Chapter 13

Vitamin D and Female Reproduction

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Abstract

Vitamin D deficiency has an impact on the reproduction of more than 40% of reproductive age women globally. Fibroids are more common among African-American females owing to their decreased milk consumption and reduced absorption of ultraviolet rays, supporting the relation between vitamin D deficiency and fibroid development. Vitamin D has an inhibitory effect on leiomyoma cells by suppression of proliferation cell nuclear antigen (PCNA), BCL-2, BCL-w, CDK1, and catechol-O-methyltransferase (COMT) protein levels. A growing evidence support the relationship between vitamin D deficiency and endometriosis through overexpression of vitamin D recseptor (VDR) and α-hydroxylase enzyme, however, it is still unclear if the endometriosis patients could benefit from vitamin D supplementation. Effect of vitamin D supplementation on the metabolic outcomes of polycystic ovary (PCO) has been studied and reveled that it is negatively correlated with fasting glucose, fasting insulin, triglycerides, C-reactive protein, free androgen index, and Dehydroepiandrosterone (DHEAS) and positively associated with quantitative insulin sensitivity check index (QUICKI), high density lipoprotein cholesterol (HDL-C), and sexual hormone binding globulin (SHBG), whereas its impact on the ovarian function is still unclear. Vitamin D deficiency may worse the obstetrical outcomes, including preeclampsia, gestational diabetes, low birth weight, increased cesarean section rate, neonatal asthma, seizures, and preterm labor. The relationship between serum levels of 25-hydroxy-vitamin D (25(OH) D) and pregnancy rates in ART is still debatable, with the need to conduct more clinical trials toward it. The in vitro antiproliferative and prodifferentiative effect of vitamin D might find a role in control of hyperplastic overactive bladder. Several studies support that vitamin D deficiency constitutes a risk factor for development of many types of cancer such as breast, ovarian, and colorectal.

Keywords: vitamin D deficiency, Female reproduction, Fibroid, Fertility, Overactive bladder

1. Introduction

Over the past decade, a global pandemic of vitamin D deficiency has grown among all racial groups. Based on the National Health and Nutrition Examination Survey analysis, the overall revalence rate of vitamin D deficiency was 41.6%, with the highest rate detected in blacks (82.1%), followed by Hispanics (69.2%) [1].

Vitamin D is a naturally occurring steroidal hormone whose primary role in the human body is calcium homeostasis, keeping bones healthy and strong. However, a recent body of research strongly indicates that vitamin D's relevance and significance extend well beyond just keeping bones healthy and strong but rather plays a more pivotal role in the body's overall health, including its role or lack thereof in chronic diseases such as diabetes, obesity, autoimmune disease(s), cardiovascular disease, and cancer [2]. This is largely attributed to vitamin D's ability to affect different types of cells by turning genes within these cells "on and off"; thereby playing a major role in controlling cellular growth, function, and death [3].

Many studies have recently investigated the relationship between levels of vitamin D levels and cancer [3]. Low levels of vitamin D have been associated with a 30–50% increased risk of colon, prostate, and breast cancer [4]. Indeed, vitamin D's growing role in human immunity might provide a logical explanation for these disease manifestations. However, data that support a definitive causal relationship between vitamin D deficiency and these cancers, as well as, further elucidate the associated benefits of vitamin D supplementation are extremely limited [4].

In female reproduction, the importance of vitamin D was initially appreciated *in vivo*, as mice who were either deficient in vitamin D or lacked the vitamin D receptor (VDR), suffered from underdeveloped uteri and an inability to form normal mature eggs, which in turn lead to infertility [5]. In humans, VDR, a member of the nuclear receptor family, is expressed in many female organs, including the ovaries (granulosa cells), uterus (endometrium and myometrium), and placenta [6]. These receptors are targeted by the active form of vitamin D (calcitriol = 1, 25 dihydroxy vitamin D) and produce an array of effects in female reproduction. For example, calcitriol regulates genes involved in estrogen synthesis [6]. It also controls several genes involved in embryo implantation [7].

Poor vitamin D status has been associated with a wide array of obstetrical complications and gynecological diseases [6, 7]. Furthermore, vitamin D has also played a progressive role in assisted reproductive techniques such as *in vitro* fertilization [8, 9]. In this chapter, we critically summarize the most recent data regarding the impact of vitamin D deficiency on female reproduction and related disorders.

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2. Vitamin D and uterine fibroids

Uterine fibroids (AKA: leiomyoma) are the most common hormone-dependent gynecologic tumors, affecting up to 70% of reproductive aged women. They arise from the proliferation of smooth muscle cells, forming a mass surrounded by a pseudocapsule of compressed muscle fibers [10, 11].

They are often asymptomatic, discovered incidentally in routine bimanual pelvic and/or ultrasound examination. Nevertheless, some leiomyomas may be complicated by a variety of symptoms including abnormal uterine bleeding, pelvic pressure, and pain, increased urinary incontinence, bowel disturbance, and are associated with infertility and recurrent abortion [12, 13]. Consequently, surgery represents the main treatment modality for symptomatic cases [11].

Hysterectomy is usually an option for women who have completed childbearing; however, many women may prefer to be treated with other conservative therapies as myomectomy to preserve her future fertility [14]. No definitive medical treatment has been established and can be used for short-term therapy. Evolving agents might have a role in the near future, such as vitamin D, green tea extract, and elagolix (oral GnRH antagonist). Furthermore, agents, such as selective E receptor modulators (SERMs) and gestrinone, can be used to decrease leiomyoma size with minimal side effects [15].

Sabry and Al-Hendy [15] have studied the potential effect of epigallocatechin-3-gallate (EGCG), one of the major green tea components, on the human leiomyoma cells. They found that EGCG inhibits the proliferation of these cells and induces apoptosis.

The pathophysiology behind the development of uterine fibroids is still not completely understood, growing evidence has supported the fact that both estrogen and progesterone play major roles in fibroid growth [16]. Al-Hendy group studied the Med12 gene somatic mutations in females with symptomatic uterine fibroids from the southern United States. They found four novel somatic mutations in the Med12 gene in uterine fibroids in this population, whereas, no mutations were identified in the Med12 gene in normal myometrium in these women [17].

Several studies revealed a two- to threefold higher incidence of uterine fibroids in African-American females as compared with other racial types, including Caucasians, Hispanics, and Asians [18]. This is supported by finding of uterine leiomyomas in 75% of hysterectomies performed on African-American women [19].

Analysis of leiomyoma phenotype performed by Baird et al. revealed that 73% of African-American females had multiple leiomyoma on ultrasound, whereas only 45% of Caucasian females pretended this phenotype [18]. The cumulative incidence of development of fibroid among African-American females is 80% by age 50 years, with annual incidence of 3% during their reproductive period [20, 21].

There are several dietary sources of vitamin D, such as fatty fish, fish oils, fortified foods, and vitamin supplements; however, sunlight exposure remains the main source of vitamin D [22]. High melanin concentrations in African-Americans have largely contributed to decreases the

absorption of ultraviolet rays from the sun. Furthermore, decreased milk consumption due to lactose intolerance diminishes the levels of vitamin D as well [23, 24].

Al-Hendy et al. have addressed a correlation between lower serum vitamin D levels and an increased risk of uterine leiomyoma in 2013 in a cohort of black and white females from North Africa. In addition, they revealed a significant inverse association between vitamin D serum levels and the severity of fibroids among African-American females [16].

These findings were supported by Baird et al. when they determine that women with sufficient levels of vitamin D were less likely to develop uterine fibroids and found that levels of vitamin D was 10% of African-Americans and 50% of Caucasians, with an adjusted odds ratio of 0.68 [25]. Also, Paffoni et al. found that women with vitamin D deficiency were more likely to have uterine fibroids, with an adjusted odds ratio of 2.4 [26].

The exact mechanism of uterine leiomyoma development is still unclear; however, there are several contributing factors, including clonal smooth muscle cell proliferations, chromosomal abnormalities, hormonal deregulation, and growth and angiogenic factors [27–30]. Catherino et al. have postulated that protein encoding genes from the extracellular matrix (ECM) were overexpressed in leiomyomas. Consequently, analysis of the ECM in leiomyoma tissue revealed a disturbed orientation of collagen fibril with reduction of its binding protein, which is called dermatopontin. Nevertheless, the latter was associated with an increase in transforming growth factor (TGF)-b3 messenger RNA levels [31].

Currently, TGF-b3 represents the only growth factor found to be overexpressed in leiomyoma samples during the secretory phase [32]. Recent COMT (catechol-O-methyltransferase) and ER-α (E receptor-α) polymorphism analyses in women from different ethnic groups was performed by Al-Hendy et al. and concluded that females with a high expression genotype for COMT were 2.5 times more likely to develop leiomyomas than females with other genotypes. That points to the vital role of submicroscopic genetic anomalies in formation of leiomyoma in African-American females [33].

Blauer et al. studied the role of vitamin D3 in the regulation of uterine leiomyomas growth and demonstrated that bioactive 1a, 25(OH) 2D3 inhibits the growth of both leiomyoma and myometrial cells derived from human tissues of premenopausal females undergoing hysterectomy. This growth inhibition was found to be a concentration dependent, being a concentration of 100 nM-the physiological level, sufficient to produce that inhibition [34, 35]. Baird et al. addressed that women with uterine leiomyomas have lower levels of serum vitamin D3 compared to their healthy counterpart women [25]. Moreover, serum levels of vitamin D3 are inversely proportional to leiomyoma sizes, supporting that vitamin D3 deficiency could be a potential risk factor for the development of uterine leiomyoma [26].

Al-Hendy group studied the mechanism of action of vitamin D on human uterine leiomyoma cell proliferation. Cells were treated with vitamin D3, followed by measurement of proliferation cell nuclear antigen (PCNA), BCL-2, BCL-w, CDK1, and COMT protein levels. They found a downregulation of PCNA, CDK1, and BCL-2 and suppression of COMT expression in human leiomyoma cells, favoring that vitamin D3 inhibits growth and induces apoptosis in cultured leiomyoma cells. In the following study, they tested the effect of vitamin D3 on TGF-b3–

induced fibrosis-related protein expression in human cells and concluded the suppressant effect of vitamin D3 onTGF-b3 in human leiomyoma cells [34].

Wei et al. conducted a study to verify the ethnic differences in tumorigenic factors of uterine leiomyomas. They identified selective genes by performing tissue microarray analyses and specific immunohistochemistry procedures involved in the development of leiomyomas and compared the results with matched myometrial tissue. They revealed that P receptor PR-A was upregulated in fibroid tissue of African-American females in comparison to other ethnic groups. Moreover, the E receptor, ER-a, was elevated in both the normal myometrial and leiomyoma tissues of African-American females when compared with other ethnic groups [35].

Recently, Al-Hendy et al. assessed the effect of vitamin D3 on leiomyoma growth in the Eker Rat model of uterine fibroids. They found that treatment with vitamin D3 significantly minimize leiomyoma size by inhibiting cell growth, proliferation-related genes (PCNA, cyclin D1 [Ccnd1], c-Myc, CDK1, CDK2, and CDK4), antiapoptotic genes (BCL2 and BCL-xl), and E receptor ER-a, and P receptors PR-A and PR-B [36]. Similarly, they found that paricalcitol, an analog of 1, 25-dihydroxyvitamin D3, significantly decreased fibroid tumor size in female nude mice as compared with placebo [37].

3. Vitamin D and endometriosis

Endometriosis is a chronic gynecological disorder affecting 5–10% of female population of reproductive age, with increased prevalence up to 30–40% among infertile women [38]. It can be defined as the presence of endometrial tissue in ectopic locations including ovaries, bladder, and bowel. The most common symptoms are dysmenorrhea, dyspareunia, chronic pelvic pain, and infertility [39].

The exact pathogenesis of the endometriosis is still questionable; however, several theories have been suggested. One of the most supporting theories is the development of immune system dysfunction, which leads to a state of chronic inflammation [40, 41].

A series of immunologic changes have been reported leading to endometriosis development, including a reduction in T -cell cytotoxicity, a functional deficit of natural-killer lymphocytes and higher concentration of activated macrophages in the peritoneal fluid, which consequently trigger a cascade of cytokines and vascular endothelial growth factors promoting proliferation of endometrial cells and angiogenesis [42, 43]. Genetic predisposition may play a role in incidence of endometriosis. It has been reported that first degree relatives have a three- to fivefold increased risk of endometriosis development [44].

Furthermore, there are several recognized endometriosis susceptibility genes, which are associated with steroid hormone action, immune response, oxidative stress, glucose homeostasis, vascular and tissue remodeling, and apoptosis [45, 46].

Several investigators studied the potential correlation between endometriosis and vitamin D. Viganò et al. addressed that the endometrium expresses the VDR and 1α -hydroxylase enzyme

irrespective of the menstrual cycle. Furthermore, they found that 1α-hydroxylase is expressed both in the eutopic and in the ectopic endometrial cells of women affected by endometriosis and that the enzyme expression is higher in the proliferative phase of the menstrual cycle [43].

Agic et al. supported these results and found an elevation of 24-hydroxylase in patients with endometriosis, indicated a very active metabolic process of vitamin D in the endometrium. These studies propose a local paracrine action of vitamin D, that could be involved either in the regulation of the immune system activity and in the cytokine production [47].

However, it is very hard to determine whether the endometriosis patients may benefit from Vitamin D supplementation, as the relationship between vitamin D and endometriosis seems to be more complicated. Hartwell and colleagues tested for the first time the metabolism of vitamin D in 42 women with endometriosis. They discovered that levels of 25(OH) D in the serum were normal, whereas the levels of 1, 25(OH) 2D3 were increased compared to the control group [48]. Lasco et al. conducted a prospective study, to examine the effect of a singleloading dose of cholecalciferol (300,000 IU) on primary dysmenorrhea; they found a significant reduction of pain in the supplemented group compared with the placebo group ($P < 0.001$) [49].

Somigliana et al. showed that the levels of 25(OH) D were significantly increased in the group of women with endometriosis, whereas the levels of 1, 25(OH) 2D3 and calcium were the same compared to the control group [50].

A prospective study was conducted by Harris et al. They reviewed 70,556 women, including 1385 with endometriosis and 69,171 matched controls regarding age, season, race, geographical region, alcohol intake, and physical activity. They found an inverse association between serum values of 25(OH) D and endometriosis: women in the highest predicted 25(OH) D quintile and highest intake of vitamin D from food had respectively a 24% and 21% lower risk of endometriosis compared with those in the lowest quintile. These results support the hypothesis that low levels of vitamin D are associated with an increased risk of endometriosis [51].

4. Vitamin D in polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy in the reproductive age women, with a prevalence of 6–19% in the general population [52–56]. The etiology of the syndrome remains largely unknown. Key characteristics of PCOS include ovulatory dysfunction, hyperandrogenism, and polycystic ovaries [57–59].

Insulin resistance (IR), yet another key feature of PCOS, plays a significant role in the development of metabolic complications such as type 2 diabetes mellitus, dyslipidemia, abdominal obesity, and increased risk of cardiovascular disease (CAD) [60, 61].

Current evidence supports the important role of vitamin D in energy metabolism and homeostasis. Animal studies have demonstrated that vitamin D signaling is directly involved in transcriptional activation of the insulin receptor gene [62] and inhibits pro-inflammatory

cytokines. Thus, the metabolic disarrangements observed in IR among PCOS patients may have a connection to the suboptimal Vitamin D level [63].

A recent systematic review and meta-analysis summarized the relationship between serum level of vitamin D and metabolic outcomes in women with PCOS, as well as determined the effects of vitamin D supplementation [64]. A pooled estimate of five observations revealed no significant difference in 1, 25(OH) 2D levels among PCOS patients as compared to the controls (SMD: 0.18; 95%CI: −0.10 to 0.45) [64].

Interestingly, vitamin D deficient PCOS patients were found to have lower HDL-C, higher fasting glucose, fasting insulin, HOMA-IR, HOMA-β, and FAI [64]. Serum levels of 25(OH) D were negatively correlated with fasting glucose, fasting insulin, triglycerides, C-reactive protein, free androgen index, and DHEAS among PCOS patients [62]. Moreover, vitamin D was found to be positively associated with QUICKI, HDL-C, and SHBG [64].

Studies addressing pretreatment and post-treatment with vitamin D supplementation have shown only significant decreases in triglyceride levels −0.45 (−0.73, −0.17) [64]. Furthermore, supplementation with vitamin D did not demonstrate any significant difference in metabolic parameters, androgen levels, and serum levels of 25(OH) D as compared to placebo [64].

In summary, clinical data support that vitamin D status is related to metabolic dysfunctions in PCOS. Moreover, vitamin D deficiency may worsen existing metabolic disarrangement in PCOS [64]. However, limited clinical evidence found no improvement of those disarrangements with a standard vitamin D supplementation. Over the past several years, there has been significant interest to vitamin D's effect on ovarian function in PCOS [65–71].

Clinical data demonstrate that 25OHD3 deficiency can be negative predictor of follicle development with clomiphene citrate stimulation [65]. However, the exact mechanism of vitamin D action on mammalian ovaries is not clearly understood. A vitamin D receptor has being identified in ovarian granulosa cells [66, 67], and animal studies suggest that the promoter for Anti-Müllerian hormone (AMH) is under vitamin D downregulation [67].

It is also well-known now that excessive ovarian production of AMH, secreted by growing follicles is an important feature of PCOS [68]. Taken into account that vitamin D signaling can modify the expression of AMH in ovaries, it is highly probable that vitamin D supplementation may also affect ovarian physiology in PCOS and possibly improve folliculogenesis. Surprisingly, there have been very few studies published. Thys-Jacobs et al. reported a study with 13 oligomenorrheic normocalcemic PCOS women who received vitamin D and calcium. Two months of treatment resulted in normalized menstrual cyclicity for 7 of 13 women [68].

In a more recent small clinical trial, 60 infertile PCOS patients were randomized into three groups: [1] vitamin D with calcium; [2] metformin only; and [3] combination of both [69]. The combination group demonstrated the higher number of dominant follicles at second- and third-month follow-up visits [69]. In another study of 67 vitamin D deficient women with and without PCOS, vitamin D supplementation was associated with decreased serum levels of AMH in PCOS patients, which suggests a possible improvement in ovarian physiology [70].

In conclusion, the results of basic research and several small clinical studies suggest that vitamin D has a positive effect on ovarian function in PCOS women; however, further clinical trials are needed.

5. Vitamin D and pregnancy

The role of vitamin D in pregnancy outcomes has recently gathered much attention. Pregnancy is a state of increased calcium demand and fetal/neonatal vitamin D status is dependent on the maternal level of vitamin D [71, 72].

Observational studies have shown consistent associations between obstetrical clinical outcomes and poor maternal vitamin D status, including preeclampsia, gestational diabetes, low birth weight, increased cesarean section rate, neonatal asthma, seizures, and preterm labor [73–75].

Although vitamin D deficiency in pregnancy is documented to be common by CDC (Center of Disease Control and Prevention) and the WHO (World Health Organization), a clear consensus for screening and management of vitamin D deficiency in pregnancy has not yet been adopted, owing to a paucity of research data regarding the role of vitamin D in pregnancy biology and limited clinical trials on the use of vitamin D supplementation to improve obstetrical outcomes [73, 76].

Studies have showed that vitamin D supplementation impacts inflammatory markers, contractile-associated proteins, estrogen receptor α, and progesterone receptor A/B ratio in human uterine smooth muscle cells. Vitamin D prevents inflammation-induced changes in myometrial cells mediated through the nuclear factor (NF)-κB pathway [77]. Deficient or low levels (hypovitaminosis) of vitamin D during pregnancy might be a risk factor for preterm birth [78, 79].

There is increasing evidence that corticotropin releasing hormone (CRH) plays a pivotal role in the control of human pregnancy and parturition. During human pregnancy, the placenta and fetal membranes produce large amounts of CRH, which steadily increases in concentration with advancing pregnancy [80]. It has been shown that CRH promotes myometrium quiescence during most of pregnancy, whereas it facilitates myometrial contractility after the onset of parturition. However, the mechanisms by which CRH exerts such dual effects remain unclear [81].

Vitamin D and CRH might interact during pregnancy through a number of pathways. The activation of CRH receptors initiate a variety of subsequent signals including protein kinase C (PKC) pathway that increase vitamin D receptor expression [82]. CRH synthesis is partly regulated through a noncanonical NF-κB pathway, which might be affected by vitamin D status [82]. A poor understanding of spontaneous preterm birth (PTB) or its risk factors and a lack of reliable biomarkers contribute to the difficulty in prevention, early diagnosis, and treatment of PTB [83].

6. Vitamin D and reproduction

Evidence from both animal and human studies strongly suggests a potential role of vitamin D in human reproduction. Assisted reproductive technology (ART) has been presented as a valuable model to study the effect of vitamin D deficiency on specific aspects of human fertility as it allows the separate evaluation of the various step of the reproductive process, including sperm function, folliculogenesis, and embryo implantation [84].

In vitro studies, it has been shown that vitamin D receptors are expressed in murine endometrium and ovary throughout the estrous cycle, whereas knockout experiments have shown that vitamin D receptor null mice experience uterine hypoplasia and impaired folliculogenesis [85].

Whereas, *in vivo* data supporting a role for vitamin D in female fertility and embryo implantation are still not conclusive. Some studies have revealed findings showing that maternal vitamin D deficiency is associated with lower pregnancy rates and others demonstrating that vitamin D deficiency does not affect the final reproductive outcome. Multiple studies investigated the association between serum levels of 25-hydroxy-vitamin D (25(OH) D) and pregnancy rates in ART with controversial results [84].

It is observed that serum 25 (OH)D levels were significantly related to implantation, clinical pregnancy, and live birth rates, although opposite trends were found according to patients ethnicity being critical in non-Hispanic whites but not in Asian ethnicity. In a second study, the same authors examined serum 25(OH) D concentration among recipients of oocyte donation, finding a positive association between vitamin D status and clinical pregnancy rate and suggesting the specific effect of 25(OH)D levels on ART outcomes to be mediated by endometrial receptivity rather than by ovarian stimulation or embryo parameters [85]. Interestingly, both cyclic and early pregnancy endometrium represent an extrarenal site of vitamin D synthesis; thus, the effect of vitamin D at the uterine level is thought to be exerted via the vitamin D receptor (VDR) through either the regulation of target genes or the hormonal effects on the local immune response [84].

A recent study has evaluated the influence of vitamin D deficiency on pregnancy rates among women undergoing In Vitro Fertilization/Intracytoplasmic Sperm Injection (IVF/ICSI) and day 5 single embryo transfer (SET). A total of 368 consecutive infertile women treated within a period of 15 months were included in the study. Serum vitamin concentration was measured retrospectively in all included patients. They found that clinical pregnancy rates were significantly lower in women with vitamin D deficiency compared with those with higher vitamin D values. Finally, even when restricting the analysis to women undergoing elective SET, vitamin deficiency was again independently associated with pregnancy rates [84].

In a cross-sectional analysis, a cohort of 1072 women with a mean age of 36.3 attending an academic infertility center were used to examine serum 25-hydroxy-vitamin D 25(OH)D) levels in relation to demographic characteristics, seasons, and general health risk factors. They found that median 25(OH) D concentration was below 30 ng/ml for 89% of the entire year. Over the whole year, 6.5% of patients had 25(OH) D levels </- 10 ng/ml, 40.1% </-20 ng/ml, and 77.4%

</-30 ng/ml. Global solar radiation was weakly correlated with 25(OH) D levels. Multivariate data analysis reveals that, 25(OH) D levels were inversely associated with basal metabolic rate (BMI); conversely, 25(OH) D levels were positively associated with height and endometriosis history. Serum 25(OH) D levels are highly deficient in women seeking medical help for couple's infertility. Levels are significantly associated with body composition, seasonal modification, and causes of infertility. Importantly, this deficiency status may last during pregnancy with more severe consequences [84].

In another cross-sectional study, Paffoni et al. investigated the IVF outcome in women with deficient 25(OH) D serum levels <20 mg/ml. They included 154 women with serum 25(OH)D <20 ng/ml and 181 women with levels of >/-20 ng/ml. They found that the clinical pregnancy rates were 20% and 31%, respectively, with an adjusted odds ratio of 2.15 for clinical pregnancy in women with vitamin D >/-20 ng/ml. Furthermore, a subgroup analysis revealed that the group with the highest serum level of vitamin D (>30 ng/ml) resulted in the highest chances of pregnancy [85].

More recently, Dressler et al. conducted a retrospective cohort study at two centers in Germany to investigate the prevalence of vitamin D deficiency among women with impaired fertility and to identify the risk factors associated. They found that 98.2% of women at center 1 and 81.3% of women at center 2 had deficient or insufficient vitamin D levels. Moreover, they found that overweight BMI and limited exposure to sun (winter, spring, and autumn trimester) were associated with vitamin D deficiency [86].

In an observation case-control study, Al-Jaroudi et al. compared the dietary vitamin D and calcium intake among subfertile women and pregnant (control) women to determine vitamin D levels. They found that vitamin D levels were significantly higher in the subfertile group compared to the control group (59.0% vs 40.4%; P<0.01) [87].

In Contrast, Franasiak et al. showed that vitamin D status was unrelated to pregnancy outcomes in women undergoing euploid blastocyst transfer [88].

They attempted to characterize the relationship between serum 25-hydroxy vitamin D (25-OH D) levels and implantation and clinical pregnancy outcomes in 517 women undergoing a euploid blastocyst embryo transfer. They concluded that serum vitamin D ranges and pregnancy outcomes did not correlate. However, their results may not apply to the patients who do not undergo extended embryo culture, blastocyst biopsy for comprehensive chromosome screening and euploid embryo transfer [88]. In a prospective cohort study, vitamin D (25OH-D) serum and follicular fluid levels were analyzed in 82 infertile women undergoing ART. They found that fertilization rate decreased significantly and the implantation rate increased (not significantly) with increasing levels of 25OH-D [89]. Using the same approach, Farzadi et al. reported a correlation between follicular fluid 25(OH) D concentration and assisted reproductive outcomes in an Iranian population [90].

In a retrospective study, serum and follicular levels of 25-OH vitamin D were collected from 80 infertile female candidates for IVF/ICSI to investigate the possible association of vitamin D with assisted reproductive outcome. They found a statically significant positive correlation between 25-OH vitamin D levels with patient age and implantation rate [91].

Although optimization of vitamin D levels is encouraged for the general reproductive health but more research is needed to understand the impact on reproductive potential. Most studies have small sample sizes, heterogeneous experimental design, and great confounders, such as obesity. Prospective studies are needed to confirm causal relationship and to investigate the potential therapeutic benefits of vitamin D supplementation in this population. Vitamin D deficiency has been shown to impair pregnancy rates in women undergoing single blastocyst transfer. Future prospective confirmatory studies are needed; preferably randomized controlled trials of vitamin D supplementation with an appropriate assessment of pregnancy outcomes.

7. Vitamin D and overactive bladder

Overactive bladder syndrome (OBS) is a highly prevalent condition, affecting 17% of the population worldwide, with more than 17 million people affected in the United States and more than 22 million adults affected in Europe [92–94].

Being a recently defined syndrome, its risk factors have not been determined yet; however, it is believed to be multifactorial. Zhang et al. concluded that the contributing risk factors are advanced age, menopause, parity >2, constipation, Hx of episiotomy, and high basal metabolic rate (BMI) [95].

Different drugs directed toward the central, peripheral sympathetic, parasympathetic, or sensory nervous pathways, as well as the detrusor muscle itself, have been studied and described [96]. Antimuscarinics have become the standard therapy for OAB, but their tolerability is limited by several adverse events, often leading to poor compliance and drug discontinuation [97].

Consequently, because the need for new drugs that provide similar or even greater clinical efficacy but with fewer side effects is evolving, those patients with OAB consistently require long-term therapy to control their symptoms [97, 98]. OBS shares epidemiological and pathophysiological features with preterm birth. Our recently published work suggests that vitamin D deficiency is a novel risk factor for preterm birth, a condition about four times more prevalent in African-Americans; who also have higher prevalence of vitamin D deficiency; as compared to their Caucasian counterparts. Furthermore, we have shown that vitamin D elicits a robust anti-inflammatory response in human myometrial cells [99]. Coyne et al. has demonstrated the prevalence of OBS in the total United States population and found that black women had a higher prevalence (32.6%), compared to Hispanic (29%) and white women (29.4%) [100].

This finding was supported by many studies as well [101, 102]. Vitamin D3 functions through the nuclear vitamin D receptor (VDR) and acts on VDR target genes. This vitamin D-mediated gene activation requires a VDR/retinoid X receptor heterodimer complex [102]. Recent studies have examined the expression of vitamin D receptors (VDRs) in the human bladder [102]. Bladder cell overgrowth and smooth muscle overactivity have been implicated in the initial steps of bladder decompensation and lower urinary tract symptoms (LUTS) [103].

The hyperplastic overactive bladder could represent an ideal candidate for treatment with paricalcitol in view of its antiproliferative and prodifferentiative effects on bladder cells in culture, which probably contribute to the control of smooth muscle cell overactivity, as well as considering the strong association of a high dietary intake of vitamin D with a decreased risk of overactive bladder [104].

Schroder et al. used a rat model of partial bladder outflow obstruction and found that VDR agonists reduced the incidence of spontaneous bladder contractions during filling through the inhibition of RhoA/Rho-kinase activity [105].

8. Vitamin D deficiency and risk of gynecological cancer in women

A number of studies have shown its association with risk of several types of cancers [106, 107]. Higher prevalence of vitamin D deficiency, together with the increased risks of certain types of cancer in those who are deficient in vitamin D3, suggesting that vitamin D deficiency may account for several thousand premature deaths from colorectal [108], breast [109], ovarian [110], and prostate [111] cancer annually [112]. People exposed to sunlight were noted to be less likely developed cancer. Thus, these findings inspired us for ensuring adequate vitamin D intake in order to reduce the risk of several gynecological cancers such as breast, ovarian, endometrial, and cervical cancers.

8.1. Vitamin D and breast cancer risk

Several case-control and laboratory tests have demonstrated an important role of vitamin D in the prevention of breast cancer. Low vitamin D intake is associated with increased risk of breast cancer in premenopausal women [106].

Daily vitamin D intake of greater than 500 IU had been shown significantly reduced breast cancer risk than those were consumed less of vitamin D [107, 113].

In a study by Lin et al. showed that higher intake of vitamin D and calcium were able to reduce the risk of premenopausal breast cancer [114]. 1,25(OH)2D3 exerts its antiproliferative effects on breast cancer cells by a number of ways, including by altering the expression of oncogenes and tumor suppressor genes, several cyclins, and cyclin-dependent kinase inhibitors p21WAF-1/CIP-1 and p27kip1 [114, 115]. 1,25(OH)2D3 also induce apoptosis in breast cancer cells by stimulating Ca2+ release from intracellular stores that result in rising cytosolic Ca2+ which triggers calpain-mediated caspase-independent programmed cell death [115]. This synergistic actions of calcium and vitamin D are probably the cause why high intake of low-fat dairy products is associated with a reduced risk of breast cancer in premenopausal women [116, 117].

Studies have shown that breast cancer death rates tend to be higher in low winter sunlight levels, whereas it is lower in sunny areas [118]. Women who are regularly exposed to sunlight and ingest sufficient amounts of vitamin D had significantly lower prevalence of breast cancer [119]. It has also been shown that women in the lowest quartile of serum levels of 1,25(OH)2D3

had a five times higher risk of breast cancer than those in the highest quartile [120]. Low levels of 1,25(OH)2D3 were also associated with faster progression of metastatic breast cancer [121]. Studies showed that high intake of vitamin D and calcium markedly reduced the incidence of mammary cancer in experimental mice and rats that were given high-fat diets [122–123]. Furthermore, high levels of vitamin D and calcium intake was able to reduce the incidence of mammary cancer in rats [123].

8.2. Vitamin D and ovarian cancer risk

Ovarian cancer is the fifth leading cause of cancer death among women in the United States [124]. Low levels of serum vitamin D was reported in ovarian cancer patients [125–127], and that low concentrations of 25(OH)D3 was associated with lower overall survival rate, whereas higher 25(OH)D3 concentrations significantly associated with longer survival among women with ovarian cancer [128].

This observation indicates that severe vitamin D deficiency may play a role in the development of more aggressive ovarian cancer. Several epidemiological studies have identified higher mortality rates of ovarian cancer in areas of higher latitude and lower levels of solar irradiation [110, 128, 130].

Most of these studies have also shown a lower mortality rate of premenopausal ovarian cancer in sunny regions [128, 129]. These findings have been supported by observational studies of dietary intake of vitamin D [131] and of pre-diagnostic serum 25(OH) D3 [132]. A study had shown that the lower level of pre-diagnostic serum 25(OH) D3 was associated with high risk of ovarian cancer in overweight women, whereas that was not the case for thinner women [132].

It is also recommended that serum 25(OH) D3 measurement could be a standard procedure that might be helpful to diagnose ovarian cancer patients with worse prognosis. In addition, supplementation of vitamin D3 at moderate doses achieving 25(OH) D3 serum concentrations of 30–80 ng/ml could be beneficial for reducing the risk of developing ovarian cancer.

8.3. Vitamin D and cervical cancer risk

An independent study in China and France also showed inverse correlation between solar UVB indices and cervical cancer incidence rate [133, 134].

In addition, a case-control study in Japan showed significant reduction of cervical cancer risk with increasing oral vitamin D intake [135]. Moreover, a recent case report indicated that patient suffering with abdominal pain due to cervical cancer-related treatment was improved after vitamin D replacement therapy [136].

These studies suggest that vitamin D deficiency might play risk for cervical cancer development that can be prevented by oral intake of vitamin D.

8.4. Vitamin D and endometrial cancer risk

A case–control study from seven cohorts evaluated the inverse association between serum concentrations of vitamin D3 and the risk of development of endometrial cancer [137–139].

It is recommended to measure serum concentrations of vitamin D3 that permits to estimate the risk of association with endometrial cancer, and proper levels of vitamin D intake could reduce the risk of development of endometrial cancer.

8.5. Vitamin D and cancer prevention

A number of epidemiological studies have demonstrated the association between vitamin D deficiency and risk of several types of cancers. Strong evidence also indicates that vitamin D3 intake is associated with reduced incidence and death rates of colon, breast, prostate, and ovarian cancers [140].

Evidence also proved that vitamin D3 intake of 2000 IU/day would lead to the reduction of breast cancer and colon cancer incidence [140]. Thus, vitamin D3 supplementation could address the high prevalence of vitamin D deficiency and could prevent many deaths from breast and colorectal cancers in the United States [140].

The measurement of serum concentrations of vitamin D3 is important to assay the risk of various cancers, and an intake of recommended levels of vitamin D3 per day could be very beneficial to prevent many deaths from cancers in the United States.

9. Conclusions and future directions

In strictly seasonal breeders, an increase in photoperiod (longer day time, more sun) affects pineal gland, which in turn alter melatonin secretion, affect gonadotropin secretion, and finally place animal in or out of estrus [141].

Humans are continuous but probably still partial seasonal breeder. The sunshine hormone (vitamin D) may have something to do with it. As female human emerge from the cloudy/rainy winters, vitamin D rises and female reproduction is optimized (effects on ovary, egg quality, endometrium (implantation), and myometrium), beside potential central effects of vitamin D on hypothalamic-pituitary axis [142].

Conception occurs soon and delivery takes place about 9 months later by early autumn, which is also optimal as it is harvest season and there is abundance of food to support the nursing mom to take care of the hungry baby. In fact, CDC life birth rates support such model and consistently show highest rates in late summer and early fall month [143]. Clearly, such innate breeding pattern in human has been influenced and largely muted by various ever evolving religious, cultural, and social traditions and etiquettes in human civilization on this planet.

The future research focusing on translational applications of various fundamental observation described in this review will likely to have major positive impact on women reproductive health. Both pharma and academia have synthesized many highly potent and safe VDR agonists that will soon undergo rigorous preclinical and subsequent clinical evaluation for utility in various female reproductive disorders. Furthermore, more clinical research should examine the possible association of vitamin D deficiency with additional adverse reproductive

outcomes. Clearly, future effort will be utilized in patients' counseling regarding screening for vitamin D status and appropriate vitamin D supplementation when indicated for overall health benefits, including bone health, reproductive health, and chronic disease risk reduction.

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