Original Article

The Role Of Vitamin D In Polycystic Ovary Syndrome

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Abstract

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders of reproductive age women and contributes to metabolic dysfunctions including insulin resistance (IR) and dyslipidemia. Vitamin D is a steroid hormone, which is involved in calcium metabolism and bone structure and has a potential role in the prevention of many illnesses, including cancers, autoimmune disorders, hypertension, diabetes, and obesity. Recently, it has been reported that vitamin D deficiency was a common complication of PCOS and vitamin D status was associated with reproductive ability, metabolic alterations, and mental health of PCOS patients. This review summarizes the advances between vitamin D status and the pathophysiological process of PCOS. Vitamin D level was negatively associated with serum androgen level. Vitamin D treatment could reduce serum androgen and anti-MüllerianHormone (AMH) levels, and decrease endometrial thickness, which resulted in improvement of menstrual cycle and folliculogenesis of PCOS patients. Moreover, vitamin D concentrations were negatively correlated with parameters of IR and body fat mass. Vitamin D supplementation has beneficial effects on IR and lipid metabolism. In addition, a positive of vitamin D on mental health of PCOS patients was proposed. Understanding the relationship between vitamin D status and the symptoms of PCOS patients is of great clinical significance to treat and prevent the progression of PCOS.

Introduction:

Poly Cystic Ovarian Syndrome (PCOS) is one of the most common metabolic and reproductive disorders among women of reproductive age (**1).**

Women suffering from PCOS present with a constellation of symptoms associated with menstrual dysfunction and androgen excess **Elhayek et al.** (**2)** with chronic and oligo-anovulation and polycystic ovarian morphology **(3).**

The poly cystic ovary syndrome is common during the reproductive age, with a global prevalence of 5–20% (**4,5).**

Although it was previously considered as a disorder of adult women, evidence suggests that PCOS is a lifelong syndrome, manifesting since prenatal age **(6).**

Previous Hypotheses:

Many hypotheses emerged trying to explain the pathophysiology of PCOS. Initially, excess intrauterine androgen had been thought to be a main culprit in the development of the disease **(7, 8).**

Human studies showed that there was no association between excessive prenatal androgen exposure and the development of PCOS in youth **(7)** and no elevation in androgen levels in the cord blood of females born to mothers with PCOS **(9).**

Another hypothesis, the adipose tissue expandability hypothesis, suggested that infants with intra-uterine growth restriction (IUGR) and spontaneous catch-up growth might develop decreased tissue expandability, meaning that they cannot store lipids appropriately in their fat tissues **(10).**

Insulin resistance might ensue contributing to PCOS and hyperandrogenemia**(10).** Insulin resistance via a post-receptor defect in the fat tissue and skeletal muscles (abnormaphosphorylation of tyrosine kinase **(11, 12).**

Insulin resistance might ensue contributing to PCOS and hyperandrogenemia**(10).**

Pathophysiology of PCO:

Uncontrolled Ovarian Steroidogenesis:

In the ovary, androgen production is regulated by LH in the theca cells, whereas estrogen synthesis from the androgens is regulated by FSH in granulosa cells **(8).**

The biosynthesis of both sex steroids is also modulated by intra- and extra-ovarian factors. Androgens and estradiol inhibit their own production via a paracrine negative feedback loop modulating the activity of cytochrome P450c17 in theca cells**(13).**

Insulin and insulin-like growth factor-1 (IGF-1) are the major extra-ovarian factors that modulate sex steroid synthesis, acting as stimulating factors of androgen production by increasing the 17-hydroxylase and 17,20-lyase activity of P450c17**(13).**

A defect of the ovarian cells (most likely theca cells) is the underlying cause of PCOS, resulting in excessive androgen synthesis and the clinical and biochemical symptoms of the disease **(3, 11).**

An intrinsic defect in theca cells can partially explain the hyper and rogenemia in patients with PCOS. Indeed, women with PCOS have theca cells that, still secrete high levels of androgens due to an intrinsic activation of steroid genesis even in the absence of trophic factors **(14).**

This intrinsic dysregulation also affects granulosa cells which produce up to 4 times higher levels of anti-mullerian hormone (AMH) in women with PCOS **(15,16).**

The rise in AMH levels in PCOS might promote GnRH release from the hypothalamus and contribute to hyperandrogenism **(17).**

Studies also show an elevated number of follicles, primarily pre-antral and small antral follicles, in females with PCOS. A defect in apoptotic processes in some maturing follicles further increases their count in PCOS patients **(18).**

Hypothalamic-pituitary abnormalities:

Increased LH pulses and overall increased daytime secretion of LH is observed early during puberty in girls with hyperandrogenism, which may indicates that abnormalities of LH may be a primary defect in PCOS. This increased LH secretion increased androgen production in the ovarian theca cells, which leads to hyperandrogenism in these females **(19).**

Follicles within the ovary have also been noted to have increased resistance to follicle stimulating hormone (FSH) **(20)**.

Most women with PCOS, LH to FSH ratios are inverted from normal, with LH increasing, usually 3 times that of FSH **(20)**.

Insulin is another factor that may increase the frequency and amplitude of GnRH and LH pulse secretion by the upregulation of GnRH gene expression in hypothalamic GnRH neurons, an effect mediated via activation of the Mitogen-Activated Protein Kinase **(**MAPK pathway) **(17).**

In addition Anti-mullerian hormone (AMH), caused a higher frequency of GnRH pulses and a reduction in FSH concentration (**3, 11)**.

Extra glandular synthesis of androgens:

Particularly in the adipose tissue, has been found to be involved in the pathophysiology of PCOS. They involve alteration in the activity of 11β-hydroxysteroid dehydrogenase **(21)** and both 5α-reductase and 5βreductase, Alterations of these enzyme systems which are involved in peripheral cortisol metabolism may in turn activate the neuroendocrine drive to support adrenal steroidogenesis and may partly explain the increased androgen production in specific subsets of women with PCOS **(22, 23).**

Insulin Resistance and oxidative stress

Decreased insulin sensitivity attributable to a post receptor binding defect in the insulin signaling pathways has been identified as an intrinsic component of PCOS, independent of obesity **(24).**

It was also reported that alteration in gene expression of some players in insulin signaling pathways by microarray gene analysis **(25, 26).**

Moreover, PCOS has been associated with increased glycol-oxidative stress secondary to mitochondrial dysfunction **(27).** Oxidative stress can itself induce insulin resistance and hyperandrogenism in patients with PCOS **(28).**

PCOS syndrome is based on endocrinological perturbation of insulin axis like hyperinsulinemia and insulin resistance. Higher circulating insulin level subsides secretion of sex hormone-binding globulin (SHBG) from liver, the fall in sex hormone binding globulin SHBG increases the level of free circulating testosterone in blood and causes hyperandrogenemia **(29).**

Hyperinsulinemia also increases GnRH pulse frequency; however, the LH surge predominates over (FSH) surge. This leads to decreased follicular maturation, increased ovarian androgen production **(30)**.

Birth weight defect:

PCOS might start in utero, mainly in neonates with risk factors implicated in the development of PCOS. This includes low birth weight and high birth weight infants who later on catch-up on their growth or constantly increase in weight postnatally **(10, 31).**

Sympathetic nerve activity and hyperandrogenism:

Many factors associated with polycystic ovary syndrome (PCOS) are also associated with increased activity in the sympathetic nervous system **(32).**

The involvement of sympathetic nervous system in PCOS pathology is supported by the greater density of catecholaminergic nerve fibres in polycystic ovaries (PCO)**(33).**

Increased ovarian sympathetic nerve activity might contribute to PCOS by stimulating androgen secretion **(34).**

Nerve growth factor (NGF) is a strong marker for sympathetic nerve activity and recently it was demonstrated that women with PCOS has enhanced ovarian NGF production (**35).**

Inflammation:

Direct correlations have been found between increased levels of inflammation markers (C-reactive protein CRP, ferritin, leukocyte tumor necrosis factor (TNF) α, interleukin (IL) 6, and IL-18 TNF-α, IL-6, IL-18) and the development of PCOS **(36, 37).**

Newly emerging issues include a pathogenic correlation of the markers of iron overload with PCOS. Increased levels of ferritin and transferrin and a higher frequency of the haptoglobin α chain have been observed, causing a reduction of anti-inflammatory cytokines and antioxidant molecules, leading to a state of chronic inflammatory response **(37, 38).**

PCOS have increased markers of lipid peroxidation, elevated levels of c-reactive protein, inflammatory cytokines, as well as higher concentrations of blood lymphocytes and monocytes **(39, 40).**

Risk factors:

PCOS can be described as an oligogenic disorder in which the interaction of a number of genetic and environmental factors determine the heterogeneous, clinical, and biochemical phenotype **(41).** A family history of PCOS is relatively common**(42).**

Some studies suggest that PCOS is a primary defect in young girls who are entering puberty and who have a family history of the disorder. Approximately 25% of patients with PCOS have elevated prolactin levels (**43, 44, 45).**

Excessive weight is associated with adverse metabolic and reproductive health outcomes in women with PCOS. For instance, female fertility decrease with a BMI > 30-32kg/m2 **(46).**

Childhood obesity is a well-documented risk factor for PCOS. Obese girls are at a higher risk of developing insulin resistance, metabolic syndrome, and PCOS later on in life **(47).**

The women with history of weight gain often proceed with the onset of oligomenorrhea and hyperandrogenism, suggesting that obesity has a pathogenetic role in subsequent development of PCOS **(48).**

Obesity can be exacerbated by poor dietary choices and physical inactivity; infectious agents and toxins may also play a role **(49).**

Signs and Symptoms:

The three most common factors associated with PCOS include ovulation irregularities, increased androgen levels, and cystic ovaries **(50, 51).**

In addition premature pubarche, premature adrenarche dehydroepiandrosterone sulfat (DHEAS) elevated , and metabolic syndrome may occur **(52, 53).**

Ovarian dysfunction typically results in oligomenorrhea or amenorrhea due to chronic oligo-ovulation or anovulation, Oligo-ovulation is defined as a menstrual cycle > 35 days in length Approximately 70% to 80% of women with PCOS present with oligomenorrhea or amenorrhea **(44).**

Hyperandrogenemia is considered the main clinical hallmark of PCOS **(Rojas et al., 54)** Hirsutism, acne, and alopecia are directly associated with elevated androgen levels, and the prevalence of polycystic ovaries on pelvic ultrasound exceeds 70% in patients with this manifestation **(50).**

Up to 40% of hirsute women who claim to be eumenorrheic are actually oligo-anovulatory **(45).**

Some reports have revealed a higher frequency of depression, drug-related and bipolar disorders, bulimia, anorexia or non-specific dietary disorders was noted among PCOS patients **(55; 56).**

Chronic hyperandrogenemia, which leads to increased aromatization of androgens to estrogens in adipose tissue, may contribute further to the development of hormone-dependent tumors, such as endometrial, mammary or ovary neoplasms (**57).** PCOS is considered the leading cause of anovulatory infertility **(58).**

Biochemical disorders:

Manifested primarily by increased production of androgens and estradiol, and the malfunctioning hypothalamic-pituitary-ovarian axis is manifested by increased secretion of LH, AMH, a higher frequency of GnRH pulses and a reduction in FSH concentration **(3; 11).**

The most common biochemical perturbation in patients with PCOS is the elevation of circulating testosterone and androstenedione levels **(58).**

In addition, there is disturbed lipid profile: an increase in very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and triglycerides (TG), and a decrease in HDL- and LDL-cholesterol, regardless of body weight coagulation disorders, increased plasminogen activator inhibitor 1 (PAI1), increases in the coronary artery calcium score and resultant increases in carotid intima-media thickness lead to an increase in the risk of cardiovascular disorders (**59).**

Phenotypes:

Since PCOS tends to present as a spectrum of diseases, the Rotterdam criteria divided the disease into four phenotypes **(60).**

- Frank or classic polycystic ovary PCOS (chronic anovulation, hyperandrogenism, and polycystic ovaries).
- Classic non-polycystic ovary PCOS (chronic anovulation, hyperandrogenism, and normal ovaries).
- Non-classic ovulatory PCOS (regular menstrual cycles, hyperandrogenism, and polycystic ovaries).
- Non-classic mild or normoandrogenic PCOS (chronic anovulation, normal androgens, and polycystic ovaries).

Women with the frank phenotype have a worse profile of metabolic and cardiovascular risk factors (i.e., higher insulin resistance and poorer lipid panel) than those with the non-classic phenotype **(55)**.

DIAGNOSIS

Guidelines:

Diagnosis of PCOS, women must fulfill two of the three characteristics: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, or polycystic ovary morphology on ultrasound with exclusion of other disorders **(45, 61).**

Even though conditions such as insulin resistance and obesity are considered intrinsic to PCOS, none of them is included in the guidelines and should therefore be used for diagnostic purposes **(62).**

In addition ruling out any pathological condition that might explain the hyperandrogenism or the menstrual irregularity **(63).** The disparity between the guidelines, although minor, has been associated with a variation in the diagnosis and the treatment protocols of PCOS **(63).** Moreover, diagnosis in adolescent females is highly debatable **(64).**

Testing near the luteal phase of the menstrual cycle are recommended for more accurate results, on the hand, testing should include an assessment of the metabolic status of the patient, i.e., measurement of her body mass index (BMI), conduction of a fasting lipid panel, and a 2-h glucose challenge test **(62).** On the other hand, screening for thyroid disorders through assessment of thyroid-stimulating hormone levels is considered important as thyroid disorders are a common cause of menstrual irregularity **(65).**

Polycystic Ovaries on Ultrasonography:

Normal physiological changes and variations in the volume and size of the ovaries during puberty make ultrasonography findings controversial for the diagnosis of PCOS **(66).**

Also, performing a transrectal or transvaginal ultrasonography in adolescents may not be always applicable, which may delay diagnosis. For diagnostic purposes, normal ovarian volume in female adolescents is considered equal to or less than 10 ml **(67).**

PCO morphology was determined according to standardized international criteria for adult women as 1 or more ovaries with a volume >10 cm^3 or 12 or more follicles between 2 and 9 mm diameter **(68).**

The Androgen Excess–PCOS Society Task Force recommended that PCOM is defined as 20 follicles per ovary using a trans vaginal probe and high resolution technology (transducer frequency 8 MHz) **(66).**

Associated morbidities:

Obesity

Women with PCOS are at a higher risk of developing obesity **(Randeva et al 69; Zeng et al 70**).

Some studies explain that females with PCOS have increased visceral and subcutaneous body fat distribution due to increased androgen production rates, this central obesity follows a masculinized body fat distribution **(71)** .And the amount of visceral fat correlates with the degree of insulin resistance **(72).**

Women with PCOS have an atherogenic lipid profile, associated with elevated levels of low-density lipoprotein, triglycerides and cholesterol, along with decreased levels of high-density lipoprotein. They are also at a higher risk of developing atherosclerosis, arterial stiffness, and altered vascular endothelium **(1).**

Metabolic syndrome:

Metabolic syndrome which is a common disorder related to visceral obesity and insulin resistance (IR) is associated with atherosclerosis and cardiovascular disease **(73, 74).** There is an increased risk of metabolic syndrome in women with PCOS **(75).**

PCOS is frequently associated with various patterns of dyslipidemia including low high density lipoprotein cholesterol (HDL-C), high levels of triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) **(76, 77).**

Cumulative evidence suggests a clear association between PCOS and the development of non-alcoholic fatty liver disease **(78, 79).**

Some evidence suggests that androgen excess may contribute to impairing glucose tolerance and beta cell function in women with PCOS **(80, 81).**

PCOS is associated with an increased risk of several comorbidities; particularly type 2 diabetes and glucose intolerance **(82).**

Experimental studies demonstrated the expression of androgen receptors in b cells **(83, 84).**

In women with PCOS, it was documented that hyperglycemia-induced oxidative stress in mononuclear cells and glucose-stimulated nuclear factor-kB (NF-kB) activation in these immune cells were involved in beta cell dysfunction in PCOS, suggesting that both oxidative stress and inflammatory processes are linked to beta cell failure in these patients **(85, 86).**

Some data suggest that androgen excess predisposes the development of diabetes mellitus T2D via the specific activation of androgen receptors (AR) signal in neurons, causing hepatic insulin resistance, and in beta cells, leading to increased oxidative stress, insulin hypersecretion, and b cell failure **(84).**

Cardiovascular risk:

PCOS is associated with an increased risk of several comorbidities; particularly cardiovascular disease (CVD) **(82).** There is an increase in inflammation, oxidative stress and impaired fibrinolysis in women with PCOS **(87).**

Obesity, insulin resistance, infertility, and oral contraceptive use associated with an increased risk of hypertension and dyslipidemia **(88).**

Neoplasms:

Chronic hyperandrogenemia, which leads to increased aromatization of androgens to estrogens in adipose tissue, may contribute further to the development of hormone-dependent tumors, such as endometrial, mammary or ovary neoplasms **(57).**

Psychological effects:

Women with PCOS are more prone to have depression, anxiety, low self-esteem, a negative body image and psychosexual dysfunction **(89).**

Pregnancy complication:

Pregnant women with PCOS should be informed of the increased rates of miscarriage, gestational diabetes, pre-eclampsia, and premature delivery **(90).**

Treatment of polycystic ovary:

Non pharmacologic measures:

Guidelines recommend exercise therapy and calorie-restricted diet as a crucial part of the management of obesity in women with PCOS. In fact, lifestyle modifications are considered as a cost-effective first line treatment and as a necessary adjunct to medication **(91, 92).**

Multiple small uncontrolled trials have shown that a body weight decrease of as little as 5% regulates the menstrual cycle, improves fertility, reduces insulin and testosterone levels, decreases the degree of acne and hirsutism, and benefits psychological wellbeing **(93).**

Pharmacologic measures:

Oral contraceptive pills:

Oral Contraceptive Pills are the most commonly used medications for the long-term treatment of women with PCOS **(91, 92)**, as first-line treatment for hyperandrogenism and menstrual cycle irregularities in

women with PCOS. By suppressing the hypothalamo-pituitary-ovarian axis **(94).** It improves acne and hirsutism **(95).**

A number of clinical trials associated the use of oral contraceptive pills in patients with PCOS with increased risk of insulin resistance **(91, 96).** Concerns have been also raised about the negative effects of oral contraceptive pills on the cardiovascular profile of females with PCOS **(97, 98**).

The mainstay of therapy for adolescents with PCOS is oral contraceptive pills which provided as treatment of hyperandrogenism (**99, 100).** And normalize menses and decrease acne and hirsutism **(101).**

Metformin:

Metformin an oral anti-diabetic biguanide drug, acts by impeding hepatic glucose production and increasing the peripheral insulin sensitivity **(102)**. Studies reported change in insulin sensitivity in PCOS patients receiving metformin **(103, 104).**

Inositol:

Inositol an insulin-sensitizing molecule. Growing evidence suggests that insulin resistance might be induced by an alteration of the metabolism of inositol phosphoglycans second messengers and mediators or by a defect in their tissue availability **(105).**

Spironolactone:

A steroid chemically related to the mineralocorticoid aldosterone, was able to improve insulin sensitivity; it also suggested its use for hyperandrogenism associated symptoms such as acne and hirsutism **(106).**

Guidelines do not provide any specific recommendations for the use of spironolactone in the management of PCOS **(107).**

Vitamin D

Vitamin D is a lipid-soluble prohormone that is vital for the maintenance of bone and muscle health by promoting the absorption and metabolism of calcium and phosphate (**108).**

In addition to food sources such as fatty fish, eggs, fortified milk and cod liver oil, the human body uses ultraviolet B (UVB) radiation from sunlight to synthesis a significant portion of vitamin D requirements (**109**).

There are two forms of vitamin D: vitamin D2 (ergocalciferol) and D3 (cholecalciferol),the skin synthesises vitamin D3 after sun exposure and it may be obtained from animal sources, while vitamin D2 is the synthetic form that is often found in fortified food and is derived from plants (**110).**

Vitamin D synthesis and metabolism:

The synthesis of vitamin D starts with the oxidation of cholesterol to 7-dehydrocholesterol (7-DHC). In the skin, 7-DHC is photolysed by Ultraviolet rays UVB (280–320 nm) to pre vitamin D, which is converted to vitamin D by photolysis-mediated thermo-isomerisation , to become biologically active, the vitamin D originating from dermal production or dietary sources undergoes a series of enzymatic conversions in the liver and kidney (**111).**

Vitamin D, bound to the vitamin D binding protein(DBP), is transported to the liver where the cytochrome P450 enzyme 25-hydroxylase (CYP2R1) adds a hydroxylgroup on carbon 25 to produce a major circulating form of vitamin D, (i.e., 25-hydroxyvitamin D [25-{OH}D] [Calcidiol]) (**112).**

CYP2R1 is able to hydroxylate vitamin D2 and vitamin D3 at position 25 (**113).** Mutation in the CYP2R1 gene results in rickets (**114**).

The inactive 25-(OH) D metabolite also circulates in the bloodstream bound to DBP and it must be further hydroxylated at a different site in the kidney tubules to gain hormonal bioactivity hydroxylation at position 1 by the mitochondrial cytochrome P450 enzyme **(115, 116).**

25-hydroxyvitamin D-1 α -hydroxylase (CYP27B1) of kidney converts 25-(OH) D to 1 α,25-dihydroxyvitamin D (1 α,25-(OH)2D; calcitriol), the most active hormonal form of vitamin D that plays an essential role in mineral homeostasis and is responsible for most of the biological action of vitamin D (116).

In the general population, the prevalence of vitamin D deficiency exists ranges from 20 to 80% **(117, 118).**

Although there is no agreement on the optimal range of vitamin D deficiency, it is predominantly characterized by serum 25(OH)D concentrations below 25–30 nmol /L(10–12 ng/mL) **(119).**

FUNCTION OF VIT D:

Calcium and bone hemostasis:

The primary role of vitamin D has been considered to be the absorption of calcium from the intestine (i.e., calcium homeostasis in the body) and is necessary for skeletal health (bone mineralization, remodeling, and maintenance), Over the years it has become increasingly clear that vitamin D not only has a function in bones, but it also affects cell proliferation and differentiation **(110).**

Regulation of gene expression:

Vitamin D is a global regulator of gene expression and signal transduction in virtually every tissue. In epithelial cells vitamin D, by binding with the vitamin D receptor (VDR), contributes to maintenance of the quiescent, differentiated phenotype and promotes pathways that defend cells against endogenous and exogenous stresses **(120).**

Several lines of evidence have shown that vitamin D reduces the risk of colorectal cancer. Other cancers that may be vitamin D-responsive include breast, lung, ovarian and prostate. Other disorders in which the role of vitamin D is being actively investigated are the autoimmune disorders such as multiple sclerosis (MS), type 1 diabetes mellitus and rheumatoid arthritis (**121).**

Anti-inflammatory effect:

Vit D decreases the expression of cyclooxygenase-2 COX-2 and increases that of 15-Hydroxyprostaglandin dehydrogenase (15-PGDH) 15-PGDH in various cells **(122, 123).**

As a result, calcitriol treatment of these cells decreases the levels of biologically active prostaglandins PGs, thereby reducing the inflammatory response and growth stimulation (123).

Vit D is known to directly modulate basal and cytokine-induced NF-κB activity in many cells including human lymphocytes **(124)** fibroblasts **(125)**, and peripheral blood monocytes **(126).**

The ability of vitamin D to reduce the production of pro-inflammatory cytokines such as IL-6 by inhibiting p38 signaling demonstrates its significant anti-inflammatory effects **(127)**. Vitamin D role on asthma pathogenesis and control has also been extensively investigated (**128).** Vit D and its analogs also directly inhibit the proliferation of endothelial cells leading to the inhibition of angiogenesis **(129, 130)**.

Vitamin D and glucose metabolism:

It also affects glucose homeostasis through manifold roles. The potential influences of vitamin D on glucose homeostasis include the presence of specific vitamin D receptor (VDR) in pancreatic β-cells and skeletal muscle, the expression of 1-α-hydroxylase enzyme which can catalyze the conversion of 25-hydroxy vitamin D [25(OH)D] to 1,25-dihydroxyvitamin D, and the presence of a vitamin D response element in the human insulin gene promoter **(131).**

Reproductive function:

VDR mRNA has been shown to be expressed in the ovaries, in mixed ovarian cells, and in purified granulosa cell cultures, indicating a role in steroidogenesis of sex hormones (**132).**

VDR knockout female mice conceive infrequently, have significantly fewer viable fetuses in utero and present with uterine hypoplasia, impaired folliculogenesis, anovulation, and absent corpora lutea (**133).**

Several studies suggest an association between vitamin D and fertility in humans. Evidence exists that vitamin D exerts some effects on female reproduction, including In vitro fertilization IVF outcome, PCOS and endometriosis, as well as on steroidogenesis in healthy women (**131, 134, 135).**

Women with higher levels of 25(OH)D in serum and follicular fluid were significantly more likely to achieve clinical pregnancy following IVF, and high vitamin D levels were significantly associated with improved parameters of controlled ovarian hyperstimulation (**136).**

Likewise, the placenta expresses the CYP27B1 gene (encoding 1α-hydroxylase) and VDR gene. In male rodents, VDR has been found in the smooth muscle of the epididymis, spermatogonia and Sertoli cells. VDR was detected in human sperm, specifically in the sperm nucleus (**137).** In addition spermatids, epididymis, seminal vesicle and prostate express VDR and vitamin D metabolizing enzymes (**134).**

Overall fertility is reduced in vitamin D-deficient diet eating female rats and have increased risk of pregnancy complications. This is not corrected by normalizing the hypocalcaemia in vitamin D-deficient female rats, but requires 1, 25(OH)2D3 also the testes of vitamin D-deficient male rats showed incomplete spermatogenesis and degenerative changes (**138**).

In men, vitamin D status might be related to spermatogenesis, semen quality and testiculopathies as well as male hypogonadism (**135).**

Men with vitamin D deficiency (<10 ng/mL) had a lower proportion of motile, progressive motile, and morphologically normal spermatozoa compared with men with sufficient vitamin D status (>30 ng/mL) (**134).**

The Role of Vitamin D in Polycystic Ovary Syndrome

Vitamin D plays a physiologic role in ovarian follicular development and luteinization via altering anti-müllerian hormone (AMH) signalling, follicle-stimulating hormone sensitivity and progesterone production in human granulosa cells(**139).**

Low 25(OH)D levels are found to be significantly correlated with insulin resistance in women with PCOS. Thus, genes involved in vitamin D metabolism have been suggested as candidate genes for the susceptibility to PCOS. A few polymorphisms in the VDR gene, such as Cdx2, Taq1, Bsm1, Apa1, and Fok1, were reported to play an influential role on insulin secretion and sensitivity in PCOS women (**140).**

Low 25(OH) D levels may exacerbate the symptoms of PCOS, including insulin resistance, ovulatory, menstrual irregularities, infertility, hyperandrogenism, obesity and elevate the risk of cardiovascular diseases (**141).**

Vitamin D supplementation can lower the abnormally elevated serum anti-müllerian hormone (AMH) levels and increase serum anti-inflammatory soluble receptor for advanced glycation end-products in vitamin D-deficient women with Poly cystic ovary in particular vitamin D and calcium supplementation in addition to metformin therapy in women with PCOS could result in the beneficial effects on menstrual regularity and ovulation (**142).**

However, **Garg et al.** (**143)** demonstrated that there was no significant beneficial effect on insulin kinetics and cardiovascular risk factors after supplementation of vitamin D, at a dose of 4,000 IU/day for six months, among women with PCOS treated with metformin **Garg et al.** (**143)**

Vitamin D and blood hemostasis:

Vitamin D metabolites and its associated molecules were reported to be an intriguing factor involved in regulatory processes related to thrombosis **(144).**

There are shreds of evidence from the clinical reports that have correlated deficiency of vitamin D with the increase in thrombotic episodes **(145 ,146).**

Wu et al. (146) demonstrated the association of low vitamin D levels with the development of deep venous thromboembolic (DVT) events in patients with ischemic stroke**.**

The anti-thrombotic effects of vitamin D on the thrombogenic and anti-thrombogenic components of the coagulation system have been very well documented **(147; 146; 148).**

Supplementation of vitamin D resulted in a significant decrease levels of circulating biomarkers of endothelial function, including adhesion molecules as E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) which has a roll in thrombosis **(149).**

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