nuclear receptor, co regulator signalling, and chromatin remodelling pathways suggest involvement of the epigenome in the steroid hormone response of endometrium and abnormalities in endometriosis. *Reprod Sci* 2012;19:152–162.
54. **Somigliana E, Panina-Bordignon P, Murone S et al.** Vitamin D reserve is higher in women with endometriosis. *Hum Reprod* 2007 Aug;22(8):2273-2278.
55. **Harris HR, Chavarro JE, Malspeis S et al.** Dairy-food, calcium, magnesium, and vitamin D intake and endometriosis: a prospective cohort study. *Am J Epidemiol* 2013 Mar 1;177(5):420-430. doi: 10.1093/aje/kws247.
56. **Faserl K, Golderer G, Kremser L et al.** Polymorphism in vitamin D-binding protein as a genetic risk factor in the pathogenesis of endometriosis. *J Clin Endocrinol Metab* 2011 Jan;96(1):E233-241. doi: 10.1210/jc.2010-1532.
57. **Borkowski J, Gmyrek GB, Madej JP et al.** Serum and peritoneal evaluation of vitamin D-binding protein in women with endometriosis. *PHMD* 2008;62:103–111.
58. **Ferrero S, Gillott DJ, Anserini P et al.** Vitamin D binding protein in endometriosis. *J Soc Gynecol Investig* 2005 May;12(4):272-277.
59. **Vilarino FL, Bianco B, Lerner TG et al.** Analysis of vitamin D receptor gene polymorphisms in women with and without endometriosis. *Hum Immunol* 2011;72:359–363. doi:10.1016/j.humimm.2011.01.006.
60. **Szczepańska M, Mostowska A, Wirstlein P et al.** Polymorphic variants in vitamin D signaling pathway genes and the risk of endometriosis-associated infertility. *Mol Med Rep* 2015 Nov;12(5):7109-15.doi: 10.3892/mmr. 2015.4309.
61. **Chavarro JE, Rich-Edwards JW, Rosner B, Willett WC.** A prospective study of dairy foods intake and anovulatory infertility. *Hum Reprod* 2007 May;22(5):1340-1347.
62. **Pittas AG, Dawson-Hughes B.** Vitamin D and diabetes. *Steroid Biochem Mol Biol* 2010;121:425-429.
63. **Wehr E, Trummer O, Giuliani A et al.** Vitamin D-associated polymorphisms are related to insulin resistance and vitamin D deficiency in polycystic ovary syndrome. *Eur J Endocrinol* 2011b;164:741–749. doi:10.1530/EJE-11-0134.
64. **Brakta S, Diamond JS, Al-Hendy A et al.** Role of vitamin D in uterine fibroid biology. *Fertil Steril* 2015; 104: 698–706 4.
65. **Al-Hendy A, Badr M.** Can vitamin D reduce the risk of uterine fibroids? *Women's Health* 2014 Jul; 10(4): 353–358.

66. **Spoto B, Pisano A, Zoccali C.** Insulin resistance in chronic kidney disease: a systematic review. *Am J Physiol Renal Physiol* 2016 Oct 5: ajprenal.00340.2016.
67. **Maghbooli Z, Hossein-Nezhad A, Karimi F et al.** Correlation between vitamin D3 deficiency and insulin resistance in pregnancy. *Diabetes Metab Res Rev* 2008 Jan-Feb;24(1):27-32.
68. **Zuhur SS, Erol RS, Kuzu I, Altuntas Y.** The relationship between low maternal serum 25- hydroxyvitamin D levels and gestational diabetes mellitus according to the severity of 25 hydroxyvitamin D deficiency. Clinics (Sao Paulo). 2013 May;68(5):658-64. doi: 10.6061/clinics/2013 (05)13.
69. **Lee JH, O'Keefe JH, Bell D et al.** Vitamin D deficiency an important, common, and easily treatable cardiovascular risk factor? *J Am Coll Cardiol* 2008 Dec 9;52(24):1949-56. doi: 10.1016/j.jacc.2008.08.050.
70. **Bodnar LM, Catov JM, Simhan HN et al.** Maternal Vitamin D Deficiency Increasesthe Risk of Preeclampsia. *J Clin Endocrinol Metab* 2007;92:3517-3522.
71. **Zehnder D, Evans KN, Kilby MD et al.** The ontogeny of 25-hydroxyvitamin D3 1??-hydroxylase expression in human placenta and decidua. *Am J Pathol* 2002 Jul; 161(1):105-114.
72. **Haugen M, Brantsaeter AL, Trogstad L et al.** Vitamin D supplementation and reduced risk of preeclampsia in nulliparous women. *Epidemiology* 2009;20(5): 720-726.